**ClinicalTrials.gov ID:** NCT04415151

**Brief Title:** Tofacitinib for Treatment of Moderate COVID-19 (I-TOMIC)

**Date:** 9/28/2020

**Document:** Protocol ONLY (SAP revised 2024)

# Investigation of Tofacitinib to Mitigate the Impact of COVID-19 (I-TOMIC) in Moderate SARS-CoV-2 (MODERATE I-TOMIC)

**Protocol Number**

2000027848

**Protocol Revision 5**

15 SEPTEMBER 2020

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NCT Number: NCT04415151

Study Phase: 2

**Confidentiality Statement:**

## REVISION HISTORY:

| Revision # | Version Date |
|---|---|
| Original | 13 April 2020 |
| 1 | 8 May 2020 |
| 2 | 18 May 2020 |
| 3 | 15 June 2020 |
| 4 | 25 June 2020 |
| 5 | 15 September 2020 |

# Synopsis

**Primary Objective/Endpoint**

- Proportion of subjects alive and not needing any form of mechanical ventilation, high flow oxygen, or ECMO at day 14.

**Secondary Objectives/Endpoints**

- Clinical improvement as measured by NIAID 8-point ordinal scale (i.e., 1 = death and 8 = Not hospitalized, no limitations on activities) at day 14.
- Clinical status using ordinal scale (days 3 through day 14): The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. The scale is as follows: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 7) Not hospitalized, limitation on activities and/or requiring home oxygen; 8) Not hospitalized, no limitations on activities.* For patients on chronic home O2 supplementation, supplemental O2 is defined as >= home O2 requirement. ** Use of NIV for chronic conditions [e.g. Obstructive sleep apnea (OSA)] is not applicable
- Time to recovery [ Time Frame: Day 1 through Day 14] (Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale: 1) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Not hospitalized, no limitations on activities).
- Time to clinical improvement (defined as a 2-point increase on the ordinal scale)".
- Clinical status on ordinal scale at day 30, 60, and 90
- Mortality rate at day 30, 60, 90
- Proportion of patients requiring ICU admission and mechanical ventilatory support
- Change from baseline in inflammatory parameters (e.g., hsCRP, procalcitonin, ferritin, D-dimers, LDH, fibrinogen, PT/PTT)
- Change from baseline in cytokines (e.g. IL-1, IL-2, IL-6, IL-8, TNF-α, IL-17A, IL-17F, IP-10, CCL5), as available
- Safety as assessed by reporting of adverse events, changes in clinical laboratory parameters (e.g., hemoglobin, hepatic transaminases, serum creatinine, bilirubin, and evidence of secondary infections)
- Intervention with additional immunomodulatory agent (i.e. IL-6 targeting therapy)
- Change in SARS-CoV-2 viral titers during intervention

**Study Duration**

- 10 months

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| **Study Design**<br>Randomized, double-blinded, placebo-controlled phase 2B study |
| **Number of Study Sites**<br>1 – Yale New Haven Health System |
| **Study Population**<br>Male and female subjects age 18 to 99 hospitalized with moderate SARS-CoV-2 infection |
| **Number of Participants**<br>60 |
| **Primary Outcome Variables**<br>• Proportion of subjects alive and not needing any form of mechanical ventilation, high flow oxygen, or ECMO at day 14. |
| **Secondary and Exploratory Outcome Variables (if applicable)**<br>• Clinical improvement as measured by NIAID 8-point ordinal scale (i.e., 1 = death and 8 = Not hospitalized, no limitations on activities) at day 14.<br>• Clinical status using ordinal scale (days 3 through day 14): The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. The scale is as follows: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 7) Not hospitalized, limitation on activities and/or requiring home oxygen; 8) Not hospitalized, no limitations on activities.* For patients on chronic home O2 supplementation, supplemental O2 is defined as >= home O2 requirement. ** Use of NIV for chronic conditions [e.g. Obstructive sleep apnea (OSA)] is not applicable<br>• Time to recovery [ Time Frame: Day 1 through Day 14] (Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale: 1) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Not hospitalized, no limitations on activities).<br>• Time to clinical improvement (defined as a 2-point increase on the ordinal scale)".<br>• Clinical status on ordinal scale at day 30, 60, and 90<br>• Mortality rate at day 30, 60, 90<br>• Proportion of patients requiring ICU admission and mechanical ventilatory support<br>• Change from baseline in inflammatory parameters (e.g., hsCRP, procalcitonin, ferritin, D-dimers, LDH, fibrinogen, PT/PTT) |

- Change from baseline in cytokines (e.g. IL-1, IL-2, IL-6, IL-8, TNF-α, IL-17A, IL-17F, IP-10, CCL5), as available
- Safety as assessed by reporting of adverse events, changes in clinical laboratory parameters (e.g., hemoglobin, hepatic transaminases, serum creatinine, bilirubin, and evidence of secondary infections)
- Intervention with additional immunomodulatory agent (i.e. IL-6 targeting therapy)
- Change in SARS-CoV-2 viral titers during intervention

# 1 Introduction

## 1.1 Introductory Statement

This document is a protocol for a human research study. The purpose of this protocol is to ensure that this study is to be conducted according to ICH GCP guidelines, and according to CFR 21 Part 312, other applicable government regulations and Institutional research policies and procedures.

# 2 Background

### 2.1.1 Preclinical Experience

- JAK inhibitors prevent CRS induced by CAR-T-cell therapy in mice, and JAK inhibition was more effective than tocilizumab[1]
- JAK inhibitor ruxolitinib improves survival, decreases cardiac inflammation and fibrosis in an experimental myocarditis model (Hyung Chun lab, unpublished data), and improves Staph-induced CRS, ARDS, and MOF in mice (Jon Koff lab, unpublished data)[2]

### 2.1.2 Clinical Experience

- Tofacitinib improves severe myocarditis in humans with DRESS[3]
- Tofacitinib improves sarcoidosis involving the skin[4] and internal organs[5]
- Ruxolitinib improves CRS associated with HLH[6,7]
- Ruxolitinib improved cytokine and inflammatory profile and ventilatory requirement in one patient with severe SARS-CoV-2 infection at Yale New Haven Hospital (Won et.al., in preparation)`

### 2.2 Background/prevalence of research topic

Patients with SARS-CoV-2 may manifest cytokine release syndrome (CRS), associated with systemic inflammation, hemodynamic instability, and multiple organ failure. CRS is among the key reasons for SARS-CoV-2 related mortality.

Multiple cytokines, including IL-6, are involved in CRS. Indeed, the IL-6 receptor antibody tocilizumab is FDA approved for the treatment of Chimeric Antigen Receptor T (CART) Cell-Induced Severe or Life-Threatening CRS. Anti-IL-6 antibody treatment is being used in some cases of SARS-CoV-2, and treatment with tocilizumab is standard of care at YNHH as of April 4, 2020. However, the only data to support the use of tocilizumab is a 21-patient retrospective case series from China.[8] A therapy targeting multiple cytokines, including IL-6, may prove effective in SARS-CoV-2 -induced CRS.

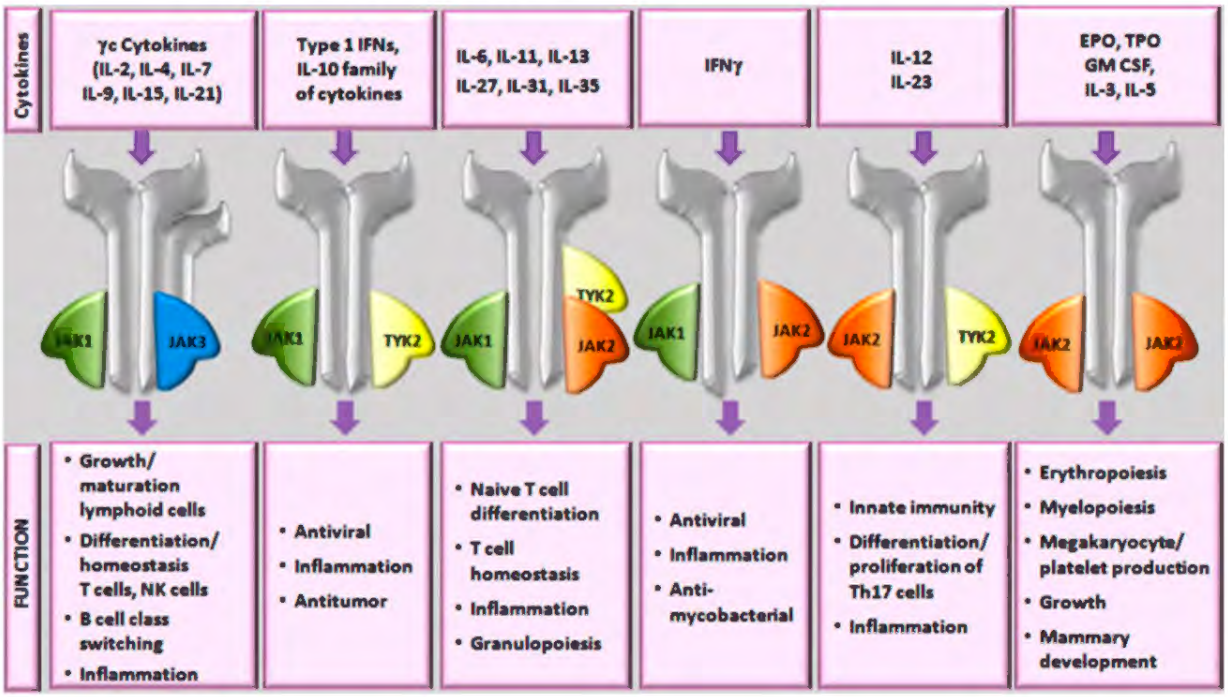
JAK-STAT signaling is a pro-inflammatory pathway that is activated downstream of multiple cytokines, including IL-6. JAK inhibitors (JAKi) are small molecule inhibitors of one or more of the Janus kinase (JAK) family of enzymes and are used to treat hematological and inflammatory diseases. Over 50 cytokines signal through the JAK-STAT pathway, and hence JAK inhibitors have the potential to suppress the activity of multiple cytokines, including IL-2, IL-4, IL-6, IL-15, interferon gamma, and IL-21.

Oral tofacitinib was approved by the FDA in 2012 for the treatment of moderately to severely active RA who have had an inadequate response to, or who are intolerant of, methotrexate. It has recently been approved for the treatment of psoriatic arthritis (PsA) and ulcerative colitis (UC). Its use is being studied in other inflammatory diseases, including juvenile idiopathic arthritis. The recommended dose of tofacitinib is 5 mg twice daily for RA and PsA and up to 10 mg twice daily for UC. The following table presents the risks as summarized in the original package insert for XELJANZ for RA. The risk profile has not changed significantly following studies of tofacitinib in other diseases.

Tofacitinib is an orally administered, synthetic small molecule that selectively inhibits the JAK family of kinases (preferentially JAK1/JAK3) and is currently FDA-approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), graft vs. host disease (GVHD) and ulcerative colitis (UC). Unlike targeted biologic therapies, which are directed at extracellular

targets such as individual soluble cytokines (e.g. TNF-α), cytokine receptors (IL-1R, IL-6R) or other cell surface receptors (CD20, CD80, and CD86), tofacitinib works intracellularly[2] and has been developed to target a number of cytokines known to have a role in inflammatory diseases (Figure 1).

**Figure 1. Tofacitinib Mechanisms of Action - Biological Significance of Signaling Through Different JAK Combinations**




Abbreviations: IL=interleukin; IFN=interferon; EPO=erythropoietin; TPO=thrombopoietin; GM-CSF= granulocyte macrophage colony-stimulating factor; CSF=colony-stimulating factor; JAK= Janus-Kinase; TYK2= tyrosine kinase 2; Th17=T-helper phenotype.
Cytokine signaling is mediated by specific JAK and STAT combinations due to preferential binding to the intracellular domains of the individual cytokine receptor chains. For example, JAK3 only associates with the γ- common chain and therefore only mediates IL-2, -4, -7, -9, -15, and -21 signaling, whereas JAK1 plays a broader role in cytokine signaling.
Adapted from reference[10].

