# Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Stone JH, Frigault MJ, Sterling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2028836

This supplement contains the following items:

1. Original protocol, final protocol, summary of protocol changes

2. Original statistical analysis plan (SAP), final SAP, summary of SAP changes

**INITIAL PROTOCOL**

Study title

# Tocilizumab to Prevent the Progression of Hypoxemic Respiratory Failure in Hospitalized Non-Critically Ill Patients with COVID-19

Study Drug and Financial Support Provided By
Roche / Genentech


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Background:

As of April 3, 2020, COVID-19 has been confirmed in over 1 million people worldwide, with an estimated symptomatic case fatality ratio of around 1.4%. [1,2] Currently without an effective treatment for SARS-CoV-2 there is an urgent need for effective treatment to curtail the rate of respiratory failure, the leading cause of mortality in COVID-19 disease. Moreover, with increasing numbers of patients requiring intensive unit level care and mechanical ventilation, nations are already having to triage patients for ventilatory support due to limited resources and healthcare systems around the world being stretched to the point of collapse, highlighting the importance of identifying interventions that could prevent the development of respiratory failure for these patients.

The disease course of COVID-19 includes an incubation period, an acute viral phase that most commonly presents with flu-like symptoms that in some individuals progresses to a severe hyperinflammatory phase marked by acute respiratory distress syndrome (ARDS) and hypoxemic respiratory failure.[3,4] Though there is spectrum of clinical course, many progress to the hyperinflammatory phase around day seven of symptoms, often requiring intensive care unit (ICU) level care and mechanical ventilation.[4] Accumulating evidence suggests that the pathophysiology underlying this profound decline is a severe inflammatory response as demonstrated by multi organ system dysfunction akin to cytokine release syndrome (CRS)/macrophage activation syndrome (MAS).[3] CRS/MAS is a systemic hyperinflammatory syndrome on a spectrum with secondary hemophagocytic lymphohistiocytosis (sHLH), typically characterized by multiorgan failure that is often triggered by viral infections in the setting of excessive immune activation, typically with marked hyperferritinemia.[5] Postmortem assessment of patients with COVID-19 have demonstrated pathologic findings consistent with MAS such as mono/lymphocytic infiltrates within the lung parenchyma with associated edema and alveolar congestion, splenic necrosis with macrophage proliferation and hemophagocytosis, as well as a lymphocyte/histiocyte predominate infiltrate of portal vasculature accompanying liver necrosis and sinusoidal congestion.[6] Cytokine profiling of patients with MAS/sHLH overlaps with that seen in patients with severe COVID-19 and includes elevated levels of IL-1, IL-2, IL-7, IL-6, G-CSF, MCP- 1, and TNF-α as well as elevated D-dimer, C-reactive protein, LDH and troponins.[5,7,8] Moreover, preliminary data from a non-randomized series of COVID-19 patients with “severe or critical COVID-19” from China who were treated with tocilizumab (in addition to standard therapies) showed they had dramatic improvement in fever, arterial oxygen saturation and inflammatory markers within the first 24-hours following administration.[9]

Taken together, these data strongly suggest an immunologic link between COVID-19 and immune dysregulation resulting in MAS. Clinical trials are already underway studying the role of immunomodulatory therapy including modulation of IL-1 and IL-6 and downstream pathways in the setting of CAR-T induced MAS (NCT04150913, NCT04071366) and agents such anakinra and tocilizumab have been used in this context with promising results and good safety profiles. There is an urgent and dire need to study the therapeutic role for immunomodulatory therapy in COVID-19 disease to both halt disease progression in patients at an individual level and prevent the inevitable saturation of healthcare resources at a systems level, to which end there are numerous ongoing international trials to expand these efforts into the setting of COVID-19 infection (ChiCTR2000029765, NCT04324021, TOCOVID-19). Based on the MGH experience thus far with COVID-19, including over 200 patients to date, the need for mechanical ventilation has been approximately 30%. With the upcoming surge anticipated between April 17$^{th}$ and 21$^{st}$ we expect the need for hundreds of

additional ICU beds. We propose a trial of IL-6 receptor blockade with tocilizumab given early in disease course to try to prevent progression of COVID-19.

Hypothesis: Early intervention with immunomodulatory therapy targeting the IL-6 axis for COVID-19 associated cytokine-release syndrome (CRS)/macrophage-activation syndrome (MAS) can limit progression of hypoxemic respiratory failure necessitating intensive care, mechanical ventilation and improve mortality.

Aim 1: To determine if IL-6 blockade can prevent progression of COVID-19 when given early in the disease process.

Aim 2: To understand the biomarkers associated with progression of COVID-19 and with improvement of illness.

Intervention: Patients will receive the standard treatment for COVID-19 per MGH guidance and also be randomized (2:1) to one of the following arms:

1. Tocilizumab 8 mg/kg x 1, to a maximum dose of 800 mg (n=195)
2. Standard of care (n=97)

Study population

| *Inclusion criteria*: | *Exclusion criteria*: |
|---|---|
| Age > 18 and < 80 years old<br>Male or female gender<br>Confirmed SARS-CoV-2 infection by NP swab PCR<br>Admitted to non-ICU level care at MGH<br><br>WITH evidence of severe COVID-19 (at least 2 of the following):<br>• Fever > 38C<br>• Pulmonary infiltrates on chest X ray<br>• Need for supplemental O2 to maintain saturation > 92%<br><br>*AND at least 1 of the following*:<br>• Ferritin > 500 ng/ml<br>• CRP > 50 mg/L<br>• LDH >250 U/L<br>• D-dimer > 1000 ng/mL | • Unable to provide verbal informed consent or have verbal agreement to participate through attestation and signature of a Witness required, as outlined in the Partners IRB's Table for Consenting in COVID Research that is More than Minimal Risk.<br>• Uncontrolled bacterial, fungal, or non-COVID viral infection<br>• Active TB or LTBI with < 1 month of treatment<br>• Any prior investigational immunologic therapy (for instance with biologic or JAK inhibitor) within 28-days or 3 half-lives of the agent<br>• Receipt of tocilizumab for the treatment of other conditions within one month of the first COVID symptom<br>• History of hypersensitivity to tocilizumab<br>• Any concurrent immunosuppressive medication that the PI believes would put the patient at higher risk |

| | |
|---|---|
| | • Oral or IV corticosteroid for non-COVID-19 indication within the last 7 days at a dose of ≥ 10 mg prednisone or equivalent per day<br>• History of diverticulitis or bowel perforation<br>• ANC <500, Platelets <50,000*<br>• AST/ALT > 5X ULN<br>• Treatment with other biologic or small-molecule immunomodulating therapy such as IL1R-antagonism, JAK inhibition, or other agents<br>• Treatment with convalescent plasma** |

* If ANC < 500 or platelet count < 50,000 in setting of recent chemotherapy or underlying malignancy, can be considered for inclusion at the discretion of study PI
** We note that anti-viral therapies may be administered to patients if given in the context of a clinical trial. Nitric oxide treatment is also permitted at the discretion of the care team, ideally in the context of a clinical trial.

Recruitment Procedures:
Upon admission to the hospital, the study team will determine if the patient meets the eligibility requirements of the study by review of the medical record. The study team will ensure that the patient meets inclusion and exclusion criteria

If the patient is eligible and expresses interest, a member of the study team will contact the primary care team to discuss potential participation. If the primary team agrees to allow the study team to approach the patient, a member of the study team will contact the patient via telephone and will explain the protocol in more detail and answer any questions the patient may have. The member of the study team will reinforce with the patient that he or she does not have to participate and the decision not to participate will not affect his or her care at any time. The patient will be told that should he or she choose to participate, he or she may contact the research team for more information. If the patient expresses interest, the primary care team will be sent an electronic version of the consent form, which the team will then send to the patient. The patient will be given sufficient time to decide if he or she want to participate in the study. The patient will be encouraged to speak with their other doctors or family members about this study. After an appropriate interval of time, the study team will then call the patient back to ascertain the patient's final decision whether or not to participate in the study. A healthcare worker not associated with the study will also join the telephone final consent call to serve as an additional witness. Both the unassociated healthcare worker and the study investigator will sign the consent and that consent will be stored. A copy of the signed consent will be given to the patient.

The study team will follow the PHRC policy on Recruitment of Research Subjects and the Partners IRB's guidance with regard to Consenting in COVID Research that is More than Minimal Risk. No identifiable information will be stored during the pre-screening process except for patients who are expected to consent to the study. All records of identifiable information will be destroyed if patients do not consent to the study.

Consent Procedures:

Subjects may be recruited in the in-patient setting. If the patient is eligible and expresses interest, a member of the study team will contact the primary care team to discuss potential participation. For subjects enrolled inpatient where the study team is unable to obtain a signed consent form due COVID-19 transmission concerns, investigators may obtain verbal agreement to participate from the subject with attestation and signature of the Witness required.

In patient consenting: Subjects

1. Consent form provided via email or other electronic means but does not include ability to sign electronically. When sent by email a copy of the email should be retained in the subject file OR Paper consent can be transported to the patient during a clinical team visit to the room.
2. Patient reads, has 3- way phone conversation with person consenting and the witness.
3. Patient signs the hard copy consent and it is retained in the room. If it is not possible for the patient to physically sign, the patient provides verbal agreement to participate.

In patient consenting: Study Investigators

1. Conducts consent process via 3-way phone conversation with patient and witness.
    a. If the primary team agrees to allow the study team to approach the patient, a member of the study team will contact the patient via telephone and will explain the protocol in more detail and answer any questions the patient may have. The member of the study team will reinforce with the patient that he or she does not have to participate and the decision not to participate will not affect his or her care at any time. The patient will be told that should he or she choose to participate, he or she may contact the research team for more information. If the patient expresses interest, the primary care team will be sent an electronic version of the consent form, which the team will then send to the patient.
2. Prints and signs paper consent document as person obtaining consent.
3. Completes *COVID-19 Attestation/Witness Form noting either the subject signed a separate copy of the consent that was retained in the isolation room, or that the subject consented verbally and the reason preventing subject signature on form.
4. Documents in a note to file or in a COVID-19 Informed Consent Checklist that the consent form was provided to the participant, consent was obtained, the method used to obtain consent, date/time, and witness name.
5. 5.The *COVID-19 Attestation/Witness Form is stored with the signed consent form in the study record and a copy of the consent form is uploaded to EPIC.

The patient will be given sufficient time to decide if he or she want to participate in the study. The patient will be encouraged to speak with their other doctors or family members about this study. After an appropriate interval of time, the study team will then call the patient back to ascertain the patient's final decision whether or not to participate in the study. A healthcare worker not associated with the study will also join the telephone final consent call to serve as an additional witness. Both the unassociated healthcare worker and the study investigator will sign the consent and that consent will be stored. A copy of the signed consent will be given to the patient.

Study Procedures

a. On the day of consent, the patient will be randomized to receive tocilizumab 8 mg/kg x 1 (not to exceed 800 mg) vs placebo at 2:1. Medication will be administered that day. Study investigators will be blinded.
b. Schedule of study related assessments: see Appendix A.
c. In person visits will be limited due to need to minimize contact with SARS-CoV-2 infected patients to minimize hospital-associated transmission.
d. To determine immunologic phenotypic changes during intervention, several endpoints will be collected to include serum for antibodies, cytokine analysis, inflammatory marker analysis as well as cellular fractions for functional and transcriptional immunophenotyping.

Study Objectives: To determine whether the use of early tocilizumab can decrease progression of COVID-19 associated respiratory failure necessitating ICU admission.

Study Design: Prospective placebo-controlled, blinded, randomized controlled trial at MGH. We plan to add additional sites through an IRB addendum. The other proposed sites are: Brigham & Women's Hospital, North Shore Medical Center, Newton-Wellesley Hospital, and Boston Medical Center.

Primary Endpoints:
Percentage of patients requiring invasive mechanical ventilation.

Secondary Endpoints:

a. Requirement for inotropes and/or vasopressors
b. Duration of mechanical ventilation
c. Clinical improvement (assessed at day 7, 14, 28 or day of discharge) defined as moving up 2 levels on the following scale:

| Clinical Improvement Scale | |
|---|---|
| 1 | Hospitalized not requiring supplemental oxygen (on ambient air) |
| 2 | Hospitalized requiring ≤ 2 L supplemental oxygen by nasal cannula |
| 3 | Hospitalized requiring 2-6 L supplemental oxygen |
| 4 | Hospitalized requiring > 6L supplemental O2 but no HF, NIV or invasive mechanical ventilation |
| 5 | Hospitalized, requiring high flow O2 or noninvasive mechanical ventilation |

| | |
|---|---|
| 6 | Hospitalized, intubation and mechanical ventilation |
| 7 | Hospitalized, ventilation plus renal replacement therapy, ECMO or inotropes |
| 8 | Death |

d. Time to hospital discharge
e. Mortality at day 7, 14 and 28
f. Duration of ICU stay (up to Day 28);
g. Duration of time on supplemental oxygen (up to Day 28);
h. The proportion of patients who require renal replacement therapy or have doubling of creatinine from baseline at Day 14 and Day 28

Exploratory Endpoints

- Change from baseline and trajectory of ferritin, LDH, CRP, and D-dimer
- Cellular immunophenotyping
- COVID serology
- Cytokine profiling, including rapid IL-6 assessment, before and after treatment
- AKI grade 2 or higher (doubling of creatinine) or need for renal replacement therapy.
- Clinically relevant inflammatory biomarker assessment includes TREM-1, procalcitonin, Pro-ADM.
- Measures of cardiac injury (troponin- difference in peak troponin level), cardiac dysfunction (NTproBNP-difference in peak NTproBNP level), or serious cardiac arrhythmias.
- Viral titers
- DNA & RNA sequencing

Follow Up:
All patients will follow-up to complete their series of outpatient visits in either the TCRC or RAC-C if discharged before 28 days.

Power Calculation and Statistical Considerations:

The following analysis populations are defined for the different types of data analysis:

- Intent-to-Treat (ITT) Population: all randomized patients;
- Modified Intent-to-Treat (mITT) Population: all randomized patients who receive study drug;
- Per-Protocol (PP) Population: all randomized patients who complete the study and do not incur a significant protocol violation; and
- Safety Population: all randomized patients who receive study drug.

All study-collected data will be summarized by treatment group for the appropriate analysis population using descriptive statistics, graphs, and/or raw data listings. Descriptive statistics for continuous variables will include the number of patients, mean, standard deviation (SD),

median, first and third quartiles, minimum and maximum values for the observed value, and change from baseline. Analysis of categorical variables will include frequency and percentage. The baseline value is defined as the last measurement collected prior to the administration of study drug, unless otherwise specified.

