To: Cancer Therapy Evaluation Program

From: Richard F. Little, M.D.

Date: June 4, 2020

Re: Amendment 1 of Protocol #TRC-10446: "Tocilizumab in Hospitalized Cancer Patients with Coronavirus 2019 (SARS-CoV-2) and Severe Complications of Coronavirus Disease 19 (COVID-19)

Protocol Changes by Principal Investigator:

#	Section	Comments
1.	Title page	The list of participating organizations has been updated.
2.	4.2	The email address CTSURegPref@ctsu.coccg.org has been corrected to CTSURegPref@coccg.org.

NCI Protocol #: TRC-10446

Local Protocol #: TRC-10446

ClinicalTrials.gov Identifier: NCT04370834

Tocilizumab in Hospitalized Cancer Patients with Coronavirus 2019 (SARS-CoV-2) and Severe Complications of Coronavirus Disease 19 (COVID-19)

Treatment Referral Center Protocol
TRC 10446

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NCI Suppled Agent: Tocilizumab (Actemra®, RO4877533, NSC 820013)

Participating Organizations: Participation is limited to the following U.S. selected NCTN, ETCTN, and NCORP sites:

GA003 / Grady Health System
GA005 / Emory University – Winship Cancer Institute
MA037 / Brigham and Women's Hospital
MA038 / Beth Israel Deaconess Medical Center
MD004 / National Institutes of Health Clinical Center
NCICCR / NCI Center for Cancer Research
NV017 / University Medical Center of Southern Nevada
NV093 / Summerlin Hospital Medical Center
WA004 / Valley Medical Center
NY043 / Montefiore Medical Center – Weiler Hospital
NY045 / Montefiore Medical Center – Moses Campus
NY313 / Montefiore Medical Center – Einstein Campus
NY327 / Children's Hospital at Montefiore
OK003 / University of Oklahoma Health Sciences Center

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. (Sign in at www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log on with CTEP-IAM username and password.

For clinical questions (*i.e.* patient eligibility or treatment-related), see the Protocol Contacts, Page 2.

For non-clinical questions (*i.e.* unrelated to patient eligibility or clinical data submission), contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU website is located at https://www.ctsu.org.

PRECIS/SYNOPSIS

This single-arm trial is intended to provide expanded access to tocilizumab for cancer patients with severe COVID-19 pulmonary complications and is intended to make tocilizumab available to those not able to participate on the randomized phase 3 trial sponsored by Hoffmann-La Roche comparing tocilizumab to placebo in patients with severe COVID-19 disease: "A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA)" (NCT04320615). The primary objective in the phase 3 trial is to compare clinical status assessed using a 7-category ordinal scale at Day 28 between arms.

Since severe COVID-19 pulmonary disease appears to be mediated by cytokine release similar to that seen in patients with cytokine release syndrome complications of CAR-T therapy for which tocilizumab is FDA approved, this expanded access trial is being conducted to provide clinical trial access to this potentially life-saving therapy in cancer patients and to collect data on clinical outcomes. This trial will address potential access disparity among adult and children cancer patients to the randomized phase 3 trial compared to the background population. FDA workshops convened with Friends of Cancer Research, American Society of Clinical Oncology, and the American Association for Cancer Research have articulated important principles for modernizing eligibility criteria to clinical trials and for access to clinical trials, particularly in the case of African Americans multiple myeloma disparities.[1,2] Recommendations include development of cohort studies to parallel the experimental arm of pivotal trials to enhance inclusion of patients underrepresented on the pivotal trials owing to restrictive eligibility criteria or other disparities.

This expanded access trial is responsive to the FDA workshop recommendations in the following ways:

- Cancer patients are at increased risk of severe COVID-19 yet will be underrepresented on the pivotal trial because of restrictive eligibility criteria that will exclude many cancer patients, particularly those with hematologic malignancies
- African American cancer patients will be underrepresented on the pivotal trial owing to both treatment disparity issues and cancer patient eligibility restrictions
- Children of all races and ethnicities with cancer will be underrepresented on the pivotal trial owing to the age restrictions of the pivotal trial as well as restrictive eligibility criteria that will limit those with cancer from participation.
- This trial will be conducted only in sites where COVACTA is not being conducted, with an emphasis on Minority Enrolling Sites of the National Cancer Institute Community Oncology Research Program (NCORP), and the Early Therapeutics Clinical Trials Network and the National Clinical Trials Network to insure enhanced minority and pediatric enrollment.
- The trial will be conducted as a collaboration between Genentech and the National Cancer Institute in a manner that is responsive to FDA workshop recommendations to ensure clinical trials access to patients who are routinely not included in pivotal therapeutic industry sponsored clinical trials
- This trial will provide critical clinical outcome data for patients who will not have access to the COVACTA trial so that if the COVACTA trial is positive, the clinical outcomes

will be reasonably described for clinical decisions regarding use of tocilizumab in cancer patients.