**Dose Rationale**

The safety and clinical pharmacology of tofacitinib has been very well characterized. The pharmacodynamics (PD) of the tofacitinib, in terms of cytokine inhibition and biomarkers of pharmacologic activity, have been characterized in *in vitro* studies, animal models, and *in vivo* clinical studies. These data indicate rapid onset, followed by sustained pharmacologic activity over the dosing period. At a 10 mg BID dose, approximately 80% suppression of IL-6 may be expected, in addition to substantial inhibition of multiple other pro-inflammatory cytokines, such as IFNγ, IL-15, IL-21, and IL-27, supporting the use of tofacitinib 10 mg BID for prevention of overexpression of cytokines in SARS-CoV-2 infected patients. Given the high mortality of COVID-19 complicated by ARDS, and the overall case mortality rate in COVID-19 patients, a tofacitinib dose of 10 mg immediate release formulation BID is

expected to provide maximal cytokine suppression while maintaining an overall positive benefit-risk profile.

If concomitant administration of a strong inhibitor of CYP3A4 (eg, ketoconazole, clarithromycin, ritonavir/lopinavir) or a moderate inhibitor of CYP3A4 that is also a strong inhibitor of CYP2C19 (eg, phenytoin, fluvoxamine, fluconazole) cannot be avoided, a reduced dose of tofacitinib 5 mg BID is recommended and will provide similar target coverage.

Because patients are likely to be discharged from the hospital soon after returning to clinical baseline, we will continue to administer tofacitinib 5 mg BID for a total duration of treatment of 14 days in order to prevent rebound of CRS that could theoretically occur with abrupt cessation of immunomodulatory therapy. In these cases, patients will be discharged home with a pill bottle labeled as investigational drug containing the appropriate number of pills (either tofacitinib or placebo).

# 3 Rationale/Significance

## 3.1 Problem Statement

Patients with SARS-CoV-2 may manifest cytokine release syndrome (CRS), associated with systemic inflammation, hemodynamic instability, and multiple organ failure. CRS is among the key reasons for SARS-CoV-2 related mortality.

## 3.2 Purpose of Study/Potential Impact

The role of JAKi in the treatment of CRS and cardiac and respiratory failure in patients with SARS-CoV-2 is supported by both preclinical and clinical data.

Taken together, we hypothesize that JAKi treatment of patients with moderate SARS-COV-2 and associated CRS and cardiac and respiratory complications will improve clinical outcomes of moderate SARS-CoV-2.

### 3.2.1 Potential Risks

(Please refer to tofacitinib package insert for complete risk profile)

**Study Drug (Tofacitinib) Risks**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Very common side effects** (these may affect 1 in 10 people or more, or >10%): none.

**Common side effects** (these may affect up to 1 in 10 people, or up to 10%): upper respiratory tract infection (nasopharyngitis, common cold), lung infection (pneumonia and bronchitis), shingles (herpes zoster), influenza (flu), sinusitis, urinary bladder infection (cystitis), sore throat (pharyngitis), increased muscle enzymes or cholesterol, weight gain, stomach (belly) pain (which may be from inflammation of the stomach lining), vomiting, diarrhea, nausea, indigestion, pain in the joints, low red blood cell count (anemia), fever, fatigue (tiredness), swelling of the feet and hands, headache, high blood pressure (hypertension), cough, rash.

**Uncommon side effects** (these may affect up to 1 in 100 people, or up to 1%): tuberculosis, kidney infection, viral infections, skin infection, herpes simplex or cold sores (oral herpes), viral infections affecting the gut, increased liver enzymes, low white blood cell count, blood creatinine increased (a possible sign of decreased kidney function), dehydration, pain in the muscles, muscle strain, tendonitis, joint swelling, ligament sprain, abnormal sensations, poor sleep, shortness of breath or difficulty breathing, sinus congestion, skin redness, itching, fatty liver, inflammation of outpouchings of your intestine (diverticulitis), tears in your stomach or intestines, some types of skin cancers (nonmelanoma-types), drug allergy (which can involve bumpy skin rash, swelling around lips and tongue, wheezing, dizziness or lightheadedness).

**Rare side effects** (these may affect up to 1 in 1,000 people, or up to 0.1%): blood infection (sepsis), joint infection, tuberculosis involving the brain and spinal cord, bones and other organs, and other unusual infections.

**EMERGING SAFETY INFORMATION - MORTALITY**

In one ongoing study in rheumatoid arthritis patients who were 50 years of age or older with at least one risk factor for heart disease, patients treated with tofacitinib 10 mg twice a day

had a higher frequency of mortality (death), compared to patients treated with tofacitinib 5 mg twice a day or a tumor necrosis factor inhibitor medication (adalimumab or etanercept). In patients treated with tofacitinib 10 mg twice a day in other tofacitinib studies, the frequency of death has not been higher than the frequency of death in patients treated with tofacitinib 5 mg twice a day.

**Minimizing risks:** Patients will be evaluated at least once daily, depending on the level of care required of their overall condition after treatment initiation.

Toxicity monitoring: Patients will be monitored at least once daily after initiation of therapy, depending on the level of care required of their overall condition. On each day an H&P will be performed and the patient will undergo laboratory monitoring including hsCRP, ferritin, LDH, D-dimer, CBC, and CMP (SOC). If there is suspected toxicity from the therapy, the dose of tofacitinib may be reduced to 5 mg BID or stopped entirely, depending on the toxicity observed or suspected.

Research blood samples: The results of the research testing will not appear in the subject's medical file. No individual identifiers will be used for any testing. All samples and data are given a unique code to remove any identifying information. Any information that identifies the subject will be kept separate from the samples and this identified information will be kept until the study is complete.

With respect to prophylactic management of VTE, we will follow the institutional standard of care algorithm at the time of the study (**Appendix 1**).

## Risk Mitigation Strategies

| Potential Risk of Clinical Significance | Summary of Data/Rationale for Risk | Mitigation Strategy |
|---|---|---|
| **Study Intervention(s) Tofacitinib** | | |
| Known risks associated with tofacitinib include the following:<br>• Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections and viral reactivation;<br>• Venous thromboembolism (VTE), including pulmonary embolism and deep venous thrombosis;<br>• Gastrointestinal perforations;<br>• Interstitial lung disease;<br>• Potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids.<br>Other risks, which are known to have long latency, such as lymphomas and other malignancies and cardiovascular events, have also been identified with tofacitinib treatment. | The list of risks are based on the SRSD for tofacitinib. | Eligibility criteria exclude participants with risk factors for venous thromboembolism, known malignancies, and active infections other than COVID-19 pneumonia, and these lab abnormalities.<br>Thromboprophylaxis with LMWH is required for all participants.<br>Treatment with tofacitinib will be discontinued if the participant has any serious infection not considered related to COVID-19, VTE, or other safety event for which the investigator determines that continued treatment with tofacitinib is not in the participant's best interest.<br>Discontinuation criteria are in place for these lab parameters. |
| • Concomitant use of CYP3A4 and CYP2C19 inhibitors and CYP inducers.<br>• Participants with moderate or severe renal impairment.<br>• Participants with moderate hepatic impairment. | Potential risks are based on the SRSD for tofacitinib. | Participants receiving medications that may interfere with tofacitinib metabolism (CYP inducers) within 28 days or 5 half-lives of the medication are excluded from the study.<br>Dose modification instructions are included in the study for<br>co-administration of CYP inhibitors and tofacitinib. |

### 3.2.2 Potential Benefits

For study subjects, the potential benefits of this trial are halted progression of and improvement in their SARS-CoV-2 infection. For society at large, this study offers the possibility of effective therapy of moderate SARS-COV-2, an often morbid and sometimes fatal disease.

# 4 Study Objectives

## 4.1 Hypothesis

We hypothesize that JAKi treatment of patients with moderate SARS-COV-2 and associated CRS and cardiac and respiratory complications will improve clinical outcomes of moderate SARS-CoV-2.

## 4.2 Primary Objective/Endpoint

The primary objective of this study is to determine whether tofacitinib improves the clinical outcomes of patients with moderate SARS-CoV-2 infection as determined by the primary outcome measure: Proportion of subjects alive and not needing any form of mechanical ventilation, high flow oxygen, or ECMO by day 14.

## 4.3 Secondary Objectives

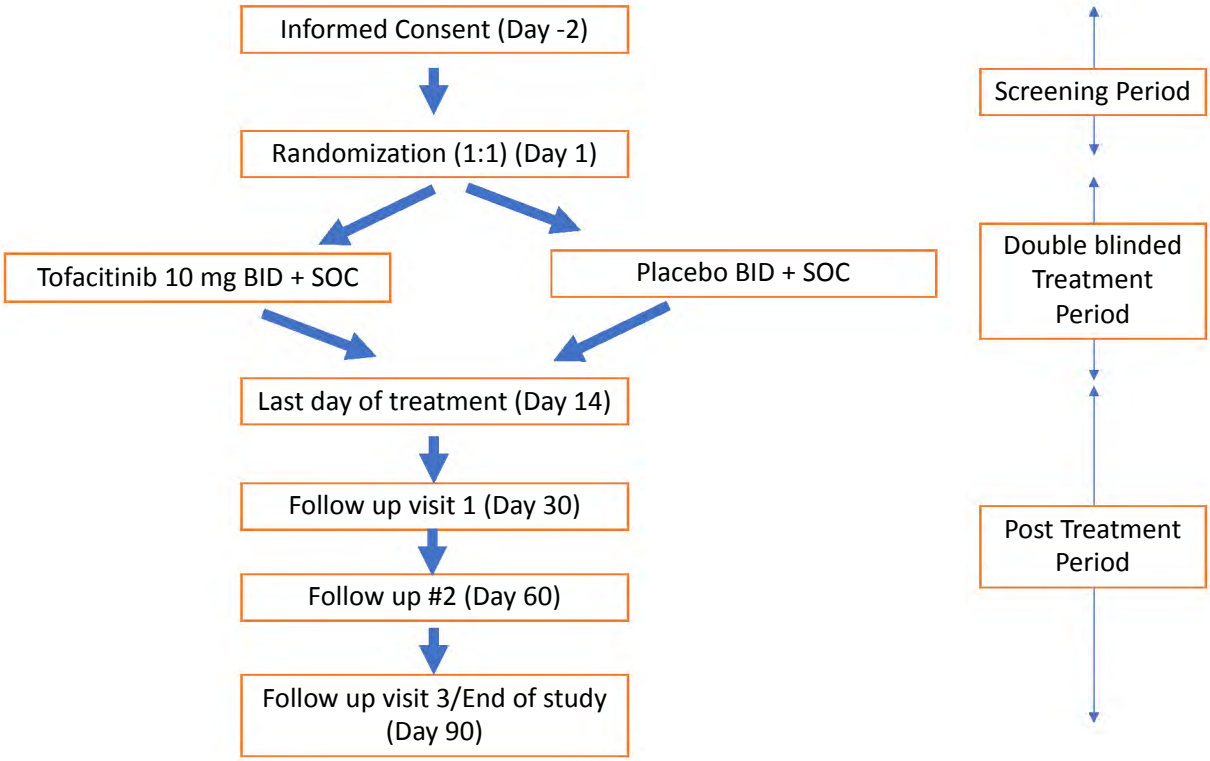
- Clinical improvement as measured by NIAID 8-point ordinal scale (i.e., 1 = death and 8 = Not hospitalized, no limitations on activities) at day 14.
- Clinical status using ordinal scale (days 3 through day 14): The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. The scale is as follows: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 7) Not hospitalized, limitation on activities and/or requiring home oxygen; 8) Not hospitalized, no limitations on activities.* For patients on chronic home O2 supplementation, supplemental O2 is defined as >= home O2 requirement. ** Use of NIV for chronic conditions [e.g. Obstructive sleep apnea (OSA)] is not applicable
- Time to recovery [ Time Frame: Day 1 through Day 14] (Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale: 1) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Not hospitalized, no limitations on activities).
- Time to clinical improvement (defined as a 2-point increase on the ordinal scale)".