An interim analysis will be performed when approximately 50% of the patients have enrolled or approximately 40% of patients have completed Day 28 or withdrawn prior to Day 28. Both efficacy and futility of the study will be assessed at the time of the interim analysis. We will submit a formal plan for this analysis as an addendum.

## Risks and Discomfort

### Risks Associated with TCZ Use

- **Infection.** Patients treated with TCZ are at increased risk for developing serious infections that may lead to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, or other opportunistic infections. The overall safety profile of TCZ in GCA patients (defined in the GiACTA trial) was comparable to the one observed in rheumatoid arthritis (RA) patients, except that there was an overall higher incidence of infections in GCA patients relative to RA patients. The rate of infections was 200.2 per 100 patient-years in the TCZ QW group and 160.2 per 100 patient-years in the TCZ Q2W group, as compared to 156.0 per 100 patient-years in the PBO+26 and 210.2 per 100 patient-years in the PBO+52 groups. The rate of serious infections was 9.7 per 100 patient-years in the TCZ QW group and 4.4 per 100 patient-years in the TCZ Q2W group, as compared to 4.2 per 100 patient-years in the PBO+26 and 12.5 per 100 patient-years in the PBO+52 groups.

- **Hypersensitivity reactions.** Hypersensitivity reactions, including anaphylaxis, have been reported in association with TCZ and anaphylactic events with a fatal outcome have been reported with intravenous (IV) infusion of TCZ. Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials of IV TCZ, 0.2% (8 out of 4009) of patients in the IV all-exposure RA population, 0.7% (8 out of 1068) in the SC 6-month controlled RA trials, and in 0.7% (10 out of 1465) of patients in the SC all-exposure population. In the systemic juvenile inflammatory arthritis (JIA) controlled trial with IV TCZ, 1 out of 112 patients (0.9%) experienced hypersensitivity reactions that required treatment discontinuation. In the polyarticular JIA controlled trial with IV TCZ, 0 out of 188 patients (0%) in the TCZ all-exposure population experienced hypersensitivity reactions that required treatment discontinuation.

- **Neutropenia.** Decreases in neutrophil counts have been observed following treatment with TCZ.

- **Thrombocytopenia.** Decreases in platelet counts have been observed following treatment with TCZ.

- **Elevated liver enzymes.** Transaminase elevations have been observed following treatment with TCZ. These elevations did not result in apparent permanent or clinically evident hepatic injury in clinical trials.

- **Lipid abnormalities.** Increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterols, and/or HDL cholesterol has been observed following treatment with TCZ.

- **Gastrointestinal (GI) perforations.** Events of GI perforation have been reported in clinical trials, primarily as complications of diverticulitis in RA patients. No GI perforations were reported in GCA clinical trials.

- **Immunosuppression and potential risk of malignancy.** Although no imbalance of malignancies was observed in controlled clinical trials of TCZ, malignancies have been identified as a concern for other immunosuppressive agents.

- **Demyelinating disorders.** The impact of treatment with TCZ on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies.

- **Live vaccines.** Vaccination with live vaccines may lead to infection in patients under immunosuppressive therapy including TCZ.

- **Pregnancy.** The limited available data with TCZ in pregnant women are not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage.

Additional information on TCZ safety can be found in the attached **Investigator's Brochure**.

## SAFETY REPORTING OF ADVERSE EVENTS

### *ASSESSMENT OF SAFETY*

### Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

### Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product

(IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with COVID-19 that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

**Serious Adverse Events**

An AE should be classified as an SAE if any of the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

***METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES***

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc.

**Adverse Event Reporting Period**

The study period during which AEs and SAEs as described in ***section J*** where the patient has been exposed to Genentech product must be reported Reporting period begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment (Modify statement depending up on section **g**).

**Assessment of Adverse Events**

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or

SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the Toclizumab (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

**Yes**

There is a plausible temporal relationship between the onset of the AE and administration of the Toclizumab, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the Toclizumab or with similar treatments; and/or the AE abates or resolves upon discontinuation of the Toclizumab or dose reduction and, if applicable, reappears upon re- challenge.

**No**

Evidence exists that the AE has an etiology other than the Toclizumab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to Toclizumab administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I)
or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

## *PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS*

### Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- “How have you felt since your last clinical visit?”
- “Have you had any new or changed health problems since you were last here?”

### Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

### a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

### b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section I), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

### c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

### d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

### e. Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v 5.0 Update current versions) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

**Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE**

| Grade | Severity |
|---|---|
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated |
| 2 | Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a] |
| 3 | Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c] |
| 4 | Life-threatening consequences or urgent intervention indicated d |
| 5 | Death related to adverse event [d] |

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE v 5.0 which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. Grade 4 and 5 events must be reported as serious adverse events

### f. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within *90 days* after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within *90days* after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

### g. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior Toclizumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject [add if applicable-including pregnancy occurring in the partner of a male study subject] who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety during follow up period

## h. Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via Toclizumab emailing Genentech a Quarterly line-listing documenting single case reports sent by *Toclizumab* to Genentech in the preceding time period.
The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Dr. Stone/Sponsor to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech

### i. AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN
    - Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in

a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

**The** *Toclizumab* **Events of Special Interest are:**

- Serious and/or medically significant infections
- Myocardial infarction/Acute coronary syndrome
- Gastrointestinal perforations
- Malignancies
- Anaphylaxis/Hypersensitvity reactions
- Demyelinating disorders
- Stroke
- Serious and/or medically significant bleeding events
- Serious and/or medically significant hepatic events

**j. Exchange OF SINGLE CASE REPORTS**

*Dr. Stone/ Sponsor* will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the Study for the Product.

Investigators must report all the above mentioned single case reports adequately to Genentech within the timelines described below. The completed MedWatch or CIOMS I form or Genentech approved reporting forms should be faxed/emailed immediately upon completion to Genentech at the following contacts:

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints *with* an AE should be sent to:

**Fax: 650-238-6067**

**Email: usds_aereporting-d@gene.com**

All Product Complaints *without* an AE should be sent to:

**Email: kaiseraugst.global_impcomplaint_management@roche.com**

It is understood and agreed that the Sponsor will be responsible for the evaluation of AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study.
These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met.

Serious adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation Reports and Product Complaints (with or without an AE), where the patient has been exposed to the Genentech Product, will be sent on a MedWatch form or CIOMS I form or on Genentech approved reporting forms to Genentech Drug Safety. Transmission of these reports (initial

and follow-up) will be either electronically or by fax and within the timelines specified below:

- **SADRs**
  Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

- **Other SAEs**
  Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **AESIs**
  AESIs shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

- **Special Situation Reports**
  **Pregnancy reports**
  While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

  **Pregnancies in Female Partners of Male Patients**
  Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 30 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

- **Other Special Situation Reports**
  In addition to all SAEs, pregnancy reports and AESIs, the following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within thirty (30) calendar days:
  - Data related to the Product usage during breastfeeding
  - Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
  - In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

- **Product Complaints**
  All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

  A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

***MEDWATCH 3500A REPORTING GUIDELINES***

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

**Follow-Up Information**

- Additional information may be added to a previously submitted report by any of the following methods:
- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at
https://www.fda.gov/media/69876/download

## REPORTING TO REGULATORY AUTHORITIES, ETHICS COMMITTEES AND INVESTIGATORS

Genentech as the Marketing Authorization Holder will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations.
*Dr. Stone / Sponsor* as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.
*Dr. Stone / Sponsor* will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.
Dr Stone /Sponsor will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

Dr. Stone/ Sponsor will be responsible for the distribution of safety information to Site IRB:

*Partners Institutional Review Board*

**For questions related to safety reporting, please contact Genentech/Roche Drug Safety:**

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

***AGGREGATE REPORTS***

***Development Safety Update Report***

*Dr. Stone* as the Sponsor of the Study, will be responsible for the preparation of their own Development Safety Update Report (DSUR) for the Study and for the submission of the report to the regulatory authorities and Ethics Committees of the concerned Member States, where applicable. *Dr. Stone /Sponsor* agrees to share a copy of their own DSUR with Genentech as soon as reasonably possible after completion.
Genentech agrees to forward to *Dr. Stone/Sponsor* an executive summary of the Genentech DSUR upon request. Furthermore, Genentech agrees that *Dr. Stone /Sponsor* may cross-reference the executive summary of the Genentech/Roche DSUR, as applicable.
***Other Reports***

*Dr. Stone/ Sponsor will* forward a copy of the Final Study Report to Genentech/Roche upon completion of the Study.

OR

*Dr. Stone /Sponsor* will forward a copy of the Publication to Genentech/Roche upon completion of the Study.

***RANDOMIZATION CODES FOR BLINDED CLINICAL TRIALS (IF APPLICABLE)***

The blind will be broken for ADR reports that are Serious and Unexpected, unless otherwise agreed with applicable regulatory authorities

***STUDY CLOSE-OUT***

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech/Roche. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech/Roche. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

actemra-gsur@gene.com
And to Genentech Drug Safety CTV oversight mail box at:
ctvist_drugsafety@gene.com

***QUERIES***

Queries related to the Study will be answered by *Dr. Stone /Sponsor* However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech/Roche shall have the final say and control over safety queries relating to the Product. *Dr. Stone /Sponsor* agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech/Roche.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

***SAFETY CRISIS MANAGEMENT***

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech/Roche shall have the final say and control over safety crisis management issues relating to the Product. Dr. Stone /Sponsor agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech/Roche.

**SAFETY REPORTING FAX**

**COVER SHEET Genentech**

**Supported Research**

AE / SAE FAX No: (650) 238-6067

| | |
|---|---|
| Genentech Study Number | |
| Principal Investigator | |
| Site Name | |
| Reporter name | |
| Reporter Telephone # | |
| Reporter Fax # | |

| | |
|---|---|
| Initial Report Date | [DD] / [MON] / [YY] |
| Follow-up Report Date | [DD] / [MON] / [YY] |

Subject Initials
(Enter a dash if patient has no middle name)

| | |
|---|---|
| [ ] - [ ] - [ ] | |

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Safety Monitoring:
Outcomes will be assessed weekly by an independent Data Safety and Monitoring Board. Endpoints will be assessed for the treatment group compared to the control arm.

Safety Analysis:
The number (percentage) of patients reporting treatment-emergent AEs and SAEs for each preferred term (PT) will be tabulated by System Organ Class (SOC), by SOC and severity, and by SOC and relationship to study drug. If more than 1 event occurs with the same PT for the same patient, the patient will be counted only once for that PT using the most severe or related occurrence for the summary by severity or relationship to study drug, respectively.
Clinical laboratory values (excluding efficacy laboratory parameters) will be summarized by treatment group, including changes from baseline at each visit.
Vital signs and change from baseline in vital signs will be summarized descriptively at each visit by treatment group.

Appendix A. Schedule of study related assessments

| | **Screen** | **Baseline** | **Frequency** |
|---|---|---|---|
| **Day +/- Window** | **−1 or 1** | **1** | **Days 4, 7, 14, and 21** |
| **ELIGIBILTY** | | | |
| Informed consent | X | | |
| Demographics & Medical History/meds | X | | |
| Review SARS-CoV-2 results | X | | |
| Physical Exam (taken from chart) [1,6] | X | X | X |
| **STUDY INTERVENTION** | | | |
| Randomization | | X | |
| Administration of study product | | X | |
| | | | |
| **STUDY PROCEDURES** | | | |
| Vital signs including $SpO_2$ | | X[5] | X |
| Clinical data collection[1] | | X[5] | X |
| Medication review | | X[5] | X |
| Adverse events | | X | Daily while hospitalized |
| | | | |
| **Screening LABs** | | | |
| Safety BMP, LFTs, CBC/diff, ESR, CRP, ferritin, LDH, troponin, NT-proBNP, D-dimer [2] | X[3] | X[4,5] | X |
| Pregnancy test for females of childbearing potential | X[3] | | |
| | | | |
| **Correlative Biomarkers** | | | |
| Blood for serum - | X[5] | X[5] | X |
| Blood for PBMC | X[5] | X[5] | X |
| Blood for SARS-CoV2 IgM/IgG | X[5] | X[5] | X |

Notes:

[1]This includes ordinal score, NEWS, oxygen requirement, Mechanical ventilator requirement, etc.

[2]Laboratory tests performed in the 48 hours prior to enrollment will be accepted for determination of eligibility.

[3]Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing.

[4,5]Baseline assessments should be performed prior to study drug administration

[6]Given limited PPE and highly infectious nature of COVID-19, visits will be performed over the phone, unless requested by the patient.

## References


1. Wu JT, Leung K, Bushman M, et al. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. Nature Medicine 2020.
2. Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. The Lancet Infectious Diseases.
3. Siddiqi HK, Mehra MR. COVID-19 Illness in Native and Immunosuppressed States: A Clinical-Therapeutic Staging Proposal. The Journal of Heart and Lung Transplantation.
4. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet.
5. Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet 2014;383:1503-16.
6. Yao XH, Li TY, He ZC, et al. [A pathological report of three COVID-19 cases by minimally invasive autopsies]. Zhonghua Bing Li Xue Za Zhi 2020;49:E009.
7. Seguin A, Galicier L, Boutboul D, Lemiale V, Azoulay E. Pulmonary Involvement in Patients With Hemophagocytic Lymphohistiocytosis. Chest 2016;149:1294-301.
8. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020;395:497-506.
9. Xu X, Han, Mingfeng,Li, Tiantian,Sun, Wei,Wang, Dongsheng,Fu, Binqing,Zhou, Yonggang,Zheng, Xiaohu,Yang, Yun,Li, Xiuyong,Zhang, Xiaohua,Pan, Aijun,Wei, Haiming. Effective Treatment of Severe COVID-19 Patients with Tocilizumab. [ChinaXiv:20200300026] (2020).