Key eligibility criteria of this trial and the pivotal COVACTA trial that will create clinical trial access barriers for cancer patients, especially African Americans and children with cancer and severe COVID-19:

Eligibility Criterion	NIH Trial	COVACTA Trial	Comments
Cancer Diagnosis	Required	Silent	Responsive to FDA workshops for modernizing eligibility for clinical trials and addressing disparities
Immune modulatory drugs	Allowed	Not allowed	COVACTA trial will render many cancer patients ineligible. Tocilizumab has been shown safe in cancer patients with cytokine release syndrome
HIV	Included	Silent	Patients safely treated with HIV and KSHV in NCI clinical trials; responsive to efforts for modernizing eligibility
Age	≥ 2 years	≥ 18 years	Tocilizumab is approved for use in both adults and children to treat cytokine release syndrome associated with cancer therapy
ANC	no lower limit	≥1000/mcL	Cancer patients, such as those in whom tocilizumab is approved, often have ANC below 500/mcL and the agent can be given safely in this setting; Benign neutropenia common in African Americans

Platelets	no lower limit	≥50,000/mcL	Cancer patients, such as those in whom tocilizumab is approved, often have platelets below 50,000/mcL and the agent can be given safely in this setting

Background: COVID-19 is a highly contagious novel pathogen causing a global pandemic leading to high rates of life-threatening or fatal complications. Patients with cancer may be at particularly high-risk to develop severe complications related to COVID-19. Mitigation strategies are urgently needed to reduce the severity of infection to reduce the burden on ICU level care and decrease the case-fatality rate.

Objectives: This National Cancer Institute clinical trial will provide tocilizumab to severely ill COVID-19 cancer patients in response to the National Emergency as declared by the President of the United States. The Aims are to 1) distribute tocilizumab to hospitals in order to potentially prevent escalation of care and to discharge severe COVID-19 cases from intensive care facilities as quickly as possible in order to keep ICU beds available to successive waves of severe COVID-19 cases, 2) to evaluate clinical outcomes in critically ill cancer patients with COVID-19 illness receiving tocilizumab.

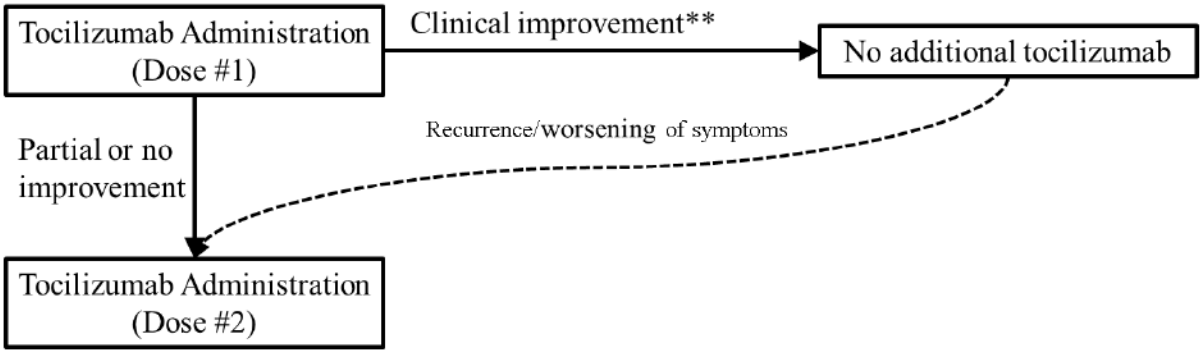
Eligibility: Hospitalized cancer subjects ≥ 2 years of age with clinical manifestations of COVID-19 infection and respiratory compromise may be eligible to receive tocilizumab.

Design: This is a multicenter, single-arm, open-label, interventional study with all enrolled subjects receiving tocilizumab.

SCHEMA:

Cohorts A and B (only Ordinal Scales 3-6 are eligible for initial dose of tocilizumab)

CLINICAL STATUS ORDINAL SCALE		
SCALE	**COHORT**	**DESCRIPTION**
1	N/A	**Discharge**
2	**A1/A2**	Non-ICU, hospital ward, NO O2
3	**A1/A2**	Non-ICU, hospital ward, on O2
4	**A1/A2**	ICU or non-ICU, requires non-invasive ventilatory support or high flow O2
5	**B1/B2**	ICU requires mechanical or imminent ventilation/intubation
6	**B1/B2**	ICU requires ECMO and additional O2 support and organ support, e.g. vasopressors, renal replacement therapy
7	N/A	**Death**



**Optimal response to tocilizumab may not be seen until 5-6 hours after completion of the initial infusion and will typically manifest with resolution of/improvement in fever prior to other clinical signs

Subjects with no objective improvement after 2 doses are unlikely to benefit from further administration of tocilizumab and alternative therapies should be considered

For those at or above 30 kg (≥):			
Cohort	**Clinical Status Description**	**Dosing for Initial Dose**	**Dosing for Second Dose***
A1	**3-4** (Not on mechanical ventilation at time of registration and no immediate plan for intubation)	4 mg/kg	8 mg/kg **(ordinal scale 2 may receive if clinically indicated)***