- Clinical status on ordinal scale at day 30, 60, and 90
- Mortality rate at day 30, 60, 90
- Proportion of patients requiring ICU admission and mechanical ventilatory support
- Change from baseline in inflammatory parameters (e.g., hsCRP, procalcitonin, ferritin, D-dimers, LDH, fibrinogen, PT/PTT)
- Change from baseline in cytokines (e.g. IL-1, IL-2, IL-6, IL-8, TNF-α, IL-17A, IL-17F, IP-10, CCL5), as available
- Safety as assessed by reporting of adverse events, changes in clinical laboratory parameters (e.g., hemoglobin, hepatic transaminases, serum creatinine, bilirubin, and evidence of secondary infections)
- Intervention with additional immunomodulatory agent (i.e. IL-6 targeting therapy)
- Change in SARS-CoV-2 viral titers during intervention

# 5 Study Design

## 5.1 General Design Description

We propose a randomized, double blinded, placebo controlled Phase 2b study of the efficacy and safety of tofacitinib in hospitalized adult (18-99 years old) male and female patients with SARS-CoV-2 and pneumonia who require supplemental oxygen and have serologic markers of inflammation but do not need mechanical ventilation (see Inclusion criteria). Sixty patients will be recruited to receive tofacitinib or placebo in addition to standard of care (SOC) in a 1:1 ratio.




### 5.1.1 Study Date Range and Duration

Subjects will be screened during hospitalization. Patients with confirmed SARS-CoV-2 infection, and meeting all other Inclusion and Exclusion criteria, will be randomized to either treatment with tofacitinib or placebo in addition to SOC during hospitalization (dose adjusted, if required), with the exception of any immunomodulatory agents (as documented in the inclusion/exclusion criteria). Tofacitinib will be administered in a dose of 10 mg PO BID until return to their clinical baseline (as defined by need for supplementary oxygen), and will continue to be administered at 5 mg PO BID for a total duration of therapy of 14 days; follow-up off tofacitinib will continue up to Day 90. We anticipate completion of subject recruitment in 6 months.

### 5.1.2 Number of Study Sites

1 (Yale-New Haven Health System)

## 5.2 Outcome Variables

### 5.2.1 Primary Outcome Variables

- Proportion of subjects alive and not needing any form of mechanical ventilation, high flow oxygen, or ECMO by day 14.

### 5.2.2 Secondary Outcome Variables

- Clinical improvement as measured by NIAID 8-point ordinal scale (i.e., 1 = death and 8 = Not hospitalized, no limitations on activities) at day 14.
- Clinical status using ordinal scale (days 3 through day 14): The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. The scale is as follows: 1) Death; 2) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); 3) Hospitalized, on non-invasive ventilation or high flow oxygen devices; 4) Hospitalized, requiring supplemental oxygen; 5) Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise); 6) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 7) Not hospitalized, limitation on activities and/or requiring home oxygen; 8) Not hospitalized, no limitations on activities.* For patients on chronic home O2 supplementation, supplemental O2 is defined as >= home O2 requirement. ** Use of NIV for chronic conditions [e.g. Obstructive sleep apnea (OSA)] is not applicable
- Time to recovery [ Time Frame: Day 1 through Day 14] (Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale: 1) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Not hospitalized, no limitations on activities).
- Time to clinical improvement (defined as a 2-point increase on the ordinal scale)".

- Mortality rate at day 30, 60, 90
- Proportion of patients requiring ICU admission and mechanical ventilatory support
- Change from baseline in inflammatory parameters (e.g., hsCRP, procalcitonin, ferritin, D-dimers, LDH, fibrinogen, PT/PTT)
- Change from baseline in cytokines (e.g. IL-1, IL-2, IL-6, IL-8, TNF-α, IL-17A, IL-17F, IP-10, CCL5), as available
- Safety as assessed by reporting of adverse events, changes in clinical laboratory parameters (e.g., hemoglobin, hepatic transaminases, serum creatinine, bilirubin, and evidence of secondary infections)
- Intervention with additional immunomodulatory agent (i.e. IL-6 targeting therapy)
- Change/clearance of SARS-CoV-2 viral titers during intervention

## 5.3 Study Population

Potential subjects will be identified by study coordinators in conjunction with treating clinicians by screening the EMR of patients with a clinical diagnosis of SARS-CoV-2. Patients whose providers feel they are appropriate for the study will be approached. Pursuant to HIPAA regulations, a log of disclosures of protected health information for recruitment/screening purposes will be kept. Eligibility will be determined by the PI, Dr. Chun, and/or co-investigators Dr. Koff or Dr. Won. To initiate the process of obtaining informed consent, the PI or study coordinator will first approach the patient's treating clinician (ex: physician, nurse practitioner, or physician's assistant) regarding possible involvement in the study. If the provider feels the patient is appropriate, they will ask if the patient would be interested in hearing about a research project they might be able to participate in. If the patient expresses interest, the PI or study coordinator will then approach the patient.

### 5.3.1 Number of Participants

A total of approximately 60 patients, both male and female, age between 18 and 99 years old, will be enrolled.

### 5.3.2 Eligibility Criteria/Vulnerable Populations

**Inclusion Criteria:**

Participants are eligible to be included in the study only if all of the following criteria apply:

**Age and Sex:**

Male or female participants between the ages of 18 and 99 years, inclusive, at screening. Refer to **Appendix 3** for contraceptive guidance for participants.

**Type of Participant and Disease Characteristics:**

1. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
2. Participants with laboratory-confirmed novel coronavirus (SARS-CoV-2) infection as determined by polymerase chain reaction (PCR) or other commercially available or public health assay prior to Day 1.

3. Participants with evidence of pneumonia assessed by radiographic imaging (chest x-ray or chest CT scan) AND Requiring ≥ 3L O2 OR ≥ 2L O2 and hsCRP > 70 mg/L
4. Participants who are hospitalized and receiving supportive care for COVID-19.

**Informed Consent:**

Participant (or legally authorized representative/surrogate) capable of giving signed informed consent.

**Exclusion Criteria:**

Participants are excluded from the study if any of the following criteria apply:

**Medical Conditions:**

1. Require mechanical ventilation or ECMO on Day 1 at the time of randomization.
2. Have current, or history of, venous thromboembolism (deep vein thrombosis or pulmonary embolism).
3. Have a personal or first-degree family history of blood clotting disorders.
4. Participants who are immunocompromised, with known immunodeficiencies, or taking potent immunosuppressive agents (eg, azathioprine, cyclosporine).
5. Participants with any current malignancy or lymphoproliferative disorders that requires active treatment
6. Females of child bearing potential who are pregnant or breastfeeding
7. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk associated with study participation or, in the investigator's judgment, make the participant inappropriate for the study.
8. Anticipated survival < 72 hours as assessed by the Investigator.

**Infection History:**

- Suspected or known active systemic bacterial, fungal, or viral infections (with the exception of COVID-19) including but not limited to:
    - Secondary bacterial pneumonia;
    - Active herpes zoster infection;
    - Known active tuberculosis or history of inadequately treated tuberculosis;
    - Known HBV, HCV, or HIV.

**Prior/Concomitant Therapy:**

Have received any of the following treatment regimens specified in the timeframes outlined below:

Within 4 weeks prior to the first dose of study intervention:

- Prior treatment with any JAK inhibitors, potent immunosuppressants, or any biologic agents including IL-6 inhibitors (eg, tocilizumab) or IL-1 inhibitors (eg, anakinra) within the past 28 days or 5 half-lives, whichever is longer.
- Prior treatment with any potent cytochrome P450 inducer, such as rifampin, within the past 28 days or 5 half-lives, whichever is longer.

Within 48 hours prior to the first dose of study intervention:

- Treatment with herbal supplements.

Received >/= 20 mg/day of prednisone or equivalent for >/=14 consecutive days in the 4 weeks prior to screening

**Diagnostic Assessments:**

- Severe hepatic impairment, defined as Child-Pugh class C.
- Severe anemia (hemoglobin <8 g/dL).
- ANY of the following abnormalities in clinical laboratory tests at screening, confirmed by a single repeat, if deemed necessary:
  - WBC <1000/mm3
  - Absolute lymphocyte count <500 cells/$mm^3$;
  - Absolute neutrophil count <1000 cells/$mm^3$.
- Alanine transaminase/aspartate transaminase (ALT/AST) > 5 times the upper limit of normal;
- Estimated glomerular filtration rate (eGFR) < 40 mL/min/1.73 m2);

**Other Exclusions:**

- Known allergy to tofacitinib.
- Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.
- Enrollment in another clinical trial to study COVID-19

**Treatment Considerations**

Guidance on the management of COVID-19 coagulopathies based on commonly available laboratory tests has been recently published by the ISTH. They found a high incidence of both severe pneumonia and lymphopenia related to COVID-19 infection in patients requiring hospitalization. In this setting, patients with increased D-dimers (3 to 4-fold increase) are more likely to die from COVID-19 infection. Subtle prolongation of prothrombin time is seen in these patients and may be prognostic of mortality. Thrombocytopenia is also seen in these patients but does not seem to be a consistent prognosticator. In addition to monitoring of D-dimer, PT, and platelet counts, the ISTH also recommends monitoring of serum fibrinogen as patients with COVID -19 infection may develop DIC as early as Day 4.

ISTH recommends a prophylactic dosing of LMWH in hospitalized subjects who have COVID-19 infection to protect against sepsis-like coagulopathies and venous thromboembolism in the absence of active bleeding or a platelet count of <25,000 cells/$mm^3$.

**Concomitant Therapy**

All participants must receive pharmacologic thromboprophylaxis with LMWH and supportive care for COVID-19 pneumonia. Therapies currently being evaluated for treatment of COVID-19 patients have multiple mechanisms of action and address different therapeutic targets. With the exception of EUAs granted by FDA, there are currently no drugs or other therapeutics approved by health/ regulatory authorities to prevent or treat COVID-19 or the severe ARDS it may cause, so it is expected that adjunctive SOC may include investigational and off-label treatments. Some of these therapies are prohibited concomitant medications with tofacitinib; others can be co- administered. Table below lists known

investigational products in clinical trials and drugs that might be administered off-label. In addition, there may be additional products that may be added to the institutional standard of care, for which tofacitinib dosage may need to be adjusted. Treatments that should not be co-administered with tofacitinib during the conduct of this study are identified. If there is any uncertainty about the concomitant use of a treatment with tofacitinib, contact the sponsor.