# FINAL PROTOCOL

PARTNERS HUMAN RESEARCH COMMITTEE
DETAILED PROTOCOL
Massachusetts General Hospital
55 Fruit Street
Boston, MA 02114

Study title
Tocilizumab to Prevent the Progression of Hypoxemic Respiratory Failure in Hospitalized Non-Critically Ill Patients with COVID-19

Study Drug and Financial Support Provided By
Roche / Genentech

Protocol Number
2020P001159

ClinicalTrials.Gov Number
NCT04356937

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted per all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Co-Principal Site Investigators:

Internal Sites

| | |
|---|---|
| Massachusetts General Hospital<br>Name: John H. Stone, MD, MPH<br>Title: Principal Investigator<br>Signed:<br>Date: | Brigham and Women's Hospital<br>Name:Woolley, Ann E., M.D.<br>Title: BWH Site PI<br>Signed:<br>Date: |
| Newton Wellesley Hospital<br>Name: Schrager, Harry MD<br>Title: BWH Site PI<br><br>Signed:<br>Date: | North Shore Medical Center<br>Name: Shah, Ruta M., M.D.<br>Title: NSMC Site PI<br><br>Signed:<br>Date: |

External Sites

| | |
|---|---|
| Boston Medical Center<br>Name: Lin, Nina MD<br>Title: BMC Site PI<br><br>Signed:<br>Date: | BILH Lahey Hospital & Medical Center<br>Name: Matthew Axelrod, MD<br>Title: Lahey Site PI<br><br>Signed:<br>Date: |
| Steward St. Elizabeth's Medical Center<br>Name: Jorge Fleisher, MD<br>Title: Steward Site PI<br><br>Signed:<br>Date | |

This will be a multicenter study. The lead site will be Massachusetts General Hospital. Participating sites will be selected based on the following criterion: availability of trial staff (i.e. investigator, coordinator, nurse, and experience enrolling and following subjects in previous clinical trials.

## STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6) and the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). All personnel involved in the conduct of this study have completed human subject's protection training.

Administrative Core

The Administrative Core consists of the BACC PI (Dr. John Stone), the director of the mechanistic study collection (Dr. Michael Mansour), Ana Fernandes (Project Manager), Liam Harvey and Payal Patel (Research Coordinators), and the Partners Clinical Trials office (John Montana). The core is overseen by Dr. John H Stone from MGH. This Core is responsible for overseeing study administration. The responsibilities of the Administrative Core include:

1. Development and maintenance of the Clinical Trial Protocol and Study Operations
2. Ensuring that the study is conducted according to the Protocol
3. Communications with clinical sites, scheduling of meetings and training sessions, responding to and documenting ad hoc communications
4. Distribution of all changes, updates and policies of reports and documents to participating clinical sites
5. Maintaining the study binder (regulatory and clinical documents)
6. Participating in protocol finalization and preparing study materials

Executive Committee

The Executive Committee will be comprised of Dr. John Stone (MGH), Dr. Michael Mansour (MGH), Dr. Matthew Frigault (MGH), Dr. Naomi Serling-Boyd (MGH), Dr. Nina Lin (Boston Medical Center), Dr. Ruta Shah (North Shore Medical Center), Dr. Ann Woolley (The Brigham & Women's Hospital), Dr. Harry Schrager (Newton-Wellesley Hospital), Dr. Matthew Axelrod (Lahey) and Dr. Jorge Fleisher (St. Elizabeth's). This Committee will meet every other week during the trial. Any concerns voiced by other study staff members will be brought to the attention of this committee. The progress of the study will be reviewed by the Executive Committee, and any issues will be identified and resolved through this Committee. The Executive Committee will be responsible for making strategic decisions regarding study protocol, resource allocation, recruitment, and protocol adherence. They will have final say on decisions for the entire trial. If conflicts arise between the Co-PIs, issues will be brought to the entire Executive Committee for resolution.

### Data Coordinating Center

The Data Coordinating Center (DCC) will be run by Ana Fernandes and Dr. Naomi Serling-Boyd. Nora Horick, BS, Brian Healy, PhD, and Andrea Foulkes, PhD, will serve as Biostatisticians for the trial. The DCC is responsible for oversight of data collection and analysis. The responsibilities of the DCC include:

1. Development and implementation of the data flow, schedules for transferring data from sites, and data tracking
2. Development of procedures for data entry, error identification, and error correction
3. Adverse event monitoring and reporting to the DSMB
4. Site monitoring via the Electronic Data Capture (EDC) to ensure adherence to the protocol and procedures
5. Quality control procedures
6. Creating reports - enrollment, adverse events, participant status (e.g., withdrawals) by site
7. Trial analyses

Data and Safety Monitoring Board

The DSMB will be appointed by Dr. Stone. The DSMB will meet after when approximately 50% of the subjects have enrolled. The DSMB will review the conduct of the trial and the safety experience of subjects. Ad hoc meetings of the DSMB may also be convened at other points in the trial as needed. Blinded (and, if requested by the DSMB, unblinded) reports will be provided by the DCC to the DSMB.

Central IRB

The Partners HealthCare IRB will play the role of central IRB for this trial. The Administrative Core and Executive Committee will be responsible for handling all communication with the central IRB. The DCC will provide all necessary reports for submission to the central IRB.

Clinical Sites

Seven clinical sites will participate in enrolling subjects for the BACC tocilizumab trial. The study sites play an essential role in answering the questions posed by this study. Each site will be responsible for enrolling participants, carrying out the study protocol, recording and transmitting study information, satisfying regulatory requirements, and providing clinical oversight. The DCC and Administrative Core will support Sites in these efforts, from training through implementation.

Site Requirements for Eligibility include:

1. Prior experience with clinical trials
2. Easy access to standard clinical laboratory assessments

The Roles and Responsibilities of the PI, co-PIs and Study Coordinator are outlined in the operations manual.

Background:

As of April 3, 2020, COVID-19 has been confirmed in over 1 million people worldwide, with an estimated symptomatic case fatality ratio of around 1.4%.[1,2] Currently there is an urgent need for effective treatment to curtail the rate of respiratory failure, the leading cause of mortality in COVID-19 disease. Moreover, with increasing numbers of patients requiring intensive unit level care and mechanical ventilation, nations are already having to triage patients for ventilatory support due to limited resources and healthcare systems around the world being stretched to the point of collapse, highlighting the importance of identifying interventions that could prevent the development of respiratory failure for these patients.

The disease course of COVID-19 includes an incubation period, an acute viral phase that most commonly presents with flu-like symptoms that in some individuals progresses to a severe hyperinflammatory phase marked by acute respiratory distress syndrome (ARDS) and hypoxemic respiratory failure.[3,4] Though there is spectrum of clinical course, many progress to the hyperinflammatory phase around day seven of symptoms, often requiring intensive care unit (ICU) level care and mechanical ventilation.[4] Accumulating evidence suggests that the pathophysiology underlying this profound decline is a severe inflammatory response as demonstrated by multi organ system dysfunction akin to cytokine release syndrome (CRS)/macrophage activation syndrome (MAS).[3] CRS/MAS is a systemic hyperinflammatory syndrome on a spectrum with secondary hemophagocytic lymphohistiocytosis (sHLH), typically characterized by multiorgan failure that is often triggered by viral infections in the setting of excessive immune activation, typically with marked hyperferritinemia.[5] Postmortem assessment of patients with COVID-19 have demonstrated pathologic findings consistent with MAS such as mono/lymphocytic infiltrates within the lung parenchyma with associated edema and alveolar congestion, splenic necrosis with macrophage proliferation and hemophagocytosis, as well as a lymphocyte/histiocyte predominate infiltrate of portal vasculature accompanying liver necrosis and sinusoidal congestion.[6] Cytokine profiling of patients with MAS/sHLH overlaps with that seen in patients with severe COVID-19 and includes elevated levels of IL-1, IL-2, IL-7, IL-6, G-CSF, MCP- 1, and TNF-α as well as elevated D-dimer, C-reactive protein, LDH and troponins.[5,7,8] Moreover, preliminary data from a non-randomized series of COVID-19 patients with “severe or critical COVID-19” from China who were treated with tocilizumab (in addition to standard therapies) showed they had dramatic improvement in fever, arterial oxygen saturation and inflammatory markers within the first 24-hours following administration.[9]

Taken together, these data strongly suggest an immunologic link between COVID-19 and immune dysregulation resulting in MAS. Clinical trials are already underway studying the role of immunomodulatory therapy including modulation of IL-1 and IL-6 and downstream pathways in the setting of CAR-T induced MAS (NCT04150913, NCT04071366) and agents such anakinra and tocilizumab have been used in this context with promising results and good safety profiles. There is an urgent and dire need to study the therapeutic role for immunomodulatory therapy in COVID-19 disease to both halt disease progression in patients at an individual level and prevent the

inevitable saturation of healthcare resources at a systems level, to which end there are numerous ongoing international trials to expand these efforts into the setting of COVID-19 infection (ChiCTR2000029765, NCT04324021, TOCOVID-19). Based on the MGH experience thus far with COVID-19, including more than 200 patients to date, the need for mechanical ventilation has been approximately 30%. With the upcoming surge anticipated between April 17th and 21st we expect the need for hundreds of additional ICU beds. We propose a trial of IL-6 receptor blockade with tocilizumab given early in disease course to try to prevent progression of COVID-19.

Hypothesis: Early intervention with immunomodulatory therapy targeting the IL-6 axis for COVID-19 associated cytokine-release syndrome (CRS)/macrophage-activation syndrome (MAS) can limit progression of hypoxemic respiratory failure necessitating intensive care, mechanical ventilation and improve mortality.

Aim 1: To determine if IL-6 blockade can prevent progression of COVID-19 when given early in the disease process.

Aim 2: To understand the biomarkers associated with progression of COVID-19 and with improvement of illness.

Intervention: Subjects will receive the standard treatment for COVID-19 per MGH guidance and be randomized (2:1) to one of the following arms:

- Tocilizumab 8 mg/kg x 1, to a maximum dose of 800 mg (n=185)
- Standard of care (n=93)

Study population

The inclusion and exclusion criteria are listed below.

**Table 1. Inclusion and Exclusion Criteria**

| *Inclusion criteria*: | *Exclusion criteria*: |
|---|---|
| 1. Age > 18 and < 86 years old<br>2. Male or female gender<br>3. Confirmed SARS-CoV-2 infection by nasopharyngeal swab PCR or serum assay for IgM antibody<br>4. Requiring hospital but not mechanical ventilation<br>Oxygen supplementation not greater than 10L delivered by any device<br>5. WITH evidence of severe COVID-19 (at least 2 of the following):<br>• Fever > 38C within 72 hours | • Unable to provide verbal informed consent or have verbal agreement to participate through attestation and signature of a Witness required, as outlined in the Partners IRB's Table for Consenting in COVID Research that is More than Minimal Risk.<br>• Patients between the ages of 79 and 86 will be excluded if they have NYHA Class III/IV heart |

| | |
|---|---|
| • Pulmonary infiltrate on chest X ray<br>• Need for supplemental O2 to maintain saturation > 92%<br>*AND at least 1 of the following*:<br>• Ferritin > 500 ng/ml<br>• CRP > 50 mg/L<br>• LDH >250 U/L<br>• D-dimer > 1000 ng/mL | failure, insulin-dependent diabetes mellitus, angina, or treatment of a malignancy (excluding non-melanoma skin cancer) within six months<br>• Uncontrolled bacterial, fungal, or non-COVID viral infection<br>• Active tuberculosis (see appendix B)<br>• Any prior investigational immunosuppressive therapy within 28-days or 3 half-lives of the agent (for instance with biologic or JAK inhibitor)<br>• Any concurrent immunosuppressive medication that the PI believes would put the patient at higher risk<br>• Receipt of intravenous tocilizumab for the treatment of a non-COVID condition within three weeks of the first COVID symptom<br>• History of hypersensitivity to tocilizumab<br>• Any concurrent immunosuppressive medication that the PI believes would put the patient at higher risk<br>• Treatment with other biologic or small-molecule immunosuppressive therapy such as IL1R-antagonism, JAK inhibition, or other agents.<br>• Treatment with convalescent plasma**<br>• History of diverticulitis or bowel perforation<br>• ANC <500, Platelets <50,000*<br>• AST/ALT > 5X ULN |

| | |
|---|---|
| | • Women who are pregnant or planning to get pregnant in the next 90 days |

* If ANC < 500 or platelet count < 50,000 in setting of recent chemotherapy or underlying malignancy, can be considered for inclusion at the discretion of study PI
** We note that anti-viral therapies may be administered to subjects on an open-label basis. Nitric oxide treatment is also permitted at the discretion of the care team. Co-treatment chloroquine, hydroxychloroquine, and/or azithromycin is permitted for subjects in this protocol on an open-label basis. Enrollment in certain open-label trials may be permissible (as currently stated), but co-enrollment in other randomized controlled clinical trials is prohibited.

Study Objectives: To determine whether the use of early tocilizumab can decrease progression of COVID-19 associated respiratory failure necessitating ICU admission.
Study Design: Prospective placebo-controlled, blinded, randomized controlled trial at seven Boston area hospitals: the MGH, the Brigham & Women's Hospital, North Shore Medical Center, Newton-Wellesley Hospital, Boston Medical Center, the Lahey Hospital and Medical Center, and St. Elizabeth's Hospital.

**Endpoints and Statistical Analysis Plan:**

The following analysis samples are defined for safety and efficacy analysis:

- Intent-to-Treat (ITT) Sample: Subjects who are randomized regardless of treatment adherence or availability of follow-up data will be included in the intention-to-treat analysis set (ITT). All analyses of the ITT will be based on each subject's randomized treatment assignment.
- Modified Intent-to-Treat (mITT) Sample: Randomized subjects who receive any amount of the study drug before intubation or death.
- Per-Protocol (PP) Sample: Randomized subjects who receive the full dose of the study drug before intubation or death. Patients who do not receive the full dose of the study drug will be excluded from the PP population. Subjects who had a major protocol deviation that may impact the validity of the efficacy analysis are excluded from the PP population
- Safety Sample: Randomized subjects who receive any amount of the study drug. Safety analyses will be based on the medication that was actually dispensed to each subject.

The primary analysis for this trial will be the analysis of the mITT population.

A final Statistical Analysis Plan (SAP) is included with this amendment. A Data Management Plan (DMP) is also submitted. All data collected within the trial will be summarized by treatment group for the appropriate analysis population using descriptive statistics, graphs, or raw data listings. Descriptive statistics for continuous variables will include the number of subjects, mean, standard deviation, median, first and third quartiles, minimum and maximum values for the observed value, and change from baseline. Analyses of categorical variables will include calculations of frequencies and percentages.

## ENDPOINTS

### Primary Endpoint:

The primary endpoint is the time from administration of the investigational agent (or placebo) to requiring mechanical ventilation and intubation, or death for subjects who die prior to intubation.

The secondary efficacy endpoints are:

1. Time from administration of the investigational medication (or placebo) to at least one point worsening on the clinical improvement scale (Table 2) for subjects requiring supplemental oxygen (score >= 3) at baseline, or at least two point worsening otherwise (score = 2 at baseline).
2. Time from administration of the investigational agent (or placebo) to absence of the need for supplemental oxygen among those who require at least supplemental oxygen at baseline.