B1	**5-6** (On mechanical ventilation at time of enrollment or imminent intubation indicated)	8 mg/kg	8 mg/kg
For those below 30 kg (<):			
Cohort	**Clinical Status Description**	**Dosing for Initial Dose**	**Dosing for Second Dose***
A2	**3-4** (Not on mechanical ventilation at time of registration and no immediate plan for intubation)	6 mg/kg	12 mg/kg **(ordinal scale 2 may receive if clinically indicated)***
B2	**5-6** (On mechanical ventilation at time of enrollment or imminent intubation indicated)	12 mg/kg	12 mg/kg

- Maximal administrated dose, for a single dose: **800 mg regardless of weight**
- Optimal response to tocilizumab may not be seen until 5-6 hours after completion of the initial infusion and will typically manifest with resolution of/improvement in fever prior to other clinical signs

*A second dose may be given if there is sustained or recurrent fever, no decrease or not more than a 1-category improvement on the 7-category ordinal scale (only stabilization or partial improvement following first dose), or a ≥1-category worsening on the 7-category ordinal scale from nadir. The second dose **may be given between 8 hours and 7 days from completion of the first dose**. In many cases a second dose may not be necessary to achieve optimal benefit.

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To enhance access to tocilizumab for patients who cannot participate in the randomized COVACTA Trial with specific emphasis on patients with cancer, especially those who belong to high-risk and minority populations and children and to provide observations on clinical outcomes associated with tocilizumab administration in cancer patients with severe COVID-19 disease.

1.2 Secondary Objective

1.2.1 To estimate the proportion of patients whose level of institutional care does not further escalate following administration of tocilizumab

1.3 Exploratory Objectives

1.3.1 To estimate the number of days ICU patients spent in the ICU

1.3.2 To evaluate the mortality rate of patients:

1.3.2.1 30-day and 60-day mortality in patients in the ICU

1.3.2.2 Evaluate the 14-, 30- and 60-day mortality rate following infusion of tocilizumab

1.3.3 To evaluate overall survival

1.3.4 To describe the proportion of patients progressing to ventilator support after tocilizumab therapy

1.3.5 Evaluate the clinical course following administration of tocilizumab

1.3.5.1 To evaluate the development of additional infections

1.3.5.2 To evaluate the side effects following tocilizumab

1.3.5.3 To evaluate impact on inflammatory markers

1.3.6 Evaluate the duration of time:

1.3.6.1 To removal from mechanical ventilator support

1.3.6.2 To step-down of institutional care requirements

1.3.6.3 To discharge from the ICU to lower level

1.3.6.4 To hospital Discharge

1.3.6.5 To resolution of clinical symptoms

1.3.6.6 To time of defervescence

1.3.6.7 To normalization of disease-related laboratory abnormalities

1.3.7 Exploratory Biologic correlates

1.3.7.1 To evaluate cytokine levels pre and post-tocilizumab, specifically evaluating IL-6

1.3.7.2 To evaluate SARS-CoV-2 viral loads pre and post-tocilizumab

1.3.7.3 To determine the pharmacokinetics of tocilizumab in order to facilitate exposure-response analysis

1.3.7.4 To correlate clinical outcomes with changes in cytokine levels and SARS-CoV-2 viral loads

2. BACKGROUND AND RATIONALE

2.1 Coronavirus SARS-CoV-2 and Severe Coronavirus Disease 19 (COVID-19) as a National Public Health Emergency

SARS-Cov-2 is a rapidly spreading pandemic coronavirus that causes a febrile illness termed Coronavirus Disease 19 (COVID-19) and can include a lethal acute respiratory syndrome.[1] The initial cluster of cases was reported by the Chinese government on December 29, 2019. On January 30, 2020 the World Health Organization declared it a global health emergency owing to its rapid global spread and concerns for high lethality. SARS-COV-2 is highly infectious by casual contact and is associated with a 2-4% mortality in affected persons.[2-4] There is no known effective therapy. COVID-19 appears to be most dangerous to the survival of those aged 60 years and over with chronic comorbid conditions, but severe illness has been documented in all age and health groups.[5] Furthermore, in older patients or in those who are immunocompromised, there may be a longer duration of time that the virus can continue to replicate before the body's own immune system can respond, leading to potentially more severe complications. The duration from exposure to illness is less than two weeks in most cases, leading to acute demands on health care resources. Common symptoms at onset include fever, cough, and myalgia or fatigue. Up to 30% of patients may develop severe complications including acute respiratory distress syndrome, requiring intensive care support. Among this group of critically ill patients, the fatality rate is high and estimated between 20-65%.[3,6] Severe acute respiratory syndrome (SARS) represents most cases at the end of life spectrum in COVID-19 natural history.