**Investigational and Off-Label Treatments for COVID-19**

| Category | Treatment | Anticipated Target | Concomitant Use with Tofacitinib |
|---|---|---|---|
| Antiviral | Remdesivir | Stops virus from replicating; does not interfere with cytochrome P450 metabolism. Approved by FDA for emergency use. | Not prohibited |
| Antimalarial | Hydroxychloroquine/ chloroquine | Used for the treatment of malaria; anecdotal data. FDA does not recommend use except in clinical trials. | Not prohibited |
| Azalide Antibiotic | Azithromycin | Has not been used for viral infections; may have some anti-inflammatory action. NIH advised against use of the combination of hydroxychloroquine and azithromycin. | Not prohibited |
| Antiviral | Combination of lopinavir and ritonavir (Kaletra) | Indicated for treatment of HIV. One study did not show efficacy, but other clinical trials are ongoing. | Requires 50% reduction in dose |
| Host Modifiers/ Immune-based Therapy | Convalescent plasma | FDA has allowed this to be used in patients with serious or life-threatening COVID-19 infections. This treatment is still considered experimental. | Not prohibited |
| Host Modifiers/ Immune-based Therapy | Hyperimmune immunoglobulin | Manufactured from convalescent plasma and is allowed to be used in the same population. This treatment is still considered experimental. | Not prohibited |
| IL-6 Inhibitor | Tocilizumab | Used to treat autoimmune conditions through inhibition of IL-6 and is in clinical trials for COVID to treat hyperinflammation. | Prohibited |
| IL-6 Inhibitor | Sarilumab | Similar to tocilizumab and is in clinical trials for COVID. | Prohibited |
| IL-6 Inhibitor | Siltuximab | Similar to tocilizumab and is in clinical trials for COVID. | Prohibited |
| IL-1 Inhibitor | Anakinra | Used to treat autoimmune conditions through inhibition of IL-1 and is in clinical trials for COVID to treat hyperinflammation. | Prohibited |
| Janus kinase Inhibitor | Baricitinib | JAK 2 selective inhibitor with ant-iinflammatory properties is in clinical trials for COVID. | Prohibited |

| | | | |
|---|---|---|---|
| Janus kinase Inhibitor | Tofacitinib | JAK 1/ JAK 3 selective inhibitor with anti-inflammatory properties is in clinical trials for COVID. | This is the compound being studied. Additional treatment is prohibited. |

Modified from the NIH Coronavirus Disease 2019 (COVID-19) Treatment Guidelines
https://www.covid19treatmentguidelines.nih.gov/

To the extent possible, the following restrictions should be followed:

- Use of strong inhibitors of cytochrome P450 3A should be avoided to the extent possible. Judicious use of strong inhibitors of CYP3A4 or a moderate inhibitor of CYP3A4 that is also a strong inhibitor of CYP2C19 is permitted, if necessary, but the dose of tofacitinib should be reduced to 5 mg BID PO with careful monitoring for adverse effects (see Tofacitinib Dose Modifications, Section **Error! Reference source not found.**).
- Concomitant use of tofacitinib with strong inducers of cytochrome P450 is not recommended, and tofacitinib should not be used if strong inducers have been discontinued less than 28 days or 5 half-lives prior to the first tofacitinib dose.
- Herbal supplementation should not be administered, as many interfere with the cytochrome P450 pathways.
- Other JAK inhibitors, biological DMARDS, or potent immunosuppressive agents, including IL-6 inhibitors (eg, tocilzumab) and IL-1 inhibitors (eg, anakinra) should not be administered during the study.
- All non-pharmacologic and nutritional supportive care measures, including nutritional supplementation and oxygenation support are permitted. All concomitant medications and nondrug treatments, with dose and frequency, should be recorded.
- Hormonal contraceptives are allowed to be used in participants who are WOCBP (**Appendix 3**).

# 6 Methods

## 6.1 Treatment

### 6.1.1 Identity of Investigational Product

Tofacitinib is an orally administered, synthetic small molecule that selectively inhibits the JAK family of kinases, and is currently FDA approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ulcerative colitis (UC). Unlike targeted biologic therapies, which are directed at extracellular targets such as individual soluble cytokines (e.g. TNF-$\alpha$), cytokine receptors (IL-1R, IL-6R) or other cell surface receptors (CD20, CD80, and CD86), tofacitinib works intracellularly[9] and has been developed to target a number of cytokines known to have a role in inflammatory diseases.

SOC will be determined by YNHH SARS-CoV-2 Therapeutics Group and may include treatment targeting SARS-CoV-2 (e.g., anti-viral therapies). However, those enrolled in our study will not receive other forms of IL-6 blocking agents (e.g. tocilizumab, sarilumab, or other JAKi), if these are part of the SOC algorithm (Please see **Appendix 1** for current algorithm).

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study intervention refers to Tofacitinib 5 mg tablets.

All participants will receive pharmacologic thromboprophylaxis with LMWH and supportive care for COVID-19 pneumonia. It is acceptable for participants to also receive experimental therapies for COVID-19, with the exception of prohibited medications listed in the eligibility criteria and concomitant medications sections of the protocol.

### 6.1.2 Dosage, Administration, Schedule

**TREATMENT DESCRIPTION**

Tofacitinib or placebo will be administered. Tofacitinib will be administered in a dose of 10 mg PO BID until return to their clinical baseline (as defined by supplementary oxygen requirement), and then will continue to be administered at 5 mg PO BID for a total treatment duration of 14 days. Follow-up off tofacitinib will continue up to Day 90.

- Tofacitinib tablets will be sourced from Pfizer, Inc. Matching placebo tablets will be provided by Pfizer, Inc..
- Participants will swallow the study intervention whole and will not manipulate or chew the study intervention prior to swallowing. If the participant is unable to swallow the study intervention whole, tofacitinib 5 mg film-coated tablets will be disintegrated in water (in a syringe) and administered as a liquid suspension through a nasal-gastric (NG) tube or percutaneous endoscopic gastrostomy (PEG) tube. Dosing of the suspension should occur within 4 hours from the time of preparation, when stored at room temperature (15-25°C), or within 24 hours, when at refrigerated temperature (2-8°C). Dosing verification was completed by Pfizer which was demonstrated through in-use stability of the prepared

suspension, compatibility of the suspension with common materials of composition for NG and PEG tubes, and accuracy of the intended dose. Since tofacitinib meets the Biopharmaceutics Class System (BCS) criteria for high solubility designation and the 5 mg IR tablet has been demonstrated to be bioequivalent to 5 mL of the oral solution (1 mg/mL) (Study A3921354 conducted under IND 117,400), we expect that disintegration of the 5 mg tablet in the syringe will not adversely impact the bioperformance.

- Study intervention administration details will be recorded on the CRF.

| | |
|---|---|
| **Intervention Name** | Tofacitinib |
| **ARM Name** | Tofacitinib plus SoC therapy |
| **Type** | Drug |
| **Dose Formulation** | Tablet |
| **Unit Dose Strengths** | 5 mg |
| **Dosage Level** | 10 mg BID |
| **Route of Administration** | Oral or per nasogastric tube |
| **Use** | Experimental |
| **IMP or NIMP** | IMP |
| **Sourcing** | Provided by Pfizer |
| **Packaging and Labeling** | Study intervention will be provided in bottles with appropriate labeling. |
| **Current/Former Names or Aliases** | CP-690550, Xeljanz® |

**REQUIRED TREATMENT MODIFICATIONS**

The following dose adjustments need to be considered during the use of 10 mg BID in this patient population when the potential exists for differences in tofacitinib exposure due to DDI or changes in renal or hepatic function:

- When a concomitantly used drug is a strong CYP3A4 inhibitor, OR when a co-administered drug is both a moderate CYP3A4 inhibitor and a strong CYP2C19 inhibitor (eg, fluconazole), a 50% reduction in dose is recommended. Therefore, a 5 mg BID dose should be used to achieve a similar exposure as that of 10 mg BID in a patient not receiving co-administered metabolic inhibitor.

    - Antivirals such as lopinavir and ritonavir are examples of potent CYP3A4 inhibitors. Cobicistat, which is used to increase concentrations of antiviral drugs, is also a potent CYP3A4 inhibitor. Examples of other co-administered drugs requiring dose reduction are ketoconazole, itraconazole, clarithromycin, telithromycin, and fluconazole (**Appendix 2).**

        - Tofacitinib dose reduction is not needed when co-administered with the following medication: azithromycin, hydroxychloroquine, chloroquine, remdesivir, favipiravir, oseltamivir, and ribavirin.

- A 50% dose reduction is recommended in patients who are in moderate or severe renal impairment (including patients on hemodialysis) and those in moderate hepatic impairment. Therefore 5 mg BID should be used in these patients, which will be

changed to 5 mg PO QD upon return to their clinical baseline (as defined by supplementary oxygen requirement).

- Tofacitinib should not be used in patients with severe hepatic impairment (Participants with Child-Pugh class C are excluded).

- Tofacitinib use is not recommended in patients receiving a potent CYP3A4 inducer (eg, rifampin, St. John's wort) or if they had discontinued use of a potent CYP3A4 inducer less than 28 days or 5 half-lives prior to the first dose of tofacitinib.

**Required Tofacitinib Discontinuations:**

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention include the following.

- WBC count <1000 /mm3
- Lymphocyte counts <250 cells/mm3.
- Absolute neutrophil counts <500 cells/mm3.
- Hemoglobin less than 8 g/dL.
- ALT or AST ≥5 times the ULN.
- Anaphylaxis or other serious allergic reaction.
- Diagnosis of venous thromboembolism.
- Any serious infection, including secondary bacterial pneumonia, or other safety event for which the investigator determines that continued treatment with tofacitinib is not in the participant's best interest.
- If IL-6 targeting agent or other non-FDA approved, compassionate use or expanded access is considered as medically necessary (AS REVIEWED BY THE PI)
- Diagnosis of thrombosis including pulmonary embolism, deep venous thrombosis, and arterial thrombosis

### 6.1.3 Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual or other specified location.
4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.
5. Study interventions should be stored in their original containers.
6. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.
7. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual or other specified location. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP Manual.

### 6.1.4 Preparation and Dispensing

A qualified staff member (investigational drug service pharmacist) will dispense the study intervention, in quantities appropriate according to the schedule (6.4.1). A second staff member will verify the dispensing.

### 6.1.5 Method of Assignment/Randomization

The Investigational Drug Service at Yale Center for Clinical Investigation will conduct the randomization. Study will be double blinded.

### 6.1.6 Blinding and Procedures for Unblinding

This study is blinded. Study intervention and matching placebo tablets will be dispensed in appropriately marked, covered dosing cups to limit the treating physician's knowledge of the treatment.

The research pharmacist will dispense the investigational product and record only the randomization code in the CRF and record the number of tablets each patient will receive independent of group assignment. As such, the research pharmacist will be unblinded.

However, as only the randomization code will be recorded in the CRF, physicians and caregivers will continue to be blinded. Only trained investigators and site staff as recorded on the delegation of authority log will have access to the CRF.

### 6.1.7 Allocation to Study Intervention

This is a blinded study; potential bias will be reduced by the following steps: randomization provided to site. The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled. The site will record the study intervention assignment on the applicable CRF, if required.

Study intervention will be dispensed at the study visits summarized (6.4.1).

Returned study intervention must not be re-dispensed to the participants.

The study-specific IRT reference manual and IP manual will provide the contact information.

### 6.1.8 Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second qualified member of the study site staff.

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When compliance of less than 70% or more than 120% of the expected number of doses of study intervention is suspected, the reason for non-compliance with the dosing regimen should be documented in the dosing log of the participant's case report form, and should be reported as a protocol deviation and unless there is a protocol stipulated reason for non-compliance with the dosing regimen, this should be recorded as a dosing error.

### 6.1.9 Packaging/Labeling

Clinical supply tablets and placebo will be used.

### 6.1.10 Storage Conditions

Tablets will be stored at and dispensed by the YNHH inpatient pharmacy or Investigational Drug Service. The pharmacy may convert the active ingredient into a suspension form.

### 6.1.11 Concomitant therapy

All participants must receive pharmacologic thromboprophylaxis with LMWH and supportive care for COVID-19 pneumonia. It is acceptable for participants to also receive experimental therapies with the exception of prohibited medications listed in the eligibility criteria and concomitant medications sections of the protocol. To the extent possible, the following restrictions should be followed:

- Use of strong inhibitors of cytochrome P450 3A should be avoided to the extent possible. Judicious use of strong inhibitors of CYP3A4 or a moderate inhibitor of CYP3A4 that is also a strong inhibitor of CYP2C19 is permitted, if necessary, but the dose of tofacitinib should be reduced to 5 mg BID PO with careful monitoring for adverse effects (see Tofacitinib Dose Modifications).
- Concomitant use of tofacitinib with strong inducers of cytochrome P450 is not recommended, and tofacitinib should not be used if strong inducers have been

discontinued less than 28 days or 5 half-lives prior to the first tofacitinib dose (**Appendix 2**).
- Herbal supplementation should not be administered, as many interfere with the cytochrome P450 pathways.
- Other JAK inhibitors, biological DMARDS, or potent immunosuppressive agents, including IL-6 inhibitors (eg, tocilzumab) and IL-1 inhibitors (eg, anakinra) should not be administered during the study.
- All non-pharmacologic and nutritional supportive care measures, including nutritional supplementation and oxygenation support are permitted. All concomitant medications and nondrug treatments, with dose and frequency, should be recorded.
- Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP.