**Table 2: Ordinal Clinical Improvement Scale**

| Clinical Improvement Scale | |
|---|---|
| 1 | Discharged (or "ready for discharge" as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or <= 2L supplemental oxygen) |
| 2 | Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen |
| 3 | Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen |
| 4 | ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen |
| 5 | ICU, requiring intubation and mechanical ventilation |
| 6 | ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g. vasopressors, renal replacement therapy) |
| 7 | Death |

### Tertiary and exploratory endpoints

Additional tertiary endpoints are:

- Time to first improvement from baseline of at least 2 points (or the maximum amount) on the ordinal scale given in Table 2.
- Ordinal Clinical Improvement Scale (Table 2) score at day: 4, 7, 14, 21, and 28.
- Time from initiation of supplemental oxygen to end of supplemental oxygen use during 28-day study follow-up period.
- Time from administration of the investigational agent (or placebo) to death.
- Mortality at 28 days after administration of investigational agent (or placebo).
- Time from administration of the investigational medication (or placebo) to intubation.
- Duration of mechanical ventilation during 28-day study follow-up period.
- ICU admission or death among those not in the ICU at the time of administration of investigational agent (or placebo).
- Time from administration of the investigational medication (or placebo) to hospital discharge.

The change over time for the following exploratory endpoints will be evaluated:

- Biomarkers: ferritin, LDH, CRP, D-dimer, ESR, troponin, NT-proBNP, IL-6, and procalcitonin.
- Cytokine profiling, including rapid IL-6 assessment.
- Clinically relevant inflammatory biomarkers including TREM-1, procalcitonin, and Pro-ADM.
- Measures of cardiac injury (troponin- difference in peak troponin level) and cardiac dysfunction (NTproBNP-difference in peak NTproBNP level).
- Viral titers.
- Cell subsets for functional and transcriptional immunophenotyping.

### Safety Endpoints

The proportion of adverse events graded by CTCAE v5.0 will be evaluated.

## Recruitment Procedures:

Upon admission to the hospital, the study team will determine if the patient meets the eligibility requirements of the study by review of the medical record. The study team will ensure that the patient meets inclusion and exclusion criteria

If the patient is eligible and expresses interest, a member of the study team will contact the primary care team to discuss potential participation. If the primary team agrees to allow the study team to approach the patient, a member of the study team will contact the patient via telephone and will explain the protocol in more detail and answer any questions the patient may have. The member of the study team will reinforce with the patient that he or she does not have to participate and the decision not to participate will not affect his or her care at any time. The patient will be told that should he or she choose to participate, he or she may contact the research team for more information.

If the patient expresses interest, the primary care team will be sent an electronic version of the consent form, which the team will then send to the patient. The patient will be given sufficient time to decide if he or she want to participate in the study. The patient will be encouraged to speak with their other doctors or family members about this study. After an appropriate interval of time, the study team will then call the patient back to ascertain the patient's final decision whether to participate in the study. A healthcare worker not associated with the study will also join the telephone final consent call to serve as an additional witness. A copy of the signed consent will be given to the patient. The study team will follow the PHRC policy on Recruitment of Research Subjects and the Partners IRB's guidance with regard to Consenting in COVID Research that is More than Minimal Risk. No identifiable information will be stored during the pre-screening process except for subjects who are expected to consent to the study. All records of identifiable information will be destroyed if subjects do not consent to the study.

## Consent Procedures:

Subjects may be recruited in the in-patient setting. If the patient is eligible and expresses interest, a member of the study team will contact the primary care team to discuss potential participation. For subjects, enrolled inpatient where the study team is unable to obtain a signed consent form due COVID-19 transmission concerns, investigators may obtain verbal agreement to participate from the subject with attestation and signature of the Witness required.

**In patient consenting: Subjects**

- Consent form provided via email or other electronic means but does not include ability to sign electronically. When sent by email a copy of the email should be retained in the subject file OR Paper consent can be transported to the patient during a clinical team visit to the room.
- Patient reads, has 3- way phone conversation/virtual visit with person consenting and the witness.
- Patient signs the hard copy consent and it is retained in the room. If it is not possible for the patient to physically sign, the patient provides verbal agreement to participate.

**In patient consenting: Study Investigators**

- Conducts consent process via 3-way phone conversation with patient and witness.
    - If the primary team agrees to allow the study team to approach the patient, a member of the study team will contact the patient via telephone and will explain the protocol in more detail and answer any questions the patient may have. The member of the study team will reinforce with the patient that he or she does not have to participate and the decision not to participate will not affect his or her care at any time. The patient will be told that should he or she choose to participate, he or she may contact the research team for more information. If the patient expresses interest, the primary care team will be sent an electronic version of the consent form, which the team will then send to the patient.
- Prints and signs paper consent document as person obtaining consent
- Completes *COVID-19 Attestation/Witness Form noting either the subject signed a separate copy of the consent that was retained in the isolation room, or that the subject consented verbally and the reason preventing subject signature on form.
- Documents in a note to file or in a COVID-19 Informed Consent Checklist that the consent form was provided to the participant, consent was obtained, the method used to obtain consent, date/time, and witness name.
- The *COVID-19 Attestation/Witness Form is stored with the signed consent form in the study record and a copy of the consent form is uploaded to EPIC.

The patient will be given sufficient time to decide if he or she want to participate in the study. The patient will be encouraged to speak with their other doctors or family members about this study. After an appropriate interval of time, the study team will then call the patient back to ascertain the patient's final decision whether or not to participate in the study. A healthcare worker not associated with the study will also join the telephone final consent call to serve as an additional witness. Both the unassociated healthcare worker and the study investigator will sign the consent and that consent will be stored. A copy of the signed consent will be given to the patient.

Consent to participate in the study will be obtained from subjects themselves whenever possible; the use of surrogates for decision-making purposes will be avoided unless absolutely necessary. If a surrogate is required to provide consent for a patient, the same consent process described in the previous section will be utilized. The PHRC preferred order of surrogates will be followed, and the study team will document the relationship of the surrogate to the patient in the research record. A healthcare worker not associated with the study will be also be included here in the conversation as a witness. The surrogate will be asked to sign and return the consent form electronically where after, both will the healthcare worker and the investigator will sign the consent.

**Consent Addendum**
Consent addendum will be discussed and provided to all subjects who test positive for LTBI prior to proceeding with any research activity. Moreover, if a patient is unable to provide informed consent due to their medical condition, then the patient's legally authorized representative will be provided with this Consent Addendum and may provide verbal consent on behalf of the subject. Verbal consent will be obtained.

## Study Procedures

Screening Visit

The following assessments will be completed:

- Informed consent
- Demographics & Medical History/meds
- Review SARS-CoV-2 results
- Physical Exam (by review of the electronic medical record)
- LABs
    - Safety Comprehensive metabolic profile, CBC/diff, ESR, CRP, ferritin, LDH, troponin, NT-proBNP, D-dimer, and procalcitonin
    - Pregnancy test for females of childbearing potential

Screening & Baseline Visit

- Physical Exam (by review of the electronic medical record)
- Randomization
- Administration of study product

    - the patient will be randomized to receive tocilizumab 8 mg/kg x 1 (not to exceed 800 mg) vs placebo at 2:1. Medication will be administered that day. Study investigators will be blinded.
- Vital signs including SpO2
- Clinical data collection
- Medication review
- Adverse events
- Comprehensive metabolic profile, CBC/diff, ESR, CRP, ferritin, LDH, troponin, NT-proBNP, D-dimer, IL-6, and procalcitonin
- Correlative Biomarkers
    - Blood for serum
    - Blood for PBMC
    - Blood for SARS-CoV2 IgM/IgG

Note: Screening and Baseline visits can be combined if all eligibility requirements are met.

**Days 4, 7, 14, 21, and 28**
In person visits, will be limited due to need to minimize contact with SARS-CoV-2 infected subjects to minimize hospital-associated transmission.

- Medication Review
- Adverse Events (daily while hospitalized)
- Vital signs including SpO2
- Clinical data collection
- Comprehensive metabolic profile, CBC/diff, ESR, CRP, ferritin, LDH, troponin, NT-proBNP, D-dimer, and procalcitonin
- Correlative Biomarkers
    - Blood for serum
    - Blood for PBMC
    - Blood for SARS-CoV2 IgM/IgG
      To determine immunologic phenotypic changes during intervention, several endpoints will be collected to include serum for antibodies, cytokine analysis, inflammatory marker analysis as well as cellular fractions for functional and transcriptional immunophenotyping.

As long as subjects are in the hospital, the assessments will proceed according to protocol study timeline with correlative biomarkers collected. However, there will be no outpatient follow-up if subject is discharged prior to day 28. On subjects' discharge day, whenever that is, sites will complete Day 28 assessments.

**Follow Up:**

Sites will complete a 28-day telephone visit after discharge (28 days after randomization) to capture adverse Event and medication review

**Study Drug**

- Tocilizumab (TCZ) will be supplied by the Sponsor as a sterile IV injection for reconstitution in 20-mL glass vials with a 10 mL fill in each (200 mg /10 mL of TCZ). An appropriate number of vials (depending on the patient's bodyweight) of TCZ will be assigned via randomization to each patient for the infusion. The TCZ vials need to be stored at a temperature of 2ºC–8ºC.
- The infusion bag of TCZ should be made up using standard hospital aseptic practice.
- The infusion bag must be made of one of the following materials: Polypropylene, Polyethylene or Polyvinyl chloride.
- The infusion bag of study medication (after it has been prepared using 0.9% saline) may be stored at 2 - 8°C or at room temperature for 24 hours providing that the infusion is prepared aseptically and should be protected from light. Before administration, allow the infusion bag of study medication to return to room temperature over 1 to 2 hours depending on ambient room temperatures.
- TCZ will be administered at room temperature by controlled infusion into a peripheral vein over a 1-hour period. In exceptional cases, this time may be extended to up to 6 hours. A central line is acceptable but please do not mix with other drugs.
- Please refer to protocol section for the management of potential hypersensitivity reaction (including anaphylaxis). If a patient has symptoms of serious hypersensitivity reactions/ anaphylaxis, or requires an interruption of the study drug because of symptoms of hypersensitivity including anaphylaxis, administration of TCZ must be discontinued immediately

TRAINING AND MONITORING OF SITES

Training of Site Investigators and Staff for the Study Protocol

- Site training will be done by Dr. John Stone and the core administrative staff on Zoom. Training will cover the following topics: Introduction to the Study, Study Protocol, Study Recruitment and Consent, Study Drugs, the EDC, Labs, Monitoring and Reporting, and Abnormal Situations. Study coordinators must attend protocol training. Topics that will be covered include protocol details, recruitment, inclusion/exclusion criteria, and EDC training. Sites will also receive additional individualized support while enrolling their first participants in the form of frequent phone calls from Central staff as well as the opportunity to complete the first visits while central staff are on the phone to answer any questions. DCC staff will also be available for personal site training on the EDC as needed and to answer questions as they arise.

- The investigators and all staff involved in the study will have completed their required Collaborative IRB Training Initiative (CITI). Each study staff member will be trained in the protocol and specific procedures for each study visit by the study investigators. New study staff members will be trained on the protocol and, if necessary, spend a visit shadowing another trained staff member before carrying out protocol tasks on their own. Prior to conducting subject visits, investigators will be asked to sign off that the site staff members have been appropriately trained in the study protocol.
- Training and delegation of responsibility will be documented in the Delegation of Responsibility Log and tracked via the trial website (where the training modules will be posted).

Training for Electronic Data Capture

One of the key training modules will focus on use of the EDC. Topics covered will include:

- Appropriate use of credentials to log-in
- EDC security
- Navigating the EDC
- Recording information on the eCRFs
- Screening
- Enrollment and Baseline
- Randomization
- Concomitant Medication
- Follow-up Visits
- Source documentation
- Submitting adverse event reports
- Revising data and audit trails

Additional one-on-one training will be provided to sites on an as-needed basis, as well as guidance for each site to get registered on the EDC.

Monitoring of Sites

- Monitoring will occur throughout the study period. Internal reports will be generated regularly to identify missed visits, missing data, and other data clarifications. Additionally, queries report will be generated by the EDC to identify missing data at the time of visits entry and out of range values. Core staff will periodically request that a site provide additional documentation and regulatory files. This documentation will be mailed, or faxed by the site and reviewed at the Coordinating Center.
- Transitional Medicine group will oversee data monitoring.

- The DCC will be able to track a site's progress via the EDC. Should a site consistently deviate from the protocol or not perform to a sufficient level, the DCC will recommend intervention by the Administrative Core. The Administrative Core will investigate the source of the deviations, and will provide additional training or coaching as needed, as well as decide to drop an enrollment site if necessary.

**Clinical Sites**

Use of the EDC will enable frequent monitoring of study sites to ensure protocol adherence. The DCC will have immediate access to all data that is entered on the EDC, and will be alerted to any issues, including the ones listed below:

- Non-compliance with protocol
- Missing data
- Out-of-range data
- Out-of-window visits

**Power Calculation and Statistical Considerations:**

A full SAP is included with this amendment. All study-collected data will be summarized by treatment group for the appropriate analysis population using descriptive statistics, graphs, and/or raw data listings. Descriptive statistics for continuous variables will include the number of subjects, mean, standard deviation (SD), median, first and third quartiles, minimum and maximum values for the observed value, and change from baseline. Analysis of categorical variables will include frequency and percentage. The baseline value is defined as the last measurement collected prior to the administration of study drug, unless otherwise specified.

The primary endpoint is the rate of requirement for invasive mechanical ventilation. The control group is assumed to have a 30% chance of requiring invasive mechanical ventilation by 28 days, which corresponds to a 70% chance of not requiring mechanical ventilation. Our assumption is that the investigational treatment tocilizumab will increase the likelihood that a patient will not require mechanical ventilation to 85%. At the outset, the target enrollment was 278 patients to achieve 85% power. However, the enrollment rate significantly slowed as the pandemic surge waned in the Boston area, and in early June the decision was made to reduce the target enrollment to 243 (80% power). With a total of 243 subjects (163 randomized to tocilizumab, 80 randomized to standard care), we will have 80% power to demonstrate such a difference, assuming two-sided tests and an alpha of 0.05.

An interim analysis was to be performed when approximately 50% of the subjects had enrolled or approximately 40% of subjects had completed Day 28 or withdrawn prior to Day 28. Both efficacy and futility of the study were to be assessed at the time of the interim analysis. However, due to the rapid study initiation and enrollment, two thirds of the target N had already been enrolled and more than 50% of the subjects had already completed the 28-day follow up at the time of the anticipated interim analysis. Because the anticipated completion of enrollment was only two weeks away at the time of the

DSMB meeting, the interim analysis for efficacy was not conducted. Rather, the DSMB reviewed the accumulated safety events in the first 180 patients enrolled.