2.1.1 Clinical Presentation of Patients with COVID-19 Infection

Based on a series of recent reports on COVID-19, the presentation of COVID-19 ranges

from asymptomatic to life-threatening, leading to fatal complications. Respiratory complications are the mainstay of the disease, ranging from asymptomatic carriers or mild symptoms to development of acute respiratory distress syndrome (ARDS) and subsequent respiratory and/or multi-organ failure. Although the case fatality rate amongst all patients with COVID-19 remains low,[2] mortality rates for those who are hospitalized or critically ill are astonishingly high.[3,4]

Amongst 191 hospitalized patients from one of two centers in Wuhan, China, 54 (28.2%) of patients died from complications of COVID-19. In a single-center study from Wuhan, China, 52 or 710 (7.3%) of patients with COVID-19 were critically ill. Amongst these critically ill patients 32 of 52 (61.5%) infection died, with the majority of deaths occurring within 1-2 weeks after admission to the ICU.[3] In this study, non-survivors were more likely to be older, more likely to develop ARDS and needed mechanical ventilation.[3]

Clinical presentation along with radiographic findings[7] are essential in identifying those patients at high risk from developing severe COVID-19 pneumonia. Based on a single center study of 201 patients with COVID-19 in Wuhan, China factors associated with ARDS and death in patients with COVID-19 included older age, neutrophilia, organ and coagulation dysfunction.[8]

2.1.2 COVID-19 Infection in Children

Preliminary reports of COVID-19 infection in children report on a generally milder clinical course than what has been seen in adults.[9,10] However, COVID-19 could cause significant morbidity and mortality, particularly in children with pre-existing conditions, those who are immunosuppressed or have chronic cardio-pulmonary disease. Indeed severe cases in children with COVID-19 have been reported and in these cases, features of cytokine storm have been present, which can present with very rapid onset.[11] Mitigation strategies to prevent severity of disease in children at high-risk of morbidity and mortality from COVID-19 are indicated.

2.1.3 Treatment of Severe COVID-19 Infection

There are currently no curative strategies for treatment of COVID-19 and efforts on optimizing disease management strategies are based on established treatment paradigms of ARDS.[12] Due to the rapid spread of SARS-CoV-2 and the incidence of patients requiring hospitalizations or ICU level care, the ability to meet the increasing demand for hospitalization and intensive care unit admissions is severely challenged.[13] Given the high-risk of mortality particularly for those requiring ICU level care, disease mitigation strategies to prevent patients from requiring ICU level care or limiting duration of intubation in those at highest-risk of ARDS may improve case-fatality rates and reduce the burden on ICU level care allowing more patients to be treated. Recent studies on remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases with in vitro activity against SARS-CoV-2, has shown benefit in patients with COVID,[14] and other studies testing anti-viral, anti-malarial and anti-cytokine directed therapies are underway.

2.2 COVID-19 in Cancer Patients

As seen with other infections, patients with cancer who become infected with SARS-CoV-2 are particularly susceptible to having more severe complications from COVID-19 disease than in those without a cancer diagnosis. In a recent study from Dai and colleagues, based on a multi-center retrospective study from 14 hospitals in the Hubei Province in China, patients with cancer and concomitant COVID-19 had a higher incidence of severe events compared to patients without cancer.[15] Specifically, they compared outcomes from 105 hospitalized patients with COVID-19 and cancer to 233 hospitalized patients with COVID-19 without cancer. Their findings suggested that patients with cancer tended to have more severe complications related to COVID-19 and that this was particularly notable in those with hematologic malignancies, lung cancer, and metastatic disease. Furthermore, in those who had recent immunotherapy or cancer related surgery, there was a higher risk of needing intensive care and also a higher death rate (Figure 1).[15] Another study from Liang and colleagues similarly found a higher risk of severe events in both those with cancer as well as in cancer survivors in a limited subset of patients (n=18).[5]