**Tofacitinib Dose Modifications:**

The following dose adjustments need to be considered during the use of 10 mg BID in this patient population when the potential exists for differences in tofacitinib exposure due to DDI or changes in renal or hepatic function:

- When a concomitantly used drug is a strong CYP3A4 inhibitor, OR when a co-administered drug is both a moderate CYP3A4 inhibitor and a strong CYP2C19 inhibitor (eg, fluconazole), a 50% reduction in dose is recommended. Therefore, a 5 mg BID dose should be used to achieve a similar exposure as that of 10 mg BID in a patient not receiving co-administered metabolic inhibitor.

    - Antivirals such as lopinavir and ritonavir are examples of potent CYP3A4 inhibitors. Cobicistat, which is used to increase concentrations of antiviral drugs, is also a potent CYP3A4 inhibitor. Examples of other co-administered drugs requiring dose reduction are ketoconazole, itraconazole, clarithromycin, telithromycin, and fluconazole (**Appendix 2**).

        - Tofacitinib dose reduction is not needed when co-administered with the following medication: azithromycin, hydroxychloroquine, chloroquine, remdesivir, favipiravir, oseltamivir, and ribavirin.

- A 50% dose reduction is recommended in patients who are in moderate or severe renal impairment (including patients on hemodialysis) and those in moderate hepatic impairment. Therefore 5 mg BID should be used in these patients which will be changed to 5 mg PO QD upon return to their clinical baseline (as defined by supplementary oxygen requirement).

- Tofacitinib should not be used in patients with severe hepatic impairment (Participants with Child-Pugh class C are excluded).

- Tofacitinib use is not recommended in patients receiving a potent CYP3A4 inducer (eg, rifampin, St. John's wort) or if they had discontinued use of a potent CYP3A4 inducer less than 28 days or 5 half-lives prior to the first dose of tofacitinib.

### 6.1.12 Restrictions

None

## 6.2 Assessments

### 6.2.1 Efficacy

The primary and secondary endpoints will be assessed during the course of the study for each subject enrolled. These are outlined separately. Data will be gathered through daily review of the medical records, including vital signs, ventilatory requirements, laboratory values, and additional clinical findings.

### 6.2.2 Safety and Pregnancy-related policy

Urine pregnancy testing for women of childbearing potential will be performed. Women who are pregnant or breast feeding will be excluded.

### 6.2.3 Adverse Events Definition and Reporting

**Definitions**

Adverse event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

Any new infection that occurs on study, regardless of the infecting agent (i.e. viral or non-viral) will be captured as an adverse event. Data captured will include site of infection and source of culture (BAL, tracheal aspirate, sputum, blood, urine etc.)

An AE or suspected adverse reaction is considered "serious" (SAE) if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- a congenital anomaly/birth defect, or
- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

**Severity**

Adverse events will be graded according to [name grading scale, e.g. CTCAE v5.0]. For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

**Relationship to Investigational Product**

All AEs must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Potentially Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Not Related – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

**Expectedness**

The Principal Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

**Reporting**

For studies conducted under an IND, there are two types of Safety Reports submitted to FDA:

- 7-Calendar-Day FDA Telephone or Fax Report: The sponsor-investigator will directly notify the FDA, within 7 calendar days after initial receipt of the information, of any adverse event that is fatal or life-threatening, unexpected, and considered at least possibly related to the investigational product.
- 15-Calendar-Day FDA Written Report: The sponsor-investigator will directly notify the FDA within 15 calendar days after initial receipt of the information, of any serious adverse event (other than those that are fatal or life-threatening) that is unexpected and considered at least possibly related to the investigational product.

Serious Adverse Events which do not meet the criteria for expedited reporting will be reported to the FDA in the IND Annual Report.

### 6.2.4 Biomarkers

Research samples (3 mL of blood for exploratory analysis (including cytokine analysis), 10 mL blood to generate plasma (for analysis of SARS-CoV-2 viral load) and 2.5 mL blood in Paxgene tubes (optimized for analysis of gene expression (RNA), and saliva samples (5mL) and/or nasopharyngeal swab for viral titer will be obtained as a part of this clinical trial to better understand SARS-CoV-2 pathogenesis and responses to tofacitinib compared to SOC. Whole blood (10 mL) may also be collected as available for lymphocyte subset analysis by flow cytometry. Sample collection times are specified in the Schedule of Activities. All research blood samples may be banked and/or used for exploratory analysis related to COVID-19 and/or the mechanism of action of the treatments administered in this study. Detailed sample collection and processing instructions will be provided under separate cover. Changes in research-based parameters will be documented.

The results will not be relayed to the subject or the subject's physician because they are for research purposes and the results may not be known for weeks after hospitalization. No results will be entered into the subject's medical record.

## 6.3 Study Procedures

### 6.3.1 Study Schedule

| **Visit Identifier**[Error! Reference source not found.] | **Screening** | **Day 1** | **Daily assessments (days 2-14)**[c,d] | **Early Termination/ Discontinuation/ End of Treatment (Day 14 or Discharge)** | **Follow-up**[Error! Reference source not found.] **(Day 28)** | **Follow-up (Day 60)** | **Follow up (Day 90)** | **Early Termination/ Discontinuation** |
|---|---|---|---|---|---|---|---|---|
| **Visit Window** | **48 hours prior to Day 1** | | | | **+/-3 days** | | | |
| Informed consent | X | | | | | | | |
| Medical history | X | | | | | | | |
| Physical examination[d] | X | X | X | X | X | | | |
| Weight[d] | X | | | | | | | |
| Vital signs[d] (pulse, blood pressure, respiratory rate[e], temperature[f]) | X | X | X | X | X | | | |
| Laboratory[d] | | | | | | | | |
| Hematology | X | X | X | X | X | | | |
| Blood chemistry | X | X | X | X | X | | | |
| Coagulation[g] | X | X | X | X | X | | | |
| Inflammation panel[h] | X | X | X | X | X | | | |
| Cardiac panel[i] | X | X | X | X | X | | | |
| Pregnancy test | X | | | | X | | | |
| Oxygen saturation by pulse oximetry ($SaO_2$)[d] | X | X | X | X | X | | | |
| 12 Lead ECG[d] | X | X | X | X | X | | | |
| Record if admitted to intensive care unit (ICU) | X | X | X | X | X | | | X |
| Registration/randomization | | X | | | | | | |
| Study drug administration | | X | X | X | | | | |
| NIAIA Ordinal scale of disease severity | X | X | X | X | X | X | X | X |

| **Visit Identifier**[Error! Reference source not found.] | **Screening** | **Day 1** | **Daily assessments (days 2-14)**[c,d] | **Early Termination/ Discontinuation/ End of Treatment (Day 14 or Discharge)** | **Follow-up**[Error! Reference source not found.] **(Day 28)** | **Follow-up (Day 60)** | **Follow up (Day 90)** | **Early Termination/ Discontinuation** |
|---|---|---|---|---|---|---|---|---|
| **Visit Window** | **48 hours prior to Day 1** | | | | **+/-3 days** | | | |
| Record hospitalization status | X | X | X | X | X | X | X | X |
| Assessment signs and symptoms of pneumonia | | X | | X | X | X | X | |
| FiO2 | X | X | X | X | | | | |
| supplemental oxygen | X | X | X | X | | | | |
| Blood for exploratory analysis[j] | | X | Day 7 | X | X | | | |
| Paxgene sample for exploratory biomarker analysis[k] | | X | Day 7 | X | | | | |
| Plasma, Saliva and/or nasal swab for SARS-CoV-2 and exploratory analysis[m] | | X | Day 7 | X | | | | |
| Whole blood for FACS analysis[n] | | X | Day 7 | X | X | | | |
| Concomitant treatment(s) | | X | X | X | X | | | X |
| Adverse event monitoring | X | X | X | X | X | X | X | X□ |

| Visit Identifier[Error! Reference source not found.] | Screening | Day 1 | Daily assessments (days 2-14)[c,d] | Early Termination/ Discontinuation/ End of Treatment (Day 14 or Discharge) | Follow-up[Error! Reference source not found.] (Day 28) | Follow-up (Day 60) | Follow up (Day 90) | Early Termination/ Discontinuation |
|---|---|---|---|---|---|---|---|---|
| **Visit Window** | **48 hours prior to Day 1** | | | | **+/-3 days** | | | |

a. Day relative to start of study intervention (Day 1).

b. Contact may occur via telephone contact and will occur up to 90 days from administration of the final dose of study intervention. Procedures listed for Follow-up Visit 1 (with exception of ordinal scale of disease severity, hospitalization status, supplemental oxygen/ventilatory support status, contraception check, concomitant medications, and AE/SAE monitoring) will only be performed if the participant is hospitalized. Otherwise these visits will be remote phone or telemedicine visits.

c. Assessments will be performed at least daily while hospitalized by the clinical service. Vital signs may be more frequent (eg, every 4 – 8 hours), per hospital practice.

d. Collected as per hospital standard of care practice

e. Note if spontaneous or mechanical ventilator setting

f. Note if oral, rectal, or core

g. Will include PT/PTT, fibrinogen, D-Dimers

h. Inflammation will include as available: hsCRP, ferritin, procalcitonin, fibrinogen, LDH, etc.

i. Cardiac panel will include as available: high sensitivity troponin, BNP, etc.

j. Cytokine panel will include, as available: IL-1, IL-2, IL-6, IL-8, IL-17A, IL-17F, TNF-α, IP-10, IFNγ, CCL5, etc. Sample will be used for cytokine assessment that may include but is not limited to IFNγ, IL-1β, IL-4, IL-6, IL-10, IL-12p70, TNFa, IP-10, and IL-2R. This sample may also be banked and/or used for additional post-hoc analyses related to COVID-19 and/or the mechanism of action of treatments administered in this study, including IgG and IgM antibodies to COVID-19.

k. Paxgene sample (optimized for RNA analysis) may be banked and/or used for exploratory assessments related to COVID-19 and/or the mechanism of action of treatments administered in this study.

l. Physical examination by a clinician will be individualized according to participant status

m. Plasma, saliva and/or nasal swab will be collected and tested for SAR-CoV2 should by performed by polymerase chain reaction (PCR), or other commercial or public health assay in any specimen prior to randomization and on an ongoing basis, as needed for patient care and per policy at YNHH. Samples may also be used for additional analyses related to COVID-19 and/or the mechanism of action of treatments administered in this study.

n. Whole blood sample may be collected as available for analysis of lymphocyte subsets by flow cytometry.

### 6.3.2 Informed Consent

Potential subjects will be identified by study coordinators in conjunction with treating clinicians by screening the EMR of patients with a clinical diagnosis of SARS-CoV-2. Patients whose providers feel they are appropriate for the study will be approached. The PI or study coordinator will first approach the patient's treating clinician (ex: physician, nurse practitioner, or physician's assistant) regarding possible involvement in the study. If the provider feels the patient is appropriate, they will ask if the patient would be interested in hearing about a research project they might be able to participate in. If the patient expresses interest, the PI or study coordinator will then discuss with the patient.