## Risks and Discomforts

### Risks Associated with TCZ Use

- **Infection.** Subjects treated with TCZ are at increased risk for developing serious infections that may lead to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, or other opportunistic infections. The overall safety profile of TCZ in GCA subjects (defined in the GiACTA trial) was comparable to the one observed in rheumatoid arthritis (RA) subjects, except that there was an overall higher incidence of infections in GCA subjects relative to RA subjects. The rate of infections was 200.2 per 100 patient-years in the TCZ QW group and 160.2 per 100 patient-years in the TCZ Q2W group, as compared to 156.0 per 100 patient-years in the PBO+26 and 210.2 per 100 patient-years in the PBO+52 groups. The rate of serious infections was 9.7 per 100 patient-years in the TCZ QW group and 4.4 per 100 patient-years in the TCZ Q2W group, as compared to 4.2 per 100 patient-years in the PBO+26 and 12.5 per 100 patient-years in the PBO+52 groups.

- **Hypersensitivity reactions.** Hypersensitivity reactions, including anaphylaxis, have been reported in association with TCZ and anaphylactic events with a fatal outcome have been reported with intravenous (IV) infusion of TCZ. Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of subjects in the 6-month controlled trials of IV TCZ, 0.2% (8 out of 4009) of subjects in the IV all-exposure RA population, 0.7% (8 out of 1068) in the SC 6-month controlled RA trials, and in 0.7% (10 out of 1465) of subjects in the SC all-exposure population. In the systemic juvenile inflammatory arthritis (JIA) controlled trial with IV TCZ, 1 out of 112 subjects (0.9%) experienced hypersensitivity reactions that required treatment discontinuation. In the polyarticular JIA controlled trial with IV TCZ, 0 out of 188 subjects (0%) in the TCZ all-exposure population experienced hypersensitivity reactions that required treatment discontinuation.
- **Neutropenia.** Decreases in neutrophil counts have been observed following treatment with TCZ.
- **Thrombocytopenia.** Decreases in platelet counts have been observed following treatment with TCZ.
- **Elevated liver enzymes.** Transaminase elevations have been observed following treatment with TCZ. These elevations did not result in apparent permanent or clinically evident hepatic injury in clinical trials.

- **Lipid abnormalities.** Increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterols, and/or HDL cholesterol has been observed following treatment with TCZ.
- **Gastrointestinal (GI) perforations.** Events of GI perforation have been reported in clinical trials, primarily as complications of diverticulitis in RA subjects. No GI perforations were reported in GCA clinical trials.
- **Immunosuppression and potential risk of malignancy.** Although no imbalance of malignancies was observed in controlled clinical trials of TCZ, malignancies have been identified as a concern for other immunosuppressive agents.
- **Demyelinating disorders.** The impact of treatment with TCZ on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in clinical studies.
- **Live vaccines.** Vaccination with live vaccines may lead to infection in subjects under immunosuppressive therapy including TCZ.
- **Pregnancy.** The limited available data with TCZ in pregnant women are not sufficient to determine whether there is a drug-associated risk for major birth defects and miscarriage.

Additional information on TCZ safety can be found in the attached **Investigator's Brochure**.

**Risks of Blood Draw**

The total blood draw volume for the study (assuming that a subject is hospitalized for 28 days) is 171 ml (36 teaspoons). This total volume of blood will be drawn over 28 days at the following intervals: baseline, and then on days 4, 7, 14, 21, and 28. If patients are discharged before 28 days, they will not have blood drawn for any visits after leaving the hospital. An additional 10 mL (2 teaspoons) will be collected at baseline amount for subjects undergoing LTBI testing. Attached appendix C for collection timetable.

## SAFETY REPORTING OF ADVERSE EVENTS

ASSESSMENT OF SAFETY

Specification of Safety Variables

- Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious
  adverse events (SAEs) per protocol. This includes all events of death, and any study specific
  issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding),
symptom, or disease temporally associated with the use of an investigational medicinal product
(IMP) or other protocol-imposed intervention, regardless of attribution.
This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with COVID-19 that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if any of the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

- The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

Adverse Event Reporting Period

The study period during which AEs and SAEs as described in section J where the patient has been exposed to Genentech product must be reported Reporting period begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should

only report SAEs that are attributed to prior study treatment (Modify statement depending up on section g).

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the Toclizumab (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

**Yes**

There is a plausible temporal relationship between the onset of the AE and administration of the Toclizumab, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the Toclizumab or with similar treatments; and/or the AE abates or resolves upon discontinuation of the Toclizumab or dose reduction and, if applicable, reappears upon re- challenge.

**No**

Evidence exists that the AE has an etiology other than the Toclizumab (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to Toclizumab administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

For subjects receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

## PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"

- “Have you had any new or changed health problems since you were last here?”

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

**a. Diagnosis vs. Signs and Symptoms**

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

**b. Deaths**

All deaths that occur during the protocol-specified AE reporting period (see Section I), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

**c. Preexisting Medical Conditions**

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

**d. Hospitalizations for Medical or Surgical Procedures**

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

**e. Assessment of Severity of Adverse Events**

The adverse event severity grading scale for the NCI CTCAE v 5.0 Update current versions) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

**Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE**

| Grade | Severity |
|---|---|
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated |
| 2 | Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a] |
| 3 | Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c] |
| 4 | Life-threatening consequences or urgent intervention indicated d |
| 5 | Death related to adverse event [d] |

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE v 5.0 which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by subjects who are not bedridden.
- If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
- Grade 4 and 5 events must be reported as serious adverse events

### f. Pregnancy

If a female subject becomes pregnant while receiving the study drug or within 90 days after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 90days after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

### g. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior Toclizumab exposure.

If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject [add if applicable- including pregnancy occurring in the partner of a male study subject] who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety during follow up period

**h. Case Transmission Verification of Single Case Reports**

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via Toclizumab emailing Genentech a Quarterly line-listing documenting single case reports sent by Toclizumab to Genentech in the preceding time period.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Dr. Stone/Sponsor to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech

**i. AEs of Special Interest (AESIs)**

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with total bilirubin $> 2 \times$ ULN
    - Treatment-emergent ALT or AST $> 3 \times$ ULN in combination with clinical jaundice

- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

The Tocilizumab Events of Special Interest are:

- Serious and/or medically significant infections
- Myocardial infarction/Acute coronary syndrome
- Gastrointestinal perforations
- Malignancies
- Anaphylaxis/Hypersensitvity reactions
- Demyelinating disorders
- Stroke
- Serious and/or medically significant bleeding events
- Serious and/or medically significant hepatic events

**j. Exchange OF SINGLE CASE REPORTS**

*Dr. Stone/Sponsor* will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the Study for the Product.

Investigators must report all the above mentioned single case reports adequately to Genentech within the timelines described below. The completed MedWatch or CIOMS I form or Genentech approved reporting forms should be faxed/emailed immediately upon completion to Genentech at the following contacts:

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints *with* an AE should be sent to:

**Fax: 650-238-6067**
**Email: usds_aereporting-d@gene.com**

All Product Complaints *without* an AE should be sent to:

**Email: kaiseraugst.global_impcomplaint_management@roche.com**

It is understood and agreed that the Sponsor will be responsible for the evaluation of AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study.

These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met.

Serious adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation Reports and Product Complaints (with or without an AE), where the patient has been exposed to the Genentech Product, will be sent on a MedWatch form or CIOMS I form or on Genentech approved reporting forms to Genentech Drug Safety.

Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

- **SAERs**
  Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

- **Other SAEs**
  Serious AE reports that are unrelated to the Product shall be transmitted to Genentech within thirty (30) calendar days of the awareness date.

- **AESIs**
  AESIs shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

- **Special Situation Reports**

  **Pregnancy reports**
  While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

  **Pregnancies in Female Partners of Male Subjects**
  Male subjects will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 30 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

- **Other Special Situation Reports**

  In addition to all SAEs, pregnancy reports and AESIs, the following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within thirty (30) calendar days:
  - Data related to the Product usage during breastfeeding
  - Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
  - In addition, reasonable attempts should be made to obtain and submit the age

or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

- **Product Complaints**

  All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

  A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

## MEDWATCH 3500A REPORTING GUIDELINES

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C & D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

1. Protocol number and title description
2. Description of event, severity, treatment, and outcome if known
3. Supportive laboratory results and diagnostics (Section B.6)
4. Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

1. Additional information may be added to a previously submitted report by any of the following methods:
   a. Adding to the original MedWatch 3500A report and submitting it as follow-up
   b. Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
2. Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at https://www.fda.gov/media/69876/download

Reporting to Regulatory Authorities, Ethics Committees and Investigators

Genentech as the Marketing Authorization Holder will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations.

Dr. Stone / Sponsor as the Sponsor of the Study will be responsible for the expedited reporting of safety reports originating from the study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

Dr. Stone / Sponsor will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

Dr Stone /Sponsor will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

Dr. Stone/ Sponsor will be responsible for the distribution of safety information to Site IRB:

Partners Institutional Review Board

For questions related to safety reporting, please contact Genentech/Roche Drug Safety:
Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

AGGREGATE REPORTS
Development Safety Update Report
Dr. Stone as the Sponsor of the Study, will be responsible for the preparation of their own Development Safety Update Report (DSUR) for the Study and for the submission of the report to the regulatory authorities and Ethics Committees of the concerned Member States, where applicable. Dr. Stone /Sponsor agrees to share a copy of their own DSUR with Genentech as soon as reasonably possible after completion.

Genentech agrees to forward to Dr. Stone/Sponsor an executive summary of the Genentech DSUR upon request. Furthermore, Genentech agrees that Dr. Stone /Sponsor may cross-reference the executive summary of the Genentech/Roche DSUR, as applicable.

Other Reports
Dr. Stone/ Sponsor will forward a copy of the Final Study Report to Genentech/Roche upon completion of the Study.
OR
Dr. Stone /Sponsor will forward a copy of the Publication to Genentech/Roche upon completion of the Study.

RANDOMIZATION CODES FOR BLINDED CLINICAL TRIALS (IF APPLICABLE)
The blind will be broken for ADR reports that are Serious and Unexpected, unless otherwise agreed with applicable regulatory authorities

STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech/Roche. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech/Roche. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

actemra-gsur@gene.com
And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

QUERIES
Queries related to the Study will be answered by Dr. Stone /Sponsor. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech/Roche shall have the final say and control over safety queries relating to the Product. Dr. Stone /Sponsor agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech/Roche.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

SAFETY CRISIS MANAGEMENT
In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech/Roche shall have the final say and control over safety crisis management issues relating to the Product. Dr. Stone /Sponsor agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech/Roche.

<u>Safety Monitoring:</u>
Outcomes will be assessed weekly by an independent Data Safety and Monitoring Board. Endpoints will be assessed for the treatment group compared to the control arm.

<u>Safety Analysis:</u>
The number (percentage) of subjects reporting treatment-emergent AEs and SAEs for each preferred term (PT) will be tabulated by System Organ Class (SOC), by SOC and severity, and by SOC and relationship to study drug. If more than 1 event occurs with the same PT for the same patient, the patient will be counted only once for that PT using the most severe or related occurrence for the summary by severity or relationship to study drug, respectively.

Clinical laboratory values (excluding efficacy laboratory parameters) will be summarized by treatment group, including changes from baseline at each visit.

Vital signs and change from baseline in vital signs will be summarized descriptively at each visit by treatment group.

Genentech
A Member of the Roche Group

**SAFETY REPORTING FAX COVER SHEET**

**Genentech Supported Research**

AE / SAE FAX No: (650) 238-6067

| | |
|---|---|
| Genentech Study Number | |
| Principal Investigator | |
| Site Name | |
| Reporter name | |
| Reporter Telephone # | |
| Reporter Fax # | |

| | |
|---|---|
| Initial Report Date | [DD] / [MON] / [YY] |
| Follow-up Report Date | [DD] / [MON] / [YY] |

Subject Initials

(Enter a dash if patient has no middle name) [ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555
PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Appendix A. Schedule of study related assessments

| | **Screen** | **Baseline** | **Frequency** |
|---|---|---|---|
| **Day +/- Window** | **−1 or 1** | **1** | **Days 4, 7, 14, 21 and 28** (Days 4 & 7, +/- 2 days Days 14,21, & 28, +/- 3 days) |
| **ELIGIBILTY** | | | |
| Informed consent | X | | |
| Demographics & Medical History/meds | X | | |
| Review SARS-CoV-2 results | X | | |
| Physical Exam (taken from chart) [1,5] | X | X | X while hospitalized |
| **STUDY INTERVENTION** | | | |
| Randomization | | X | |
| Administration of study product | | X | |
| **STUDY PROCEDURES** | | | |
| Vital signs including $SpO_2$ | | X[5] | X while hospitalized |
| Clinical data collection[1] | | X[5] | X while hospitalized |
| Medication review | | X[5] | X |
| Adverse events | | X | Daily while hospitalized |
| 28-day telephone visit | | | after discharge (28 days after randomization) |
| **LABs** | | | |
| Safety CMP, CBC/diff, ESR, CRP, ferritin, LDH, troponin, NT-proBNP, D-dimer, and procalcitonin [2] | X[3] | X[3,4] | X[3] |
| IL-6 | | X[3,4] | |
| Pregnancy test for females of childbearing potential | X[3] | | |
| **Correlative Biomarkers** | | | |
| Blood for serum - | | X[5] | X |
| Blood for PBMC | | X[5] | X |
| Blood for SARS-CoV2 IgM/IgG | | X[5] | X |

Notes:

[1]This includes ordinal score, NEWS, oxygen requirement, Mechanical ventilator requirement, etc.

[2]Laboratory tests performed in the 48 hours prior to enrollment will be accepted for determination of eligibility.

[3]Any laboratory tests performed as part of routine clinical care within the specified visit window can be used for safety laboratory testing.

[4,]Baseline assessments should be performed prior to study drug administration

[5]Given limited PPE and highly infectious nature of COVID-19, visits will be performed over the phone, unless requested by the patient.