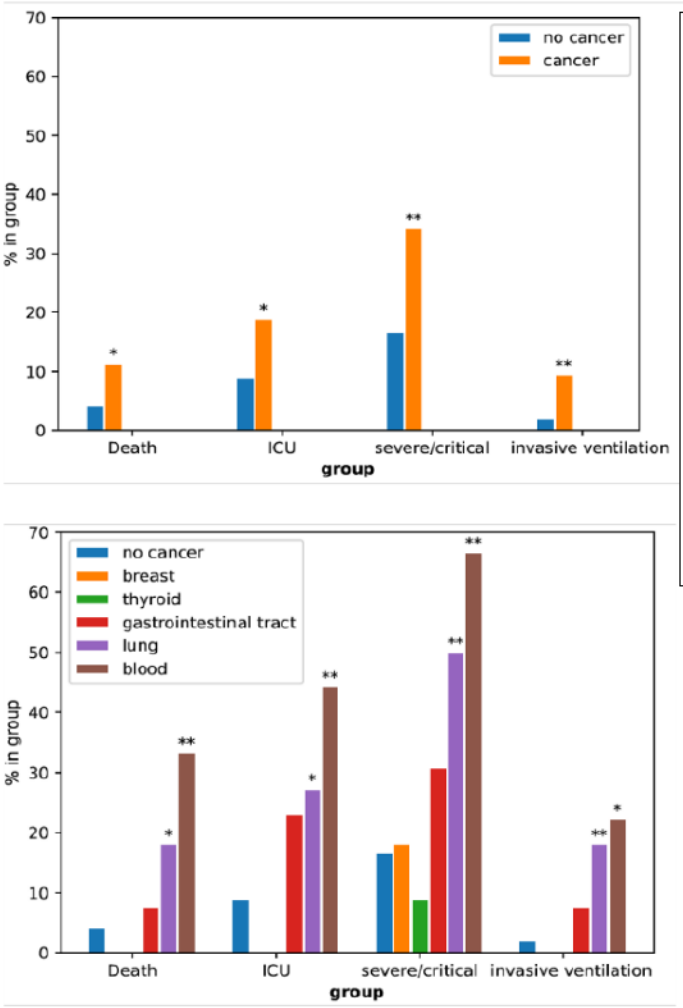


Figure 1. Severe conditions in patients with and without cancer, and patients with different types of cancer. Severe conditions include death, ICU admission, having severe/critical symptoms (Difficulty in breathing/Shock/Acute kidney injury/ARDS/Arrhythmia/ MODS) and usage of invasive mechanical ventilation. ICU=intensive care unit, ARDS=Acute Respiratory Distress Syndrome, MODS= Multiple Organ Dysfunction Syndrome.
Top panel: Incidence of severe condition among COVID-19 patients with cancer and without cancer
Bottom panel: Incidence of severe condition among COVID-19 patients with different types of cancer.

2.3 Severe acute respiratory distress syndrome (ARDS) and cytokine release syndrome (CRS)

Cytokine release syndrome (CRS) is a supra-physiologic inflammatory process which can be seen in the context of inflammation, infection or immune activation. CRS as a manifestation has gained significant notoriety in recent years with the advances in cellular therapy and T-cell associated CRS.[16] Associated with a host of multi-organ manifestations, CRS can range from mild to severe and typically presents with the onset of fevers. The clinical presentation can include hypotension, coagulopathy, hypoxia, and hepatic transaminases amongst other features and anti-cytokine directed therapies have been imperative in managing the toxicity.

Severe acute respiratory distress syndrome (ARDS) can be associated with cytokine release syndrome (CRS) or cytokine storm, and this is mediated in large part by interleukin-6 (IL-6). [17] In COVID-19, higher plasma levels of cytokines including IL-6, IL-2, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), interferon-γ-inducible protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP-1 α), and TNF-α were found in ICU patients consistent with cytokine storm. [6,18] The presentation associated with severe COVID-19 infection has implicated the presence of a cytokine storm that may be amenable to cytokine directed therapies.[19,20] Treatment with methylprednisolone decreased the risk of death in patients with ARDS in one study in patients with COVID-19,[8] potentially supporting the role of anti-cytokine directed therapy in ameliorating the immune response to COVID-19.

2.4 Tocilizumab (Provided by CTEP)

Tocilizumab is a recombinant humanized monoclonal antibody directed against the interleukin-6 receptor (IL-6R). It binds both soluble and membrane-bound IL-6R and inhibits IL-6-mediated signaling through these receptors. It was initially FDA approved for utilization in rheumatoid arthritis (in 2010) and juvenile idiopathic arthritis (2011). Tocilizumab is FDA approved for children and adults, starting at an age $\geq$ 2 years.

Refer to the Tocilizumab package insert for details on nonclinical and clinical studies.

2.4.1 Tocilizumab in CAR T-cell Associated CRS

Based on its utilization in treatment of CAR T-cell associated CRS, it received FDA approval in the treatment of severe or life-threatening CRS in adults and in pediatric patients 2 years of age and older.[21]

Tocilizumab is administered intravenously (IV) and dosing is weight based.[22] It can be used alone or in combination with corticosteroids.

Tocilizumab has also been used at lower dosing (4 mg/kg) in both CRS and other rheumatologic diseases. It is unknown what dose of tocilizumab would be effective in treating CRS associated with ARDS or SARS.

2.4.2 Pre-emptive Utilization of Tocilizumab in CRS

With increasing utilization of CAR T-cell therapy in hematologic malignancies, and a goal to avoid severe toxicities, tocilizumab has been effectively employed in pre-emptive strategies to reduce the severity of CRS. [23] Specifically in patients with low-grade CRS, initiation of tocilizumab has been effective in preventing higher-grade CRS.

2.4.3 Tocilizumab in COVID-19

The levels of the cytokines appear to be associated with disease severity and prognosis. On this basis Xiaoling Xu and colleagues treated 21 severely ill patients with COVID-19 with the monoclonal antibody tocilizumab, an IL-6 receptor antagonist that is US FDA approved for cytokine release syndrome and several autoimmune-related arthritides. [24] All patients were on putative COVID-19 therapeutics including lopinavir, methylprednisolone, oxygen and other supportive care measures at baseline. Eighteen patients received tocilizumab at a flat 400 mg IV dose once and 3 patients received a second dose at the same dose due to fever within 12 hours. The clinical symptoms improved in all treated patients. Nineteen patients (90.5%) have been discharged, including two of the most critically ill patients, as of the results being made publicly available. Therefore, it appears that tocilizumab can effectively treat severe COVID-19-related SARS by blocking the IL-6-associated febrile and inflammatory storm response. Anecdotal reports from off-label use of tocilizumab in hospitalized patients suggest a rational in COVID-19 disease.