The patient or legally authorized representative/surrogate will be offered participation in the study during their hospitalization. Proper written, informed consent and HIPAA authorization will be obtained prior to patient participation in this trial. Patients will be provided with an unsigned consent form by a health care worker who has entered their room, and notified that a member of the study team will discuss the protocol with them over phone/video call. The overall protocol (including objectives, procedures and duration), potential risks and benefits, voluntary nature and ability to withdraw will be

discussed with each patient and/or their legally authorized representative/surrogate. The patient and/or their legally authorized representative/surrogate will have all questions answered before being asked to sign the ICF. Verification of comprehension of the consent will be obtained by asking the subject to describe in their words the purpose and risks of the study. The patient and/or their legally authorized representative/surrogate will be instructed that his or her care will not be affected by his or her decision to participate, or not. If the patient and/or their legally authorized representative/surrogate voluntarily agrees to participate in the trial, he or she will be asked to sign the ICF. The subject and/or their legally authorized representative will keep the copy of the ICF and HIPAA authorization form signed by them. Due to contamination of the document by infectious material, a photograph of the informed consent document with attestation by the person entering the photograph into the study record that states how that photograph was obtained and that it is a photograph of the informed consent signed by the patient will be added to the patient's study records as documentation that the patient signed the informed consent document (in accordance with FDA-2020-D-1106).

### 6.3.3 Screening

The screening visit will include the following assessments:

- Informed consent
- Medical history: includes collecting the following information: age, sex, race, medical comorbidities, medications, smoking and alcohol history, and family history
- Vital signs, weight, and pulse oximetry
- Targeted physical exam including an assessment of lungs, heart, circulation/perfusion
- Chest X-ray (CXR)
- Electrocardiogram (ECG)
- Blood and urine laboratory tests including lactate dehydrogenase (LDH), complete blood count with differential (CBC), comprehensive metabolic panel (CMP), cytokine panel, cardiac panel, coagulation, inflammation panel, viral serologies (including SARS-CoV-2), tuberculosis testing, and urinalysis
- Urine pregnancy testing and contraception check for women of childbearing potential

### 6.3.4 Enrollment

After Screening, if the subject meets criteria, they will be enrolled. Baseline labs including hsCRP, ferritin, LDH, D-dimer, CBC, and CMP will be measured twice daily (per SOC). Research blood samples will be obtained prior to drug administration on Day 1 and then again on Day 2 and every 48 hours thereafter. All subjects will be randomized to either tofacitinib 10 mg twice daily or SOC. Patients will be monitored at least once daily after initiation of therapy during the duration of their hospitalization, and will be followed up after discharge.

### 6.3.5 On Study Visits

**Days 1-14:**

Once eligibility is confirmed, patients will be randomly assigned to receive treatment with either tofacitinib or placebo. Patients will receive 10 mg tofacitinib orally twice daily starting at the time of study enrollment until they exhibit clinical improvement, as

defined by need for supplemental oxygen to the baseline level. After this, patients will receive 5 mg tofacitinib orally twice daily. Total tofacitinib treatment duration will not exceed 14 days. All dosing of study drug will be in addition to current standard of care treatment. Research blood samples will be obtained prior to drug administration and again every 48 hours. Patients may undergo additional viral testing with a repeat nasal swab and/or blood collection at 7 and 14 days after enrollment. Standard of care laboratory tests will be measured twice daily. Patients will be assessed daily while hospitalized for the following clinical, research, and laboratory parameters:

- Targeted physical exam
- Electrocardiogram (ECG)
- Blood and urine laboratory tests including lactate dehydrogenase (LDH), complete blood count with differential (CBC), comprehensive metabolic panel (CMP), cytokine panel, cardiac panel, coagulation, inflammation panel, and urinalysis
- Adverse events
- Concomitant therapies
- Record of ICU admission
- Record use of supplemental oxygen

### 6.3.6 End of Study and Follow-up

After patients complete study treatment, they will be contacted to follow up on their condition. This may occur via telephone or telehealth and will occur on day 28 +/- 3 days after the time of enrollment and then again at days 60 and 90 days. On day 28 follow-up, blood sample for exploratory analysis may be collected. At the time of follow up visits/calls, patients will be asked about:

- Adverse events
- Concomitant therapies
- All efforts will be made to contact subjects for follow-up, including: telephone calls, texts, and emails to the subject and/or close contacts. Vital status of all subjects will be ascertained either by contacting the subjects and/or subjects' close contacts or by a vital records search.

### 6.3.7 Removal of subjects

**Required Tofacitinib Discontinuations:**

- White blood cell count < 1000 cells/mm3
- Lymphocyte counts <250 cells/mm3.
- Absolute neutrophil counts <500 cells/mm3.
- Hemoglobin less than 8 g/dL.
- ALT or AST ≥5 times the ULN.
- Anaphylaxis or other serious allergic reaction.
- Diagnosis of thrombosis including pulmonary embolism, deep venous thrombosis, and arterial thrombosis.
- Diagnosis of venous thromboembolism.
- Any serious infection, including secondary bacterial pneumonia, or other safety event for which the investigator determines that continued treatment with tofacitinib is not in the participant's best interest.

- If IL-6 targeting agent or other non-FDA approved, compassionate use or expanded access is considered as medically necessary (as reviewed by the investigator)

Subjects who discontinue study treatment will be followed up through Day 90 after discontinuation.

## 6.4 Statistical Method

### 6.4.1 Statistical Design

### 6.4.2 Sample Size Considerations

Assume true probability of a participant survived and not needing any form of mechanical ventilation, high flow oxygen, or ECMO at day 14 is 40%. Randomizing 60 participants with a 1:1 ratio (tofacitinib+SOC: Placebo+SOC), the study will have 73% power (two-sided alpha=0.1) assuming an odds ratio of 3.5 for tofacitinib+SOC VS Placebo+SOC. No multiplicity adjustments will be performed for any secondary endpoint or exploratory endpoint analyses.

## 6.5 Planned Analyses

There will be two analyses for reporting results from this study. The first will occur when all patients have completed the requirements for the day 14 efficacy endpoints, including the primary endpoint. This will be the primary analysis for these endpoints. The second will be after all participants have completed the 90 day follow-up where mortality and final safety will be reported.

The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

### 6.5.1 Primary Objective Analysis

Proportion of subjects alive, not needing any form of mechanical ventilation, high flow oxygen, or ECMO, and haven't received a recue therapy at day 14, will be summarized by treatment arm. Treatment comparisons will be based on a logistic regression model. Odds ratio with 90% confidence interval will be presented.

Full Analysis Set (FAS) is defined as all randomized participants receiving at least one dose of study intervention. Participants will be analyzed according to the intervention to which they were randomized. Efficacy analysis will be based on FAS.

For all primary analyses, data will be censored after subject received rescue therapy. Rescue therapy is defined as IL-6 targeting agent or other non-FDA approved, compassionate use or expanded access is considered as medically necessary (AS REVIEWED BY THE PI) (section 6.1.2). Per protocol, subjects will discontinue from study treatment prior to taking rescue therapy. Additional secondary analyses may be conducted including all the data after rescue therapy.

### 6.5.2 Secondary Objectives Analyses

For the ordinal scale of disease severity, the proportion of patients in each category will be summarized by treatment group. A proportional odds model will be fit to compare tofacitinib

plus SOC versus placebo plus SOC. The odds ratio will be estimated along with its 90% confidence interval.

Endpoints such as time to recovery and time to improvement will be summarized with Kaplan Meier estimation and compared used log-rank tests. Cox proportional hazard model will be used to estimate hazard ratios.

For the binary outcomes, such as mortality rate at days 30, 60, and patients requiring ICU admission and mechanical ventilatory support, the analysis methods will be the same as for the primary endpoint.

For endpoints such as duration of invasive mechanical ventilation, invasive mechanical ventilation free days, death is a competing event, i.e if a patient dies before invasive mechanical ventilation, the duration of ventilation is unknown. This will be analyzed using competing risk model proposed by Andersen and Gill (1982). Generalized cox model will be used to estimate the hazard ratio for the treatment effect.

### 6.5.3 Exploratory Objectives Analyses (if applicable)

Not applicable.

### 6.5.4 Safety

Included as secondary objective.

All safety analyses will be performed on the Safety Analysis Set. All safety data will be summarized descriptively through appropriate data tabulations, descriptive statistics, categorical summaries, and graphical presentations.

Change from baseline in inflammatory parameters or cytokines will be summarized by descriptive statistics (N, mean, standard error of the mean, minimum, 1st, 2nd (ie, median) and 3rd quartiles and maximum).

Safety Analysis Set (SAF) is defined as all participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received. All safety analysis will be based on SAF.

### 6.5.5 Analysis of Subject Characteristics

Demographics and medical history will be summarized by treatment group.

### 6.5.6 Interim Analysis (if applicable)

Safety data will be reviewed by a Yale DSMB after the first 5 patients are enrolled and again after every 10 patients enrolled thereafter.

### 6.5.7 Health economic evaluation

Not applicable

### 6.5.8 Other

Not applicable

### 6.5.9 Subsets and Covariates

Summary statistics for the primary endpoint may be performed by subgroups below.

- Age (years) group ((<40, ≥40);
- Sex (Male, Female);
- Race (White, Black or African American, Other);

### 6.5.10 Handling of Missing Data

For efficacy endpoints,

- Patients will be followed up after discharge via telehealth visits or other approaches. If a subject discontinues from study treatment early but did not withdraw consent, the schedule of activities will remain the same and data collection will continue. Due to the nature of the study, we expect that there will not be many missing data. Thus, the missing values for binary endpoints due to discharge or where no other information is available will be considered as treatment successes.

- Time to event endpoint: subjects who complete the study without the event of interest or those who withdraw before experiencing the event of interest will have their event times right censored at the last available measurement time (or visit) used to define whether the subject experienced the associated event.

- Ordinal endpoints: observed data will be analyzed.

For safety endpoints, observed data will be analyzed.

# 7 Trial Administration

### 7.1 Ethical Considerations: Informed Consent/Assent and HIPAA Authorization

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. All patients who are eligible to participate in this study will give informed consent prior to undergoing any study procedures.

### 7.2 Institutional Review Board (IRB) Review

The protocol, ICF, and supporting documents will be submitted to the IRB for review and approval. Approval of the protocol will be obtained before initiating any research activity. Any change to the protocol or study team will require an approved IRB amendment before implementation. The IRB will determine whether informed consent and HIPAA authorization are required.

The IRB will conduct continuing review at intervals appropriate to the degree of risk, but not less than once per year.

A study closure report will be submitted to the IRB after all research activities have been completed.

Other study events (e.g. data breaches, protocol deviations) will be submitted per Yale University IRB's policies.

### 7.3 Subject Confidentiality

Subject confidentiality is held in strict trust by the research team. Subject medical record review will be limited to the just the elements needed to complete the study. Only authorized HIPAA and GCP trained study team members will be allowed to extract research data from medical records and enter it into the study's electronic database. No direct subject identifiers will be entered into this database.

Each subject will be assigned a unique study number. A master list linking the unique study number to the human subject will be maintained in a secured spreadsheet only accessible to authorized study team members.

### 7.4 Deviations/Unanticipated Problems

If the study team becomes aware of a problem (e.g. data breach, protocol deviation) that potentially affects subject safety or data integrity, the event will be reported to the IRB.

### 7.5 Data Collection

Research data will be collected from patients' clinical record (paper charts and EMR, blood and urine samples and cardiac pressure monitoring data collected during the study). Data will be recorded in electronic databases (Forte & Oncore), and stored in password-protected software on Yale's secure server.

### 7.6 Data Quality Assurance

Data collection and study documentation will be limited to the site study staff, ensuring consistency in data collection procedures. Yale's core laboratory will be used exclusively for laboratory assessments involved in safety and efficacy analyses.

### 7.7 Study Records

Study-specific documents including regulatory documents, protocols, consents forms, and case report forms will be stored in paper charts which will be kept in a locked office on site, only accessible to site study staff.