## References


1. Wu JT, Leung K, Bushman M, et al. Estimating clinical severity of COVID-19 from the transmission dynamics in Wuhan, China. Nature Medicine 2020.
2. Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. The Lancet Infectious Diseases.
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4. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult insubjects with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet.
5. Ramos-Casals M, Brito-Zeron P, Lopez-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet 2014;383:1503-16.
6. Yao XH, Li TY, He ZC, et al. [A pathological report of three COVID-19 cases by minimally invasive autopsies]. Zhonghua Bing Li Xue Za Zhi 2020;49:E009.
7. Seguin A, Galicier L, Boutboul D, Lemiale V, Azoulay E. Pulmonary Involvement in Subjects With Hemophagocytic Lymphohistiocytosis. Chest 2016;149:1294-301.
8. Huang C, Wang Y, Li X, et al. Clinical features of subjects infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020;395:497-506.
9. Xu X, Han, Mingfeng,Li, Tiantian,Sun, Wei,Wang, Dongsheng,Fu, Binqing,Zhou, Yonggang,Zheng, Xiaohu,Yang, Yun,Li, Xiuyong,Zhang, Xiaohua,Pan, Aijun,Wei, Haiming. Effective Treatment of Severe COVID-19 Subjects with Tocilizumab. [ChinaXiv:20200300026] (2020).

## Appendix B: Latent Tuberculosis Risk Assessment during the collection of informed consent

Given the risk of tuberculosis infection in the setting of immunomodulation, the following guidance is made for evaluation of latent and active tuberculosis:

Scenario 1:

1. History: Active tuberculosis highly suspected or diagnosed[1].
2. Testing: Positive microbiology data or concerning radiography including unexplained cavitary disease supporting active tuberculosis infection.
3. Decision:
    - Patient is not eligible for tocilizumab trial.

Scenario 2:

1. History: Patient origin from a highly endemic part of the world. Low risk for active TB by history[1].
2. Testing: None available, no IGRA or testing documented in chart.
3. Decision:
    - Patient to be screened for tuberculosis ideally with IGRA (T-spot or Quantiferon) if not available, use TST[2]
    - Ideally, this testing will be sent before the patient receives the investigational treatment, but treatment with tocilizumab or placebo can proceed while the results of IGRA testing are pending
    - Proceed with enrollment in tocilizumab trial
    - If LTBI testing is positive, the patient will be evaluated for the start of possible treatment for LTBI if that is appropriate in the context of his overall clinical situation. If the clinical situation is not amenable to starting LTBI treatment or if the start of treatment can be reasonably deferred, then the start of LTBI treatment may be deferred until the outpatient setting. Consultation from the Infectious Diseases service will be obtained as needed. If treatment is deferred until discharge, the need for the initiation of LTBI will be conveyed to the subject's outpatient physician at the time of discharge.

Scenario 3:

1. History: Patient origin from a highly endemic part of the world. Low risk for active TB by history[1].
2. Testing: Positive IGRA or testing documented in chart, no treatment documented
3. Decision:
    - Proceed with enrollment in tocilizumab trial
    - The patient will be evaluated for the start of possible treatment for LTBI if that is appropriate in the context of his overall clinical situation. If the clinical situation is not amenable to starting LTBI treatment or if the start of treatment can be reasonably deferred, then the start of LTBI treatment may be deferred until the outpatient setting. Consultation from the Infectious Diseases service will be obtained as needed. If treatment is deferred until discharge, the need for the initiation of LTBI will be conveyed to the subject's outpatient physician at the time of discharge.

Scenario 4:

1. History: Patient origin from a highly endemic part of the world. Low risk for active TB by history[1].
2. Testing: Positive LTBI testing documented in chart, has completed treatment for LTBI
3. Decision:
    - Proceed with enrollment in tocilizumab trial.

**Note**:

[1] History of prolonged duration of symptoms should exceed 1 month. Key points to explore:

- Typical COVID symptoms can be 2-3 weeks.
- Preceding cough before acute symptoms requiring hospitalization
- If COPD, asthmatic, bronchiectasis, was the preceding cough different from baseline
- If history > 1 month, suspicion should be made for non-COVID respiratory process including tuberculosis.

[2] At MGH, T-spot can be sent 24/7 except for during holidays and the day before holidays in which case Quantiferon can be sent. Please adjust to your site specifics.

## SUMMARY OF PROTOCOL CHANGES

- Additional language about compliance included in the final protocol
- Additional details about adverse event reporting included in the final Protocol
- Information about new trial sites added over the course of the trial
- Entry criteria broadened by modification of some inclusion criteria and elimination of some exclusion criteria
- Detailed discussion of plans for the analysis of endpoints provided in the final protocol. Final Statistical Analysis Plan submitted with the final protocol version
- Clarification that among multiple endpoints listed as secondary endpoints in the original protocol, only two were designated specifically as secondary endpoints. The remainder of the endpoints were identified as either tertiary or exploratory endpoints in the final protocol
- Clarification of the Ordinal Scale to be used for the assessment of certain secondary endpoints provided in the final protocol
- Details about the management of patients with latent tuberculosis provided in the final protocol (Appendix B)

## Appendix C: Timetable of research specimen collection with matrix

| Specimen | | Swab | Plasma | Serum | Blood RNA | PBMC |
|---|---|---|---|---|---|---|
| Vessel/Tube | | Nasal Swab and Oropharyngeal Swab (do not use NP) | EDTA Lavendar Top | 1x SST Red/Gray Top (or 2x SST Gold Top) | BD PaxGene Blood RNA tube | BD Vacutainer™ CPT™ Mononuclear Cell Preparation Tube |
| Image | |  |  |  |  |  |
| Whole Blood Volume (ml) | | - | 8 | 10 | 2.5 | 8 |
| Timeline (day) | 1* | x | x | x | x | x |
| | 4 | | x | x | x | x |
| | 7 | x | x | x | x | x |
| | 14 | | x | x | x | x |
| | 21 | | x | x | x | x |
| | 28 | x | x | x | x | x |
| # of Timepoints | | 3 | 6 | 6 | 6 | 6 |
| Total Blood (ml) /specimen | | 0 | 48 | 60 | 15 | 48 |
| Total Blood (ml) for entire study | | 171 | | | | |

*Day 1 blood draw prior to infusion is mandatory. In subsequent time points (days 4, 7, 14, 21, and 28), if blood draw difficult, attempt following day.

INITIAL STATISTICAL ANALYSIS PLAN

**Statistical analysis plan (June 9, 2020)**

The following analysis populations are defined for the different types of data analysis:

- Intent-to-Treat (ITT) Population: all randomized subjects.
- Modified Intent-to-Treat (mITT) Population: all randomized subjects who receive any amount of the study drug before intubation or death.
- Per-Protocol (PP) Population: all randomized subjects who receive the full dose of the study drug before intubation or death. Patients who do not receive the full dose of the study drug will be excluded from the PP population.
- Safety Population: all randomized subjects who receive study drug. (The Safety Population is identical to the mITT).

The primary analysis for this trial will be the analysis of the mITT population.
All data collected within the trial will be summarized by treatment group for the appropriate analysis population using descriptive statistics, graphs, or raw data listings. Descriptive statistics for continuous variables will include the number of subjects, mean, standard deviation, median, first and third quartiles, minimum and maximum values for the observed value, and change from baseline. Analyses of categorical variables will include calculations of frequencies and percentages.

**Primary Endpoints:**

The primary endpoint is the time to mechanical ventilation or death. The time to event will be the time from administration of the investigational agent (or from randomization if the investigational agent was not administered) to the time of initiation of mechanical ventilation for subjects who are intubated and the time of death for subjects who die prior to intubation. All subjects who do not have either event by the end of the follow-up period will be censored at 28 days. The treatment groups will be compared used a log-rank test stratified by study site, and the p-value from the log-rank test will be the primary p-value. The difference between the treatment groups will be estimated using the hazard ratio from a stratified Cox proportional hazards model. The type I error rate for this study will be 0.05, and the primary outcome will be tested at this level since there are no interim analyses. The 95% confidence interval for the hazard ratio will be reported in addition to the P-value.

**Secondary Endpoints:**

1) Time to improvement. Time to improvement will be assessed by changes in subjects' status, ranked on the ordinal scale shown in Table 1. Time to improvement will be measured from baseline to improvement of 2 points or more. Subjects who die during the trial will not be censored at the time of death. Rather, these subjects will be censored at the end of the study to indicate that they did not have an improvement event by the end of the study. If subjects improve initially but then die, the improvement will not be considered in the analysis. The groups will be compared using a log-rank test

stratified on study site. The hazard ratio comparing the groups will be estimated using a stratified Cox proportional hazards model.

Table 1: Ordinal Clinical Improvement Scale

| Clinical Improvement Scale | |
|---|---|
| 1 | Discharged (or "ready for discharge" as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or <= 2L supplemental oxygen) |
| 2 | Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen |
| 3 | Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen |
| 4 | ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen |
| 5 | ICU, requiring intubation and mechanical ventilation |
| 6 | ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g. vasopressors, renal replacement therapy) |
| 7 | Death |

2) Time to progression to non-invasive ventilation or high-flow oxygen, defined as >6L. Time to progression will be measured from the time the investigational medication is administered until the time of progression to non-invasive ventilation or high-flow oxygen. We will compare the groups using a stratified log-rank test and estimate the hazard ratio comparing the groups using a stratified Cox proportional hazards model.
3) The raw ordinal scale scores at days 4, 7, 14, 21, and 28 in subjects treated with tocilizumab therapy versus controls will be compared at each time point using a random intercept proportional odds logistic regression model. This model will be used to model all measurements together to estimate the differences between the treatment groups at each time point. This model will include a fixed effect for time, treatment group, time by treatment group interaction, study site and the study site by time interaction. The parameters of interest will be the time by treatment interaction terms which will equal the difference in the change with time comparing the treatment groups.
4) Time to absence of the need for supplemental oxygen. Time to absence of the need for supplemental oxygen will be measured from time of investigational treatment administration. We will use the same approach as that employed for the comparison of time to clinical improvement. Only subjects on supplemental oxygen at the time of randomization will contribute to this analysis. Subjects who die will be censored at 29 days, and the groups will be compared using a stratified log-rank test and stratified Cox proportional hazards model.
5) Duration of supplemental oxygen. The duration of supplemental oxygen will be compared between the groups. For this analysis, we will include all subjects in the analysis by assigning all subjects who did not receive supplemental oxygen a value of 0. Subjects who died following supplemental

oxygen will be given a value of the number of days from when supplemental oxygen began until the end of the follow-up period. The groups will be compared using a Wilcoxon rank sum test.

6) Time to improvement in NEWS2 score to ≤ 2 or discharge from the hospital. For time to improvement in the NEWS2 score to ≤ 2 or discharge from the hospital, we will use the same approach as time to clinical improvement. Subjects who die will be censored at the end of the study to indicate that they did not have an improvement event by the end of the study. The groups will be compared using a stratified log-rank test and stratified Cox proportional hazards model.
7) Time to death. Time to death will be measured from the time the investigational medication is administered until the time of the subject's death. We will compare the groups using a stratified log-rank test and estimate the hazard ratio comparing the groups using a stratified Cox proportional hazards model.
8) Mortality at 28 days. Mortality at 28 days will be compared using a Mantel-Haenszel test to allow stratification on study site. The relative risk will be estimated using the Mantel-Haenszel method. If we have missing mortality data on any subjects, we will estimate the proportion of subjects who died in each treatment group using the estimate from the Kaplan-Meier curve in each group. Then, we will compare the two groups using the approaches described in Klein et al (citation: Klein JP, Logan B, Harhoff M, Anderson PK. Analyzing survival curves at a fixed point in time. Statistics in Medicine. 2007;26:4505–4519.)
9) Time to intubation. Time to intubation will be measured from time of investigational treatment administration to the time of intubation. For this analysis, death will be treated as a competing risk. The analysis will compare the cause-specific hazard in the treatment groups using a Cox proportional hazards model. We will also compare the cumulative incidence functions between groups using the approach of Fine and Gray.
10) Duration of mechanical ventilation. The duration of mechanical ventilation will be compared between the groups using two approaches. First, we will include all subjects in the analysis by assigning all subjects who were not intubated a value of 0. Subjects who died following intubation will be given a value of the number of days from when mechanical ventilation began until the end of the follow-up period. The groups will be compared using a Wilcoxon rank sum test. Second, we will analyze only subjects who were intubated and compare the time on mechanical ventilation using a stratified log-rank test. Subjects who die without being taken off the ventilator will be censored at a duration of mechanical ventilation longer than the longest time.
11) The proportion of subjects requiring ICU admission between baseline and 28 days will be measured as the number of subjects requiring ICU admission over their hospitalization over the number of evaluable subjects (i.e., the number of subjects not in the ICU at the time of investigational treatment administration). The groups will be compared using a Mantel-Haenszel test

to allow stratification on study site. The relative risk will be estimated using the Mantel-Haenszel method.

12) Safety and tolerability, defined as adverse events graded by CTCAE v5.0, will be compared using a Mantel-Haenszel test to allow stratification on study site. The relative risk will be estimated using the Mantel-Haenszel method.
13) The time to discharge from the hospital in subjects, measured from the time of investigational treatment administration to time of discharge, will be compared using a stratified log-rank test. Subjects who die will be censored at Day 29 to indicate that they never left the hospital during the study.
14) The time to requiring inotropes and/or vasopressors will be compared using a stratified log-rank test and estimate the hazard ratio comparing the groups using a stratified Cox proportional hazards model.

**Exploratory Endpoints**

- We will estimate the change over time in nine biomarkers (ferritin, LDH, CRP, D-dimer, ESR, troponin, NT-proBNP, IL-6, and procalcitonin) using a linear mixed effects model with an unstructured covariance matrix, a fixed effect for time, treatment group, time by treatment group interaction, study site and the study site by time interaction. The parameters of interest will be the time by treatment interaction terms which will equal the difference in the change with time comparing the treatment groups.
- We will estimate the change over time in cytokine profiling, including rapid IL-6 assessment, using a linear mixed effects model with an unstructured covariance matrix, a fixed effect for time, treatment group, time by treatment group interaction, study site and the study site by time interaction. The parameters of interest will be the time by treatment interaction terms which will equal the difference in the change with time comparing the treatment groups.
- We will estimate the change over time in clinically relevant inflammatory biomarkers including TREM-1, procalcitonin, and Pro-ADM using a linear mixed effects model with an unstructured covariance matrix, a fixed effect for time, treatment group, time by treatment group interaction, study site and the study site by time interaction. The parameters of interest will be the time by treatment interaction terms which will equal the difference in the change with time comparing the treatment groups.
- We will estimate the change over time in measures of cardiac injury (troponin-difference in peak troponin level) and cardiac dysfunction (NTproBNP-difference in peak NTproBNP level) using a linear mixed effects model with an unstructured covariance matrix, a fixed effect for time, treatment group, time by treatment group interaction, study site and the study site by time interaction. The parameters of interest will be the time by treatment interaction terms which will equal the difference in the change with time comparing the treatment groups. We will also compare the time to serious cardiac arrhythmias between the treatment groups using a stratified log-rank test.