A randomized, double-blind, placebo-controlled multicenter study to evaluate the safety and efficacy of tocilizumab in hospitalized adults with severe COVID-19 pneumonia is actively accruing (ClinicalTrials.gov NCT04320615). In this study, patients will be randomized to receiving either placebo or a single dose of tocilizumab 8 mg/kg (max dose 800 mg), with an option to receive one additional dose. Cancer patients with hematologic malignances or bone marrow involvement by disease may potentially not be eligible for the randomized study due to eligibility criteria based on neutrophil and platelet counts. However, this cohort of cancer patients is likely to be most at risk of severe complications from COVID-19 based on recent data.[15]

2.4.4 Pharmacokinetics of Tocilizumab

Although higher doses of tocilizumab (8-12 mg/kg) are typically utilized for treatment of CAR T-cell related CRS, lower dosing (4 mg/kg) has effectively been employed. Furthermore, it is unknown if lower doses could be effective for cytokine storms not related to CAR T-cell therapy, where cytokine levels are significantly elevated. The dose used by Xu and colleagues was a flat dose of 400 mg, which could widely correspond to a dose range from 4-8 mg/kg based on the size of the patient (e.g., 400 mg=6.67 mg/kg for a 60 kg adult).

Based on pharmacokinetic/pharmacodynamic data[25] and unpublished data generated by Genentech, a 4 mg/kg IV dose elicited a similar onset and magnitude of IL-6 pathway inhibition as the 8 mg/kg dose. The primary difference was a shorter duration of inhibition

with the 4 mg/kg dose compared to the higher dose in the presence of higher levels of IL-6R; which could be further optimized by a second dose of 4 mg/kg if needed.

2.4.5 Risks of Tocilizumab

Based on data in patients with autoimmune disease where tocilizumab is more chronically used, the main risk of tocilizumab includes infection. As per the package insert, as there is a higher incidence of infections in the elderly population (65 years of age and older), in general, caution should be used when treating the elderly.[22] Although tocilizumab is relatively contraindicated in the setting of active infection, given the high morbidity and mortality rate of SARS-CoV-19 and the association of higher levels of IL-6 in those patients who ultimately go on to have fatal outcomes as a result of COVID-19,[4] the ability to reduce the inflammatory response to infection may ultimately improve outcomes in those with SARS.

In the context of CAR T-cell related therapy, the infection risk imparted by a few doses of doses of tocilizumab appears to be less than that for chronic therapy given in settings such as rheumatoid arthritis. Considering the patient population receiving CAR T-cells, the vast majority of whom have hematologic malignancies, abnormal marrow function, pre-existing cytopenias (including severe neutropenia) and are immunocompromised, utilization of tocilizumab for 1-2 doses has not been definitively associated with any increased risk of infection.[26,27] Additionally, tocilizumab administered at 8 mg/kg every two weeks for up to 6 doses in HIV-associated Kaposi Sarcoma Herpes Virus-multicentric Castleman disease (MCD) was safe and transiently effective in reducing IL-6 mediated clinical sequelae of MCD [28]

2.5 Study Rationale and Justification for the Use of Tocilizumab in Hospitalized Cancer Patients with COVID-19

There are currently no active therapies for severe COVID-19 disease. Prolonged intensive care requirements create a shortage of additional capacity for new emerging cases leading to increased mortality among those unable to be availed of potentially life-saving supportive care. This protocol is intended to provide tocilizumab as a disease mitigating strategy with potentially lifesaving benefit to COVID-19 cancer patients who may be at higher risk of complications from COVID-19. If effective, the strategy will promote an essential public health response to the COVID-19 epidemic by decreasing time spent in the ICU by cancer patients at high risk of requiring prolonged intensive care so that beds are made available to next wave of severe COVID-19 patients with or without cancer. Additionally, if effective, tocilizumab may allow more timely initiation or continuation of cancer therapy for those with underlying malignancies. For aggressive and potentially curative cancers, tocilizumab could provide a path for not only preventing COVID-19 mortality, but also for allowing administration of life-saving cancer therapy. As successive waves of critically ill patients are admitted to the ICU, treated, and released, if the strategy is successful, the ability of existing health care resources to provide care to emerging cases can be improved.

The rapid global spread of COVID-19 has created a severe health and socioeconomic disturbance in the United States. The President declared a National Emergency on March 13, 2013 to enhance the Nation's response to this crisis.[29] Rapid development and launch of interventional clinical trials must be immediately prioritized so that potential effective treatments can be delivered to patients who have life threatening COVID-19 complications. Data from such trials can rapidly inform the scientific foundation for other new clinical trials. This National Cancer Institute clinical trial to provide tocilizumab to severely ill COVID-19 cancer patients is in response to the National Emergency as declared by the President of the United States.

The purpose of this protocol is to rapidly distribute tocilizumab to and collect response and toxicity data to further evaluate the potential effectiveness of tocilizumab in severe cases of COVID-19 in cancer patients based on the early report of its effectiveness.[24] This will also be the first trial of tocilizumab open to enrollment of hospitalized children with cancer and COVID-19 disease.

Furthermore, based on the established pharmacokinetics of tocilizumab and lack of information on what dose of tocilizumab is needed to achieve benefit, this trial will also allow for the assessment of the efficacy of a lower dose of tocilizumab in patients who are less severely ill.

2.5.1 Treatment Cohorts

Treatment is intended for only 2 doses.

Dosing of Tocilizumab: Please refer to the Precis.