### 7.8 Access to Source Documents

Source documents will consist mostly of EMR entries but may also include paper case report forms if study-pertinent information cannot be found in EMR. Only the study team will have access to both electronic and paper source documents.

### 7.9 Data or Specimen Storage/Security

Data will be de-identified, as described above, both during and after the study. The electronic data will be stored and secured on Yale computers containing encryption software. Paper study records will be kept in a locked office on site, only accessible to site study staff.

### 7.10 Retention of Records

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

### 7.11 Study Monitoring

### 7.12 Data Safety Monitoring Plan

A data safety monitoring board will be formed, comprised of clinicians at the site who are not named investigators in the study, to ensure intensive safety monitoring.

The DSMB will be responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency. During the review process, the DSMB will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. Either the principal investigator, DSMB, or the IRB have the authority to stop or suspend the study or require modifications.

We do not view the risks associated with tofacitinib as minimal. Although we have assessed the proposed study as one of greater than minimal risk, the potential exists for anticipated and/or unanticipated adverse events, serious or otherwise, to occur since it is not possible to predict with certainty the absolute risk in any given individual or in advance of first-hand experience with the proposed study methods. Therefore, we will monitor the data and safety of the proposed study.

**Attribution of Adverse Events:**

Adverse events will be monitored for each subject participating in the study and attributed to the study procedures by the principal investigator Dr. Hyung Chun according to the following categories:

a.) Definite: Adverse event is clearly related to investigational agent.

b.) Probable: Adverse event is likely related to investigational agent.

c.) Possible: Adverse event may be related to investigational agent.

d.) Unlikely: Adverse event is likely not to be related to the investigational agent.

e.) Unrelated: Adverse event is clearly not related to investigational agent.

**Plan for Grading Adverse Events:**

The following scale will be used in grading the severity of adverse events noted during the study:

1. Mild adverse event

2. Moderate adverse event

3. Severe

**Serious Adverse Events:**

In addition to grading the adverse event, the PI will determine whether the adverse event meets the criteria for a Serious Adverse Event (SAE). An adverse event is considered serious if it:

1. is life-threatening OR

2. results in in-patient hospitalization or prolongation of existing hospitalization OR

3. results in persistent or significant disability or incapacity OR

4. results in a congenital anomaly or birth defect OR

5. results in death OR

6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition, OR

7. adversely affects the risk/benefit ratio of the study

An adverse event may be graded as severe but still not meet the criteria for a Serious Adverse Event. Similarly, an adverse event may be graded as moderate but still meet the criteria for an SAE. It is important for the PI to consider the grade of the event as well as its "seriousness" when determining whether reporting to the IRB is necessary.

**Plan for reporting Reportable Adverse Events and other unanticipated problems involving risks to subjects or others to the IRB:**

The principal investigator will report the following types of events to the IRB: a) adverse events that are serious or life-threatening AND unanticipated (or anticipated but occurring with a greater frequency than expected) AND possibly, probably or definitely related to the drug; and b) other unanticipated problems involving risks to subjects or others. These adverse events or unanticipated problems involving risks to subjects or others will be reported to the IRB in accordance with IRB Policy 710, using the appropriate forms found on the website.

The principal investigator will conduct a review of all adverse events upon completion of every study subject. The principal investigator will evaluate the frequency and severity of the adverse events and determine if modifications to the protocol or consent form are required.

### 7.13 Study Modification

If the protocol, ICF, or any supporting document needs to be amended, modifications will be submitted to the IRB and FDA as needed, prior to implementing changes (unless changes pertain to the safety of participants, in which case a deviation would be reported).

### 7.14 Study Discontinuation

If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

### 7.15 Study Completion

The IRB and FDA will be notified upon completion of this study.

### 7.16 Conflict of Interest Policy

Yale policies require investigators engaged in human subjects research to disclose annually. The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the appropriate conflict of interest review committee has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest. All investigators will follow the applicable conflict of interest policies.

### 7.17 Funding Source

The study will be funded by Pfizer.

### 7.18 Publication Plan

Results of the study will be published by the investigators.

# 8 Appendices

**Appendix 1. Current YNHH COVID-19 treatment algorithm (please see attached)**



APPROVED BY THE YALE UNIVERSITY IRB 9/28/2020

**Appendix 2. Table of Potent Inhibitors of CYP3A4, Moderate Inhibitors of CYP3A4 and Potent Inhibitors of CYP2C19, and Potent CYP Inducers***

| | **Potent Inhibitors CYP3A4** | **Moderate Inhibitors of CYP3A4 and Potent Inhibitors of CYP2C19** | **Potent CYP Inducers** |
|---|---|---|---|
| **Antibiotics** | Clarithromycin<br>Telithromycin | | Rifampin |
| **Anticonvulsant** | | Phenytoin | Barbiturates<br>Fosphenytoin<br>Phenobarbital<br>Primidone<br>Carbamazepine |
| **Antidepressants** | Nefazodone | Fluvoxamine | St. John's Wort |
| **Antifungals** | Itraconazole<br>Ketoconazole | Fluconazole | |
| **Antihyperglycemic** | | | Troglitazone (withdrawn in US) |
| **Narcotic** | Suboxone | | |
| **Protease Inhibitors** | Atazanavir<br>Darunavir<br>Indinavir<br>Lopinavir<br>Nelfinavir<br>Ritonavir<br>Saquinavir<br>Tipranavir<br>Cobicistat | | |
| **Stimulants** | | | Modafinil |

*This is not a complete list of all CYP inhibitors and inducers with potential DDI with tofacitinib.

## Appendix 3. Contraceptive Considerations

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100 fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

**Female Participant Reproductive Inclusion Criteria**

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

OR

- WOCBP should consider pregnancy planning and prevention during the treatment period and for up to 28 days after the last dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:
- Documented hysterectomy;
- Documented bilateral salpingectomy;
- Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female:
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a:
- High FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
- Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

**Contraception Methods**

Contraceptive use by women should be consistent with local availability/regulations regarding the use of contraception.

## Appendix 4. Tofacitinib 10 mg BID, Relative to 5 mg BID, in COVID-19

### *COVID-19 and hyperinflammation*

Coronavirus disease – 2019 (COVID-19) is a viral disease caused by a novel coronavirus, SARS-CoV-2 that can cause a severe acute respiratory syndrome (ARDS). While several types of cytokine storm syndromes are recognized (Behrens 2017), a cytokine profile resembling secondary haemophagocytic lymphohistiocytosis is associated with COVID-19 disease severity. Predictors of fatality from a recent retrospective, multicenter study of 150 confirmed COVID-19 cases in Wuhan, China, included elevated ferritin and IL-6, suggesting that mortality might be due to virally driven hyperinflammation (Ruan 2020). The management of the cytokine storm is one of the major unmet medical needs in the treatment of COVID-19.

### *Efficacy of tofacitinib 10 mg BID, relative to 5 mg BID, on inflammatory response*

Tofacitinib has not been evaluated previously for short-term treatment of airway inflammatory response related to COVID-19 or other diseases. In COVID-19 patients with pneumonitis who are at risk for progression to ARDS, rapid onset of anti-inflammatory effects, followed by sustained inhibition of inflammatory mediators over the dosing period is desirable.

Therefore, potential benefits of tofacitinib were assessed based on expected modulation of inflammatory mediators in COVID-19 patients, based on *in vitro* studies and *in vivo* characterization of anti-inflammatory effects in RA patients. These data indicate:

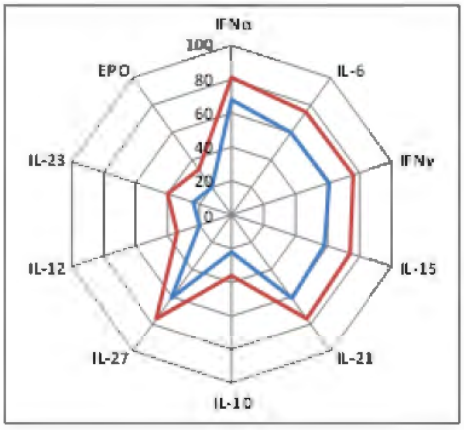
(1) Based on *in vitro* IC50 values for suppression of inflammatory mediators, the higher systemic exposure of tofacitinib at 10 mg BID, compared to 5 mg BID, is expected to result in greater suppression of inflammatory mediators *in vivo*.

(2) Dose-response of tofacitinib on markers of systemic inflammation *in vivo* in RA patients (IP-10, CRP) indicates that 10 mg BID provides substantially higher suppression of these inflammatory markers, and may also provide a faster onset of effect, compared to 5 mg BID.

*(1) In vitro studies*

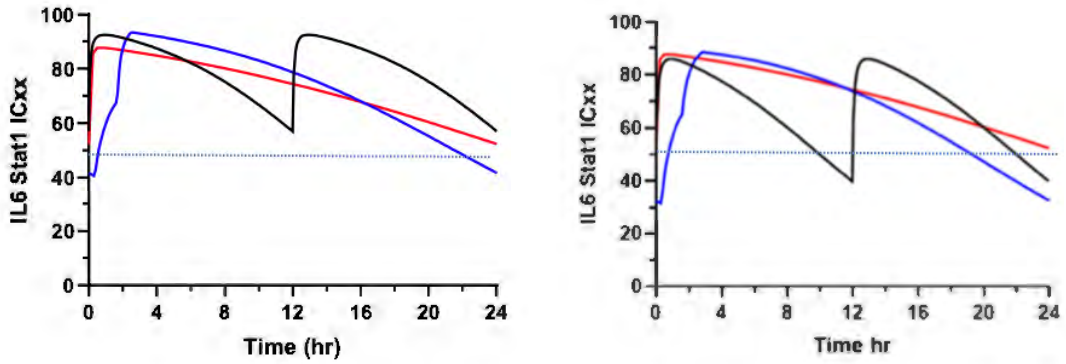
Potency of tofacitinib binding to JAK subtypes and cytokine inhibition were determined in vitro in cell based and whole blood assays (Dowty et al 2019). The expected percent inhibition of various cytokines in humans, at the average plasma tofacitinib concentrations expected at the 5 mg and 10 mg BID dose levels, are shown in the spider plot in Figure 1. At the 10 mg BID dose, approximately 80% suppression of IL-6 may be expected, in addition to substantial inhibition of multiple other cytokines such as IFNγ, IL-15, IL-21, and IL-27. The expected magnitude of cytokine suppression is lower at the 5 mg BID dose, with approximately 60% predicted suppression of IL-6.

**Figure 1. Predicted percent inhibition of cytokines in humans by tofacitinib 5 mg BID (blue line) and 10 mg BID (red line) based on in vitro whole blood potency assay and predicted average plasma tofacitinib concentrations**




The time course of predicted IL-6 inhibition over a steady-state dosing interval is shown in Figure 2 for tofacitinib IR 10 mg BID, the equivalent MR dose of 22 mg QD, and baricitinib 4 mg QD. The y-axis (ICxx) represents the inhibitory concentration (IC) for a given % inhibition of IL-6 activity as shown on the axis. Tofacitinib IR 10 mg BID is expected to provide concentrations above the IC50 value throughout the dosing interval and up to IC85 at peak concentration, indicating sustained pharmacologic activity. Tofacitinib IR 5 mg BID is not expected to provide sustained exposure above the IC50 of IL-6 inhibition over a 24-hour period, as shown in Figure 3.