- We will estimate the change over time in viral titers using a linear mixed effects model with an unstructured covariance matrix, a fixed effect for time, treatment group, time by treatment group interaction, study site and the study site by time interaction. The parameters of interest will be the time by treatment interaction terms which will equal the difference in the change with time comparing the treatment groups.
- We will estimate the change over time in cell subsets for functional and transcriptional immunophenotyping using a linear mixed effects model with an unstructured covariance matrix, a fixed effect for time, treatment group, time by treatment group interaction, study site and the study site by time interaction. The parameters of interest will be the time by treatment interaction terms which will equal the difference in the change with time comparing the treatment groups.

FINAL STATISTICAL ANALYSIS PLAN

**Statistical analysis plan**

| | |
|---|---|
| **Principal Investigator:** | John Stone, MD, MPH |
| **Protocol Number and Title:** | 2020P001159<br>Tocilizumab to Prevent the Progression of Hypoxemic Respiratory Failure in Hospitalized Non-Critically Ill Patients with COVID-19 |
| **Protocol Version and Date:** | Version 4.0, 18 August 2020 |
| **Author(s):** | Nora Horick, Principal Biostatistician<br>Brian Healy, Biostatistician<br>Andrea Foulkes, Senior Biostatistician |
| **SAP Version:** | Version 1.0 |
| **SAP Version Date:** | 18 August 2020 |

## Revision History

| **Version #** | **Date** (dd-mmm-yyyy) | **Document Owner** | **Revision Summary** |
|---|---|---|---|
| Version 1.0 | 18-Aug-2020 | Nora Horick | Initial Release Version |
| | | | |
| | | | |
| | | | |
| | | | |

**Signature**

I confirm that I have reviewed this document and agree with the content.

| APPROVALS | |
|---|---|
| | |
| Nora Horick, MS<br>Principal Biostatistician | **Date (dd-Mmm-yyyy)** |
| Andrea Foulkes, ScD<br>Senior Biostatistician | **Date (dd-Mmm-yyyy)** |
| | |
| John Stone, MD, MPH<br>Principal Investigator | **Date (dd-Mmm-yyyy)** |

**Table of Contents**

## STUDY DESIGN AND CONDUCT

### Overview

As of April 2020, COVID-19 had been confirmed in more than 1 million people worldwide, with an estimated symptomatic case fatality ratio of around 1.4%. [1,2] There remains an urgent need for effective treatment to curtail the rate of respiratory failure, the leading cause of mortality in COVID-19 disease. With increasing numbers of patients requiring intensive unit level care and mechanical ventilation, some nations are having to triage patients for ventilatory support due to limited resources and healthcare systems around the world being stretched to the point of collapse, identifying interventions that could prevent the development of respiratory failure for these patients is critical.

Clinical data suggest an immunologic link between COVID-19 and immune dysregulation resulting in macrophage activation syndrome (MAS). Clinical trials are already underway studying the role of immunomodulatory therapy including modulation of IL-1 and IL-6 and downstream pathways in the setting of CAR-T induced MAS (NCT04150913, NCT04071366) and agents such anakinra and tocilizumab have been used in this context with promising results and good safety profiles. Based on the MGH experience thus far with COVID-19, the need for mechanical ventilation has been approximately 30%. We propose a trial of IL-6 receptor blockade with tocilizumab given early in disease course to try to prevent progression of COVID-19.

This is a prospective placebo-controlled, blinded, randomized controlled trial at seven Boston area hospitals: the MGH, the Brigham & Women's Hospital, North Shore Medical Center, Newton-Wellesley Hospital, Boston Medical Center, the Lahey Hospital and Medical Center, and St. Elizabeth's Hospital.

### Study Objectives

The objective of the study is to determine whether the use of early tocilizumab can decrease progression of COVID-19 associated respiratory failure and death.

### Study Population

Study eligibility and exclusion criteria are provided in **Table 1**.

**Table 1: Study participant inclusion and exclusion criteria**

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| 1. Age > 18 and < 86 years old<br>2. Male or female gender<br>3. Confirmed SARS-CoV-2 infection by nasopharyngeal swab PCR or serum assay for IgM antibody<br>4. Requiring hospital but not mechanical ventilation, with oxygen supplementation not greater than 10L delivered by any device | 1. Unable to provide verbal informed consent or have verbal agreement to participate through attestation and signature of a Witness required, as outlined in the Partners IRB's Table for Consenting in COVID Research that is More than Minimal Risk.<br>2. Patients between the ages of 79 and 86 will be excluded if they have NYHA Class III/IV heart failure, |

| | |
|---|---|
| 5. Evidence of severe COVID-19 (at least 2 of the following):<br>• Fever > 38C within 72 hours<br>• Pulmonary infiltrate on chest X ray<br>• Need for supplemental O2 to maintain saturation > 92%<br>*AND at least 1 of the following*:<br>• Ferritin > 500 ng/ml<br>• CRP > 50 mg/L<br>• LDH >250 U/L<br>• D-dimer > 1000 ng/mL | insulin-dependent diabetes mellitus, angina, or treatment of a malignancy (excluding non-melanoma skin cancer) within six months<br>3. Uncontrolled bacterial, fungal, or non-COVID viral infection<br>4. Active tuberculosis<br>5. Any prior investigational immunosuppressive therapy within 28-days or 3 half-lives of the agent (for instance with biologic or JAK inhibitor)<br>6. Any concurrent immunosuppressive medication that the PI believes would put the patient at higher risk<br>7. Receipt of intravenous tocilizumab for the treatment of a non-COVID condition within three weeks of the first COVID symptom<br>8. History of hypersensitivity to tocilizumab<br>9. Any concurrent immunosuppressive medication that the PI believes would put the patient at higher risk<br>10. Treatment with other biologic or small-molecule immunosuppressive therapy such as IL1R-antagonism, JAK inhibition, or other agents.<br>11. Treatment with convalescent plasma<br>12. History of diverticulitis or bowel perforation<br>13. ANC <500, Platelets <50,000<br>14. AST/ALT > 5X ULN<br>15. Women who are pregnant or planning to get pregnant in the next 90 days |

## Treatment Allocation and Concealment

Individuals determined eligible based on the study inclusion and exclusion criteria are randomized to receive tocilizumab 8 mg/kg x 1 (not to exceed 800 mg) vs placebo in a 2:1 randomization ratio using randomly permuted blocks of size 3 and 6. Randomizations are stratified by study site.

The randomization schedule is generated using Sealed Envelope, a web-based randomization service, by the unblinded study Biostatistician. The randomization schedule is provided to the research pharmacist designated for the study in each trial center. The research pharmacist prepares the study drug for infusion on the day of dosing based on the randomization schedule and labels the infusion bag with the subject number

but no treatment assignment information. The investigators, study coordinators, study subjects are blinded to the treatment assignment and do not have access to the randomization schedule.

The unblinded treatment information can be provided to the DSMB to facilitate the evaluation of any clinically important increase in the rate of a serious suspected adverse reaction when the treatment information is required to determine if an expedited safety report must be submitted to regulatory agencies. The unblinded biostatistician would provide the treatment assignment of that subject.

If knowledge of the study drug ingredients is needed to manage the subject's condition, the investigator may contact the research pharmacist at the site to obtain the treatment assignment. In the event of an unblinding request, Dr. Stone will also be notified before unblinding is performed. If unblinding occurs for any reason, the time and reason for breaking the blind will be recorded. The number of patients unblinded by arm will be reported.

The unblinded statisticians may review clinical data and identify missing data fields and forward the issues to the study team to facilitate DSMB review. The unblinded statistician may also provide findings on data that are inconsistent across various Case Report Forms. These findings are to be forwarded to the clinical data monitor for query issuance and resolution. The unblinded biostatisticians do not discuss any results or other information that may inadvertently unblind the study team until the database is locked and treatment assignments are unblinded.

### Responsibilities

Dr. John Stone and colleagues have designed the study protocol. Dr. Stone is responsible for the conduct of the trial. The Data Coordinating Center (DCC) is managed by Ana Fernandes and Dr. Naomi Serling-Boyd in collaboration with the MGH Biostatistics Center. Nora Horick, MS and Brian Healy, PhD, are the unblinded Biostatisticians. Andrea Foulkes, PhD is the blinded Biostatistician for the trial. The DCC and the MGH Biostatistics Center are responsible for the oversight of data collection and analysis. The responsibilities of the DCC include:

1. Development and implementation of the data flow, schedules for transferring data from sites, and data tracking;
2. Development of procedures for data entry, error identification, and error correction;
3. Adverse event monitoring and reporting to the DSMB;
4. Site monitoring via Electronic Data Capture (EDC) to ensure adherence to the protocol and procedures;
5. Quality control procedures;
6. Creating reports - enrollment, adverse events, participant status (e.g., withdrawals) by site; and
7. Trial data analysis

### Timing of Statistical Analyses

The final analysis of safety and efficacy endpoints will be conducted when 1) randomization is complete; 2) all randomized subjects have completed treatment, withdrawn from the study, or died; and 3) and all surviving randomized subjects have completed the 28-day study follow-up.

## STUDY ENDPOINTS

### Efficacy endpoints

The primary endpoint is the time from administration of the investigational agent (or placebo) to requiring mechanical ventilation and intubation, or death for subjects who die prior to intubation.

The secondary efficacy endpoints are:

3. Time from administration of the investigational medication (or placebo) to at least one point worsening on the clinical improvement scale (Table 2) for subjects requiring supplemental oxygen (score >= 3) at baseline, or at least two point worsening otherwise (score = 2 at baseline).
4. Time from administration of the investigational agent (or placebo) to absence of the need for supplemental oxygen among those who require at least supplemental oxygen at baseline.

**Table 2: Ordinal Clinical Improvement Scale**

| Clinical Improvement Scale | |
|---|---|
| 1 | Discharged (or "ready for discharge" as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or <= 2L supplemental oxygen) |
| 2 | Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen |
| 3 | Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen |
| 4 | ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen |
| 5 | ICU, requiring intubation and mechanical ventilation |
| 6 | ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g. vasopressors, renal replacement therapy) |
| 7 | Death |

### Tertiary and exploratory endpoints

Additional tertiary endpoints are:

- Time to first improvement from baseline of at least 2 points (or the maximum amount) on the ordinal scale given in Table 2.
- Ordinal Clinical Improvement Scale (Table 2) score at day: 4, 7, 14, 21, and 28.
- Time from initiation of supplemental oxygen to end of supplemental oxygen use during 28-day study follow-up period.
- Time from administration of the investigational agent (or placebo) to death.
- Mortality at 28 days after administration of investigational agent (or placebo).
- Time from administration of the investigational medication (or placebo) to intubation.
- Duration of mechanical ventilation during 28-day study follow-up period.
- ICU admission or death among those not in the ICU at the time of administration of investigational agent (or placebo).
- Time from administration of the investigational medication (or placebo) to hospital discharge.

The change over time for the following exploratory endpoints will be evaluated:

- Biomarkers: ferritin, LDH, CRP, D-dimer, ESR, troponin, NT-proBNP, IL-6, and procalcitonin.
- Cytokine profiling, including rapid IL-6 assessment.
- Clinically relevant inflammatory biomarkers including TREM-1, procalcitonin, and Pro-ADM.
- Measures of cardiac injury (troponin- difference in peak troponin level) and cardiac dysfunction (NTproBNP-difference in peak NTproBNP level).
- Viral titers.
- Cell subsets for functional and transcriptional immunophenotyping.

### Safety Endpoints

The proportion of adverse events graded by CTCAE v5.0 will be evaluated.

## SAMPLE SIZE DETERMINATION

The primary endpoint is the rate of requirement for invasive mechanical ventilation. The control group is assumed to have a 30% chance of requiring invasive mechanical ventilation by 28 days, which corresponds to a 70% chance of not requiring mechanical ventilation. Our assumption is that the investigational treatment tocilizumab will increase the likelihood that a patient will not require mechanical ventilation to 85%. With a total of 278 subjects (185 randomized to tocilizumab, 93 randomized to standard care), we will have 85% power to demonstrate such a difference, assuming two-sided tests and an alpha of 0.05. With a total of 243 subjects (163 randomized to tocilizumab, 80 randomized to standard care), we will have 80% power to demonstrate such a difference, assuming two-sided tests and an alpha of 0.05. At the outset, the target enrollment was 278 patients

to achieve 85% power. However, the enrollment rate significantly slowed as the pandemic surge waned in the Boston area, and in early June the decision was made to reduce the target enrollment to 243 (80% power) and the protocol was amended to reflect this change.

An interim analysis was to be performed when approximately 50% of the subjects had enrolled or approximately 40% of subjects had completed Day 28 or withdrawn prior to Day 28. Both efficacy and futility of the study were to be assessed at the time of the interim analysis. However, due to the rapid study initiation and enrollment, two thirds of the target N had already been enrolled and more than 50% of the subjects had already completed the 28-day follow up at the time of the anticipated interim analysis. Because the anticipated completion of enrollment was only two weeks away at the time of the DSMB meeting, the interim analysis for efficacy was not conducted. Rather, the DSMB reviewed the accumulated safety events in the first 180 patients enrolled. This change of conduct is described in the protocol amendment.

## GENERAL STATISTICAL CONSIDERATIONS

### Statistical Software

All statistical analyses will be performed using SAS (SAS Institute, NC, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

### Analysis Population

The following analysis samples are defined for safety and efficacy analysis:

- Intent-to-Treat (ITT) Sample: Subjects who are randomized regardless of treatment adherence or availability of follow-up data will be included in the intention-to-treat analysis set (ITT). All analyses of the ITT will be based on each subject's randomized treatment assignment.
- Modified Intent-to-Treat (mITT) Sample: Randomized subjects who receive any amount of the study drug before intubation or death.
- Per-Protocol (PP) Sample: Randomized subjects who receive the full dose of the study drug before intubation or death. Patients who do not receive the full dose of the study drug will be excluded from the PP population. Subjects who had a major protocol deviation that may impact the validity of the efficacy analysis are excluded from the PP population
- Safety Sample: Randomized subjects who receive any amount of the study drug. Safety analyses will be based on the medication that was actually dispensed to each subject.

The primary efficacy analysis and summary level tables on patient characterisitics will be based on the mITT sample.