3. PATIENT SELECTION

3.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

3.1.1 Cancer Diagnosis: Subjects must have an active cancer diagnosis or have completed therapy within 12 months of initiation of protocol specified therapy. This includes:

- Subjects with a new cancer diagnosis who have not yet initiated cancer therapy.
- Subjects on active or have recently completed cancer-directed therapy including chemotherapy, radiation therapy, immunotherapy or hormonal therapy amongst others.
    - Myelosuppressive chemotherapy for patients in remission (*e.g.*, adjuvant chemotherapy for breast cancer, AML consolidation) is prohibited until clinical recovery (1 or 2 on the 7-category ordinal scale).
- Subjects on any investigational therapy for their underlying cancer, investigational COVID-19 anti-viral agents, or convalescent serum aimed at treating COVID-19 disease are eligible. Investigators are reminded to check whether the other investigational study(s) the patient is participating on specifically exclude tocilizumab and to adjudicate best clinical management decision for the specific patient.
- Subjects who have undergone hematopoietic stem cell transplant within the past 12 months, or are continued on GVHD therapy, are also eligible

3.1.2 COVID-19 Diagnosis: Patients hospitalized with COVID-19 pneumonia confirmed by:

- Radiographic findings concerning for COVID-19 pneumonia AND
- Confirmatory SARS-CoV2 positive result using any testing assay, or (with or without a confirmatory test) with suspicion of COVID-19 disease owing to belonging to a high-risk demographic group or living and/or working in high-risk settings or with known exposure AND
- SpO2 on room air ≤93% or PaO2/FiO2 <300 mmHg

3.1.3 Age ≥ 2 years.

3.1.4 Patients must have adequate organ function as assessed by the treating investigator to administer tocilizumab:

- AST and ALT <10 x institutional upper limit of normal
- Patients with low blood counts attributable to cancer therapy or underlying malignancy are eligible

3.1.5 Patients may be on other therapies for COVID-19 including investigational and not limited to corticosteroids, azithromycin, chloroquine, hydroxychloroquine

- For patients already enrolled on other investigational studies for COVID-19, study investigators should verify that co-enrollment on this study is permissible as per the eligibility of the other study.

3.1.6 Human immunodeficiency virus (HIV)-infected patients are eligible for this trial unless they have opportunistic complications of AIDS other than the cancer they have.

3.1.7 For patients with evidence of chronic hepatitis B virus (HBV) infection, should be on suppressive therapy, if indicated.

3.1.8 Patients with a history of hepatitis C virus (HCV) infection should be on treatment if indicated.

3.1.9 The effects of Tocilizumab on the developing human fetus are unknown.

- Pregnancy: Based on animal data, may cause fetal harm. Tocilizumab may be given if in the physician's judgment the patient's life is threatened without potential effective therapy
    - Women of childbearing potential must agree to use birth control or remain abstinent for the duration of the study and for at least 28 days following the last dose of tocilizumab. Pregnancy tests should be done based on the discretion of the patient and physician.
    - Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother.
    - Men must agree to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, for the duration of the study and for at least 28 days following the last dose of tocilizumab.

3.1.10 Ability to understand and the willingness to sign a written informed consent document. Participants with impaired decision-making capacity (IDMC) who have a legally-authorized representative (LAR) and/or family member available will also be eligible.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from enrollment:

3.2.1 Prior or concurrent utilization of IL-6 specific targeting strategies for treatment of COVID-19 that showed no benefit after maximum dosing; (patients who have only received 1 prior dose and there was evidence of potential benefit may be eligible).
- This includes siltuximab, tocilizumab, and sarilumab

3.2.2 Known hypersensitivity or history of severe allergic reaction to tocilizumab or other monoclonal antibodies.

3.2.3 Any serious medical condition or active uncontrolled infections (besides COVID-19) that, in the investigator's judgement, preclude the subject's safe participation in the study.
- Examples: Active TB infection

3.2.4 Active diverticulitis because of severe flairs in disease leading risk of bowel perforation

3.2.5 Patients in whom, in the opinion of the treating physician, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments, will be excluded from the study.

3.2.6 Patients receiving or planning to receive any investigational agents other than tocilizumab are ineligible for this study, with the following exceptions:
- Investigational agents directed at a patient's underlying cancer are allowed.
- Investigational SARS-CoV-2 anti-viral agents
- Convalescent serum directed at COVID-19 disease

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (*i.e.*, clinical site staff requiring write access to Oncology Patient Enrollment Network (OPEN), Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR: MD, DO, or international equivalent,
- NPIVR: advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- AP: clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications (*e.g.*, Roster Update Management System [RUMS], OPEN, Rave,),
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,
- Act as the site-protocol Principal Investigator (PI) on the IRB approval;

In addition, all investigators act as the Site-Protocol PI, or consenting/treating/drug shipment, must be rostered at the enrolling site with a participating organization (*i.e.*, Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Sites must use the NCI Central Institutional Review Board (NCI CIRB) as the IRB of record and must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB approval) must meet the following five criteria to complete processing of the IRB approval record:

- Holds an Active CTEP status,
- Rostered at the site on the IRB approval (*Only US Sites may participate*) and on at least one participating roster,
- If using NCI CIRB, rostered on the NCI CIRB Signatory record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- Only US Sites may participate
- An active Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization, and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Participating Organization on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select NCI, and protocol number TRC-10446

- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.2 Protocol Specific Requirements For TRC-10446 Site Registration

- Specimen Tracking System Training Requirement:
  - All site staff planning to do data entry in Rave for TRC-10446 (i.e., Rave CRA or Rave CRA (LabAdmin) role) must complete the on-line specimen tracking training, which is administered via the Compliance, Learning, and SOP Solutions (CLASS) system.
  - Completion of this training is required for individual Rave CRAs/Rave CRA (LabAdmins) to receive Rave invitations for the study, i.e., to be able to access the study in Rave and enter data/manage specimen tracking.
  - A Rave CRA/Rave CRA (LabAdmin) at a site that receives site registration approval for TRC-10466 (or is added to the site roster after it has received approval) will receive an automated email from CLASSHelpDesk@westat.com with the training assignment and instructions for accessing CLASS.
  - Completion of the training will be automatically communicated to the Regulatory Support System (RSS) and to Medidata Rave, and the individual will receive an invitation to TRC-10466 in Rave. *There is no need to submit a training completion certificate to the CTSU through the Regulatory Submission Portal.*
  - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN, NCTN or NCORPS study (either within CLASS, or via the procedure in place prior to CLASS), the training does not need to be completed again. However, new versions of the Specimen Tracking System may require new training.
  - For questions about the training content or the tracking system itself, please contact STS Support at Theradex for the training (STS.Support@theradex.com, Theradex phone: 609-799-7580).
  - For questions or concerns about accessing the training in CLASS, please contact the CLASS Help Desk CLASSHelpDesk@westat.com.

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal, log on to the CTSU members' website → Regulatory → Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Checking Site Registration Status

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website
- Click on *Regulatory* at the top of your screen
- Click on *Site Registration*
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account.
- Be on an LPO roster, NCTN including COG, NCORPS or ETCTN Corresponding roster, or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.3.2 Remote Informed Consent Process

Patients must provide informed consent to participate in this study. Remote consent procedures are found here:
https://www.ncicirb.org/content/nci-cirb-information-about-covid-19.

This may be used in order to limit contact and promote social distancing in response to COVID-19 containment measures. Before using these Remote Consent Procedures, sites must update their Study Specific Worksheet (SSW) or the Signatory Institution Worksheet (SIW) with the CIRB to state Remote Consent Procedures are used at their site.

4.3.3 Special Instructions for Patient Enrollment

- All biospecimens collected for this trial must be submitted using the Rave Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through special Rave user roles: "CRA Specimen Tracking" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository.
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions can be found in Section 5.3.

4.3.4 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN link of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within five days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

All biospecimens are optional, but highly encouraged because of their potential scientific value in addressing the COVID-19 pandemic

5.1 Summary Table for Specimen Collection

Time Point	Specimen	Send Specimens To:
Baseline (at time of initial dose)		
	• 7ml Whole Blood in Purple top EDTA tube	Biopathology Center (BPC)
	• 7ml Whole Blood in Green top sodium heparin tube	Biopathology Center (BPC)
Every 12 hours four times following the first dose of tocilizumab (12, 24, 36, 48 hours)		
	• 7ml Whole Blood in Purple top EDTA tube	Biopathology Center (BPC)
	• 7ml Whole Blood in Green top sodium heparin tube	Biopathology Center (BPC)
72 hours after initial dose		
	• 7ml Whole Blood in Purple top EDTA tube	Biopathology Center (BPC)
	• 7ml Whole Blood in Green top sodium heparin tube	Biopathology Center (BPC)
7 days after initial dose[1]		
	• 7ml Whole Blood in Purple top EDTA tube	Biopathology Center (BPC)
	• 7ml Whole Blood in Green top sodium heparin tube	Biopathology Center (BPC)
[1]If the patient is still hospitalized		
Note: For pediatric patients, all blood collections are optional. Baseline and 72 hour specimens should be prioritized for collection and 5 ml in heparinized tube is prioritized over EDTA tube. For the every 12 hour collection schedule, pediatric patients should only have two collections.		

5.2 Specimen Procurement Kits and Scheduling

5.2.1 Specimen Procurement Kits

Shipping kits only are provided for this study. Institutional supplies must be used for all specimen collection.

Shipping kits can be ordered online via the Kit Management system: (https://ricapps.nationwidechildrens.org/KitManagement).

Users at the clinical sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Please note that protocol may include more than one type of kit. Each user may order four kits per day for this protocol. Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website.

5.2.2 Scheduling of Specimen Collections

Please adhere to the following guidelines when scheduling procedures to collect blood:

- Fresh blood specimens may be collected and shipped Monday through Friday.

5.3 Specimen Tracking System Instructions

5.3.1 Specimen Tracking System Overview and Enrollment Instructions

For the Rave Specimen Tracking System (STS), the following information will be requested:

- Protocol Number
- CTEP Investigator Identification (CTEP ID)
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this protocol that uses the Rave Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact STS Support at STS.Support@theradex.com.

A shipping manifest **must** be included with all sample submissions.

5.3.2 Specimen Labeling