**Figure 2. Inhibitory tofacitinib concentration for a given % inhibition of IL-6 activity (ICxx) over a steady-state dosing interval. *Left Panel*: tofacitinib IR 10 mg BID (black line), tofacitinib MR 22 mg QD (blue line), and baricitinib 4 mg QD (red line); *Right Panel*: tofacitinib IR 5 mg BID (black line), tofacitinib MR 11 mg QD (blue line), and baricitinib 4 mg QD (red line). The light blue horizontal line represents the IC50 value.**



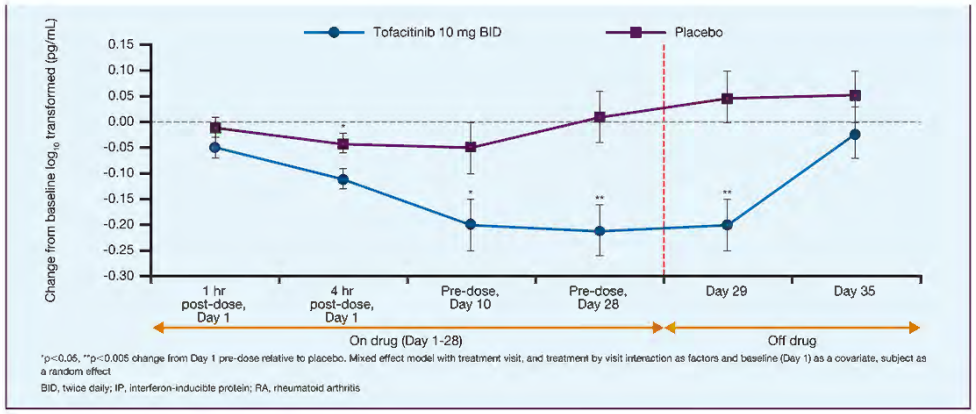

*(2) Clinical studies*

Biomarkers in the JAK signaling pathway, such as interferon gamma-induced protein 10 (IP-10) and CRP, were measured in multiple clinical studies in RA patients treated with

tofacitinib. Both these markers are known to be elevated in COVID-19 patients with inflammatory response.

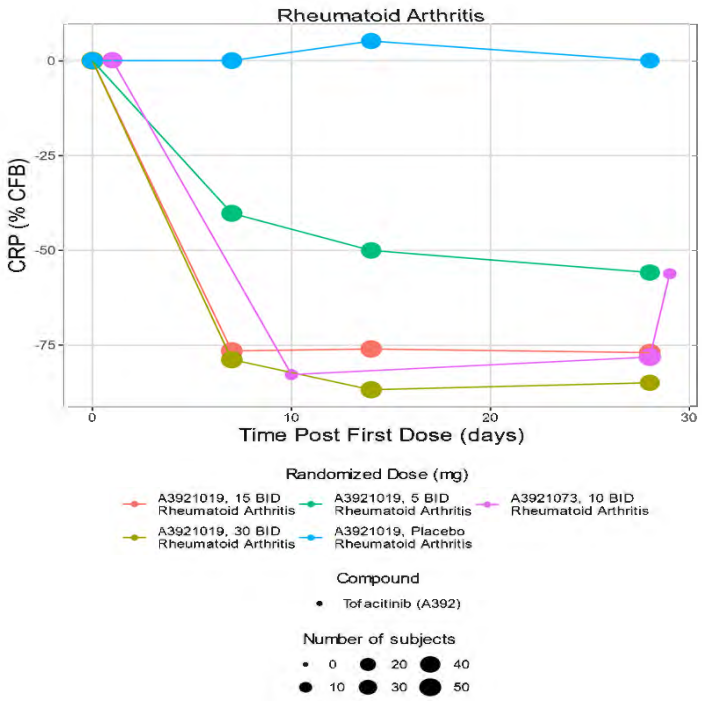
In Study A3921073 in RA patients, serial IP-10 and CRP measurements were performed early after initiation of treatment and following the end of the treatment phase, to characterize onset and offset of pharmacologic activity of tofacitinib. The effect of 10 mg BID tofacitinib treatment, relative to placebo, on IP-10 concentration is shown in Figure 3. Onset of pharmacologic activity within the 4 hours after the first dose is suggested by the significant difference from placebo at this time point. This indicates that 10 mg BID may be beneficial in terms of rapid onset of effect.

**Figure 3. IP-10 Serum Levels in RA Patients Receiving Tofacitinib 10 mg BID (A3921073)**




In clinical studies in RA patients, CRP suppression was generally higher at 10 mg BID, compared to 5 mg BID. In Study A3921019, median CRP (% of baseline) was suppressed in a dose-dependent manner, with approximately 50% suppression at 5 mg BID by Day 14, and >75% suppression at higher doses. In Study A3921073, >75% median CRP suppression was observed by Day 10 following tofacitinib 10 mg BID dosing (Figure 4).

**Figure 4. Median CRP (% change from baseline) in Studies A3921019 and A3921073 in RA patients**




***Short-term safety of tofacitinib 10 mg BID, relative to 5 mg BID***

In the context of understanding benefit-risk, there are known risks that need to be considered for JAK inhibitors, both as a class and for selective JAK subtypes. The contribution of secondary bacterial infection to COVID-19 related mortality is unknown, and immunomodulation with biologic or targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs) may increase the risk of secondary infections in COVID-19 patients. JAK inhibitors are also known to increase the risk of thromboembolism, therefore use of tofacitinib in this population should be managed in the context of the higher background risk of thromboembolism in COVID-19 disease.

Therefore, thrombosis risk of tofacitinib was assessed in the context of short-term treatment in COVID-19 patients, based on large clinical studies in RA and UC patients. These data indicate:

(1) Short-term exposure to tofacitinib 10 mg BID has not been associated with an increased risk of thrombosis (either arterial or venous) when compared to 5 mg BID.

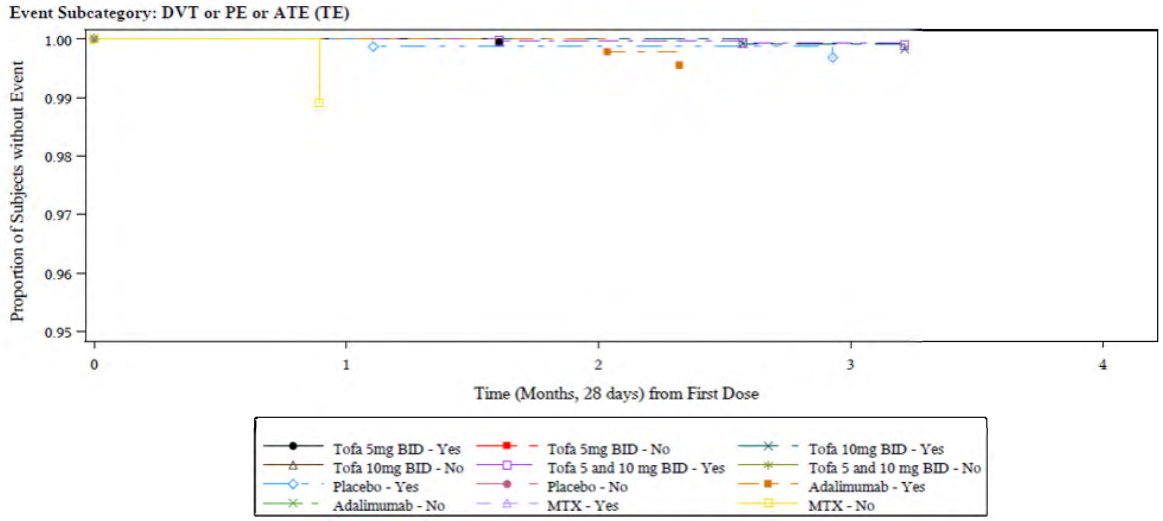
(2) In pooled RA month 0-3 data, there were no events reported among tofacitinib 5 mg BID or 10 mg BID treated patients who did not have baseline VTE risk factors such as previous VTE, previous heart failure, or age ≥60 years.

(2) No thrombosis events were reported for 10 mg BID patients during the first 14 days of treatment and time to first reported thrombotic event was 72 days and 216 days in RA and UC patients, respectively, treated with 10 mg BID.

*Venous or arterial thrombosis*

Short-term exposure to tofacitinib 10 mg BID has not been associated with an increased risk of thrombosis (either arterial or venous) when compared to 5 mg BID (Pfizer Data on File, Sandborn et al 2019). In pooled data from tofacitinib Phase 2 and Phase 3 RA studies, 3 thrombotic events were reported during month 0-3, all events occurring at day 45 (patient receiving tofacitinib 5 mg BID) or later, and no events were reported among tofacitinib 5 mg BID or 10 mg BID treated patients who did not have baseline venous thromboembolic event (VTE) risk factors such as previous VTE, previous heart failure, or ≥60 years of age (Figure 5).

**Figure 5. Proportions of subjects without embolic and thrombotic events by baseline VTE risk factors in RA Phase 2 Phase 3 studies (Month 0-3)**




Total follow up time calculated up to the day of the first event, subject to a risk period of 28 days beyond the last dose or to the data cutoff date. VTE risk factor is defined for a subject meeting any of the following criteria: Day 1 use of oral contraceptives or hormone replacement therapy, previous heart failure, previous VTE, age ≥60 years, BMI ≥30 kg/m$^2$, smoking, Day 1 antidepressant use, or Day 1 aspirin use. Data cutoff date Feb 2017. DVT, deep vein thrombosis; PE, (PE); ATE, arterial thromboembolic event.

In the clinical development program for UC, no thrombotic events were reported in patients receiving 8 weeks of tofacitinib 10 mg BID induction therapy (Sandborn et al). In completed studies in RA and UC patients treated with tofacitinib 10 mg BID, there were no events during the first 14 days of treatment and time to first reported thrombotic event was 72 days and 216 days in RA and UC patients, respectively (Table 1).

**Table 1. Days of treatment prior to first reported thrombotic event in completed studies in RA and UC patients**

| | 5 mg | 10 mg | Pbo | MTX | ADA |
|---|---|---|---|---|---|
| **RA** | **45** | **72** | **31** | **25** | **57** |
| **UC** | **N/A** | **216** | **3** | **N/A** | **N/A** |

***Benefit/risk assessment and dose recommendation***

Based on the above discussion, there appears to be a meaningful dose-dependent difference in effect on inflammation favoring the higher dose whereas there is no apparent short-term, dose-dependent risk increase for thrombosis. Taken together, in combination with the appropriate risk minimization measures, the benefit/risk is considered more favorable with tofacitinib 10 mg BID relative to 5 mg BID and the higher dose is therefore suggested as appropriate for evaluation in COVID-19 patients. Specifically, the following rationale supports evaluation of 10 mg BID:

- At the 10 mg BID dose, plasma tofacitinib concentrations are maintained above the IC50 for IL-6 inhibition throughout a 24-hour dosing interval at steady-state, unlike the lower dose of 5 mg BID. Along with other PD data discussed, the 10 mg BID dose provides better anti-inflammatory effects, than 5 mg BID, for controlling potential increase in cytokines and progression to ARDS.
- Tofacitinib 5 and 10 mg BID have been extensively studied in RA, PsA and UC clinical development programs and the short-term and long-term safety profile of tofacitinib 10 mg BID is well characterized.
- Tofacitinib 10 mg BID is the approved dose - in the EU and globally - for induction therapy up to 16 weeks in UC patients with potential for longer term use if needed for maintenance of treatment benefit.
- Short-term exposure to tofacitinib 10 mg BID has not been associated with an increased risk of thrombosis (either arterial or venous) when compared to 5 mg BID and time to first reported thrombotic event in patients treated with tofacitinib 10 mg BID was 72 days and 216 days in RA and UC patients, respectively.
    - Protocol risk minimization measures include:
        - Patients with severe hearth failure (NYHA 3 or 4), history of recurrent DVT or PE are excluded per protocol.
            - In pooled RA studies, there were no events reported during the first 3 months of tofacitinib 5 mg BID or 10 mg BID treatment in patients who did not have baseline VTE risk factors such as previous VTE, previous heart failure, or age ≥60 years.
        - All patients will receive Low Molecular Weight Heparin subcutaneously at prophylactic dosage.
- Therefore, the benefit/risk of short duration treatment appears more favorable with tofacitinib 10 mg BID relative to 5 mg BID for the control of potential hyperinflammation in COVID-19 and the use of 10 mg BID appears to be justified based on currently available information.

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