### Subject Disposition

Subject disposition data will be listed. A disposition table will present, by treatment arm and overall, the number and/or percentage of subjects who signed the informed consent

and entered the study (i.e., were screened, screen failed and randomized), completed study drug administration, withdrew from the study, completed the study, and discontinued treatment after randomization. The reasons for early withdrawal after randomization will be summarized.

Assignment to the analysis sets (ITT, mITT, PP and Safety) will be summarized.

### Demographic and Baseline Characteristics

Baseline characteristics including pre-existing conditions, medications and demographic information will be summarized by treatment group using descriptive statistics and visual displays. Descriptive statistics for continuous variables will include the number of subjects, mean, standard deviation, median, first and third quartiles, minimum and maximum values for the observed value, and change from baseline. Analyses of categorical variables will include calculations of frequencies and percentages.

### Transformations

Continuous data that are strongly rightward skewed (skewness greater than 3) will be log transformed prior to analysis.

### Multiplicity Adjustments

A single primary analysis is planned and the criterion for statistical significance will control the type-1 error rate at a level of 0.05. Testing of secondary efficacy endpoints will be performed using a Bonferroni-Holm correction to ensure an overall two-sided type 1 error rate of less than 0.05. Nominal p-values will also be reported. No correction for multiple comparisons will be used for the tertiary and exploratory analyses.

### Missing Data

If a participant is lost to follow-up prior to 28 days, all time-to-event outcomes will be censored at the time of last contact. Date and time will be used to define event times whenever it is possible to do so without imputing the time value; otherwise only dates will be used.

### Stratification

All analyses will be stratified by site and a combined treatment effect will be estimated. If a study site has low enrollment (<12 individuals) then data on this site will be combined with the smallest site with at least 12 individuals prior to stratified analysis.

### Re-admission

Data collected during re-admissions occurring within the 28-day study period will be used to define outcome variables.

## EFFICACY ANALYSIS

### Primary and secondary endpoints

Primary endpoint: time from administration of the investigational agent (or placebo) to requiring mechanical ventilation and intubation, or death for subjects who die prior to

intubation. The treatment groups will be compared using a log-rank test stratified by study site, and the p-value from the log-rank test will be the primary p-value. Subjects who do not have either event by the end of the follow-up period will be censored at 28 days. Subjects missing 28 day follow-up will be censored at last contact. The difference between the treatment groups will be estimated using the hazard ratio from a stratified Cox proportional hazards model. The type I error rate for this study will be 0.05, and the primary outcome will be tested at this level. The 95% confidence interval for the hazard ratio will be reported in addition to the p-value.

Secondary endpoint: Time from administration of the investigational medication (or placebo) to at least one point worsening on the clinical improvement scale (Table 2) for subjects requiring supplemental oxygen (score >= 3) at baseline, or at least two point worsening otherwise (score = 2). We will compare the groups using a stratified log-rank test and estimate the hazard ratio comparing the groups using a stratified Cox proportional hazards model. This composite endpoint based on the clinical ordinal scale given in Table 2 is defined as: a) time to progressing to a score of 4-7 for individuals who start with a score of 2 or 3; or b) progressing to a score of 5-7 for individuals starting with a score of 4.

Secondary endpoint: Time from administration of the investigational agent (or placebo) to absence of the need for supplemental oxygen among those who require at least supplemental oxygen at baseline. Time to absence of the need for supplemental oxygen will be measured from time of investigational treatment administration. Only subjects on supplemental oxygen at the time of randomization will contribute to this analysis. The groups will be compared using a stratified log-rank test and stratified Cox proportional hazards model and subjects who die prior to reaching this endpoint, including subjects whom supplemental oxygen was discontinued as a part of comfort measures preceding death, will be censored at 29 days.

### Tertiary and exploratory endpoints

Time to first improvement from administration of the investigational agent (or placebo) of at least 2 points (or the maximum amount) on the ordinal scale given in Table 2. Time to improvement will be assessed by changes in subject status, ranked on the ordinal scale shown in Table 2. Time to improvement will be measured from administration of the investigational agent (or placebo) to improvement of 2 points or more. Subjects who die prior to reaching this endpoint will be censored at 29 days. The groups will be compared using a log-rank test stratified on study site. The hazard ratio comparing the groups will be estimated using a stratified Cox proportional hazards model.

Ordinal Clinical Improvement Scale (Table 2) score at day: 4, 7, 14, 21, and 28. The raw ordinal scale scores at days 4, 7, 14, 21, and 28 in subjects treated with the investigational agent vs. placebo will be compared at each time point using a random intercept proportional odds logistic regression model. This model will be used to model all measurements together to estimate the differences between the treatment groups at each time point. This model will include a fixed effect for time, treatment group, time by treatment group interaction, and study site. The parameter of interest will be the time by treatment interaction term which will equal the difference in the change with time

comparing the treatment groups. Ordinal scale score at discharge will be carried forward following discharge to reflect that the subject remained discharged and recalculated if needed to reflect post-discharge re-hospitalization or death.

Time from initiation of supplemental oxygen to end of supplemental oxygen use during 28-day study follow-up period. The duration of supplemental oxygen will be compared between the groups. For this analysis, we will include all subjects in the analysis by assigning all subjects who did not receive supplemental oxygen a value of 0. Subjects who died prior to discontinuation of supplemental oxygen or for whom supplemental oxygen was discontinued as a part of comfort measures preceding death will be given a value of the number of days from when supplemental oxygen began until the end of the follow-up period. The groups will be compared using a stratified Wilcoxon rank sum test.

Time from administration of the investigational agent (or placebo) to death. Time to death will be measured from the time the investigational medication is administered until the time of the subject's death. The groups will be compared using a stratified log-rank test and a stratified Cox proportional hazards model will be used to estimate the hazard ratio comparing the groups.

Mortality at 28 days after administration of investigational agent (or placebo). Mortality at 28 days will be compared using a Mantel-Haenszel test to allow stratification on study site. The relative risk will be estimated using the Mantel-Haenszel method. If we have missing mortality data on any subjects, we will estimate the proportion of subjects who died in each treatment group using the estimate from the Kaplan-Meier curve in each group. Then, we will compare the two groups using the approaches described in Klein et al. (citation: Klein JP, Logan B, Harhoff M, Anderson PK. Analyzing survival curves at a fixed point in time. Statistics in Medicine. 2007;26:4505–4519.)

Time from administration of the investigational medication (or placebo) to intubation. Time to intubation will be measured from time of investigational treatment administration to the time of intubation. For this analysis, death will be treated as a competing risk. The analysis will compare the cause-specific hazard in the treatment groups using a Cox proportional hazards model. We will also compare the cumulative incidence functions between groups using the approach of Fine and Gray.

Time from initiation of mechanical ventilation to end of mechanical ventilation during 28-day study follow-up period. The duration of mechanical ventilation will be compared between the groups using two approaches. First, we will include all subjects in the analysis by assigning all subjects who were not intubated a value of 0. Subjects who died following intubation will be given a value of the number of days from when mechanical ventilation began until the end of the follow-up period. The groups will be compared using a stratified Wilcoxon rank sum test. Second, we will analyze only subjects who were intubated and compare the time on mechanical ventilation using a stratified log-rank test. Subjects who die without being taken off the ventilator will be censored at a duration of mechanical ventilation longer than the longest time.

ICU admission or death among those not in the ICU at the time of administration of investigational agent (or placebo). The proportion of subjects who require ICU admission or die between baseline and 28 days will be measured as the number of subjects who require ICU admission during their hospitalization or die over the number of evaluable subjects (i.e., the number of subjects not in the ICU at the time of investigational treatment administration). The groups will be compared using a Mantel-Haenszel test to allow

stratification on study site. The relative risk will be estimated using the Mantel-Haenszel method.

Time from administration of the investigational medication (or placebo) to initial hospital discharge. The time to initial discharge from the hospital in subjects, measured from the time of investigational treatment administration to time of discharge, will be compared using a stratified log-rank test. Subjects who die prior to reaching this endpoint will be censored at 29 days.

Exploratory endpoints:

We will estimate the change over time in nine biomarkers (ferritin, LDH, CRP, D-dimer, ESR, troponin, NT-proBNP, IL-6, and procalcitonin) using a linear mixed effects model with an unstructured covariance matrix, a fixed effect for time, treatment group, time by treatment group interaction, study site and the study site by time interaction. The parameters of interest will be the time by treatment interaction terms which will equal the difference in the change with time comparing the treatment groups.

We will estimate the change over time in cytokine profiling, including rapid IL-6 assessment, using a linear mixed effects model with an unstructured covariance matrix, a fixed effect for time, treatment group, time by treatment group interaction, study site and the study site by time interaction. The parameters of interest will be the time by treatment interaction terms which will equal the difference in the change with time comparing the treatment groups.

We will estimate the change over time in clinically relevant inflammatory biomarkers including TREM-1, procalcitonin, and Pro-ADM using a linear mixed effects model with an unstructured covariance matrix, a fixed effect for time, treatment group, time by treatment group interaction, study site and the study site by time interaction. The parameters of interest will be the time by treatment interaction terms which will equal the difference in the change with time comparing the treatment groups.

We will estimate the change over time in measures of cardiac injury (troponin- difference in peak troponin level) and cardiac dysfunction (NTproBNP-difference in peak NTproBNP level) using a linear mixed effects model with an unstructured covariance matrix, a fixed effect for time, treatment group, time by treatment group interaction, study site and the study site by time interaction. The parameters of interest will be the time by treatment interaction terms which will equal the difference in the change with time comparing the treatment groups. We will also compare the time to serious cardiac arrhythmias between the treatment groups using a stratified log-rank test.

We will estimate the change over time in viral titers using a linear mixed effects model with an unstructured covariance matrix, a fixed effect for time, treatment group, time by treatment group interaction, study site and the study site by time interaction. The parameters of interest will be the time by treatment interaction terms which will equal the difference in the change with time comparing the treatment groups.

We will estimate the change over time in cell subsets for functional and transcriptional immunophenotyping using a linear mixed effects model with an unstructured covariance matrix, a fixed effect for time, treatment group, time by treatment group interaction, study site and the study site by time interaction. The parameters of interest will be the time by

treatment interaction terms which will equal the difference in the change with time comparing the treatment groups.

### Sensitivity Analysis

For the primary endpoint, sensitivity to stratified analysis will be evaluated by applying an analysis that is not stratified by site.

For all endpoints corresponding to improvement (e.g. time to first improvement from baseline of at least 2 points (or the maximum amount) on the ordinal scale given in Table 2) sensitivity to inclusion of patients who improve and subsequently worsen will be performed by removing these individuals from analysis.

Primary and secondary endpoint analysis estimates will be reported for PP samples.

### Subgroup Analysis

Differences in treatment efficacy for primary the endpoint will be evaluated in multiple pre-defined subgroups defined by sex, race/ethnicity, age category (<65, >=65) , obesity (BMI>=30), diabetes and baseline labs, incuding IL-6, CRP, Ferritin and D-dimer. These differences in treatment efficacy will be assessed using the stratified Cox proportional hazards model including a fixed effect for treatment, a fixed effect for each of the pre-defined subgroups and an interaction between treatment and the subgroup. The interaction will represent the difference in the treatment effect. Both subgroup specific hazard ratios and the p-value for the treatment by subgroup interaction will be reported.

## SAFETY ANALYSIS

Safety and tolerability will be estimated in the Safety Sample. Safety and tolerability, defined as adverse events (AEs) graded by CTCAE v5.0, will be compared using a Mantel-Haenszel test to allow stratification on study site. The relative risk will be estimated using the Mantel-Haenszel method.

Only treatment-emergent AEs, defined as AEs with date of onset on or after the time of treatment administration, will be reported. AEs reported on the Day 28 follow-up form will be included.

AEs will be summarized by treatment group, severity (serious vs non-serious), grade, and relationship to study medication as indicated by the investigator. The following rules will be applied:

- The number and proportion of patients with an AE reported on one or more study days will be summarized for each AE catgory.
- AE grade will be defined as the highest grade reported for that AE category
- AE relatedness to tocilizumab will be defined as the highest degree of relatedness reported for each AE category.
- AEs in the following categories will only be reported if grade 3 or higher: neutropenia, thrombocytopenia, infection, bleeding, AST/ALT elevation
- We will grade AST/ALT elevations. The grading only applies to post-day 1 values. The grading algorithm involves first determining whether the day 1 value

is elevated (y/n) based on an upper limit for normal (ULN) that is both site- and gender-specific—see Table 3. Grade for post-day 1 elevations is determined by the ratio of the current value to (1) the ULN if day 1 value is not elevated or (2) the day 1 value if the day 1 value is elevated as described in Table 4.

**Table 3: Upper limits of normal (ULN) values for AST and ALT by study site and gender**

| Site | Gender | AST_ULN | ALT_ULN |
|---|---|---|---|
| BILH | Male | 40 | 40 |
| BILH | Female | 40 | 35 |
| BMC | Male | 39 | 67 |
| BMC | Female | 39 | 67 |
| BWH | Male | 50 | 50 |
| BWH | Female | 50 | 50 |
| MGH | Male | 40 | 55 |
| MGH | Female | 32 | 33 |
| NSMC | Male | 41 | 50 |
| NSMC | Female | 41 | 35 |
| NWH | Male | 40 | 49 |
| NWH | Female | 40 | 49 |
| SEMC | Male | 41 | 63 |
| SEMC | Female | 41 | 54 |

**Table 4: Grading algorithm for post-baseline AST/ALT elevations**

| Grade | Grade if normal baseline | | Grade if abnormal baseline |
|---|---|---|---|
| **1** | **ULN - 3x ULN** | | **1.5x - 3x baseline** |
| **2** | **>3x ULN - 5x ULN** | | **>3x - 5x baseline** |
| **3** | **>5x ULN - 20x ULN** | | **>5x - 20x baseline** |
| **4** | **>20x ULN** | | **>20x baseline** |

AEs of special interest include the following:

- Death
- Infections
- Myocardial infarction
- Gastrointestinal perforation
- Hypersensitivity reaction to infusion
- Deep venous thrombosis
- Pulmonary embolism
- Stroke

- Seizure
- Abnormal liver function test
- Neutropenia
- Thrombocytopenia
- Bleeding events
- Malignancy
- Demyelinating disorder

SUMMARY OF CHANGES IN STATISTICAL ANALYSIS PLAN (SAP)

The initial SAP provided only a broad discussion of the approaches planned to the primary, secondary, and tertiary endpoints.

The final SAP included all of the elements in the Table of Contents below:

**Table of Contents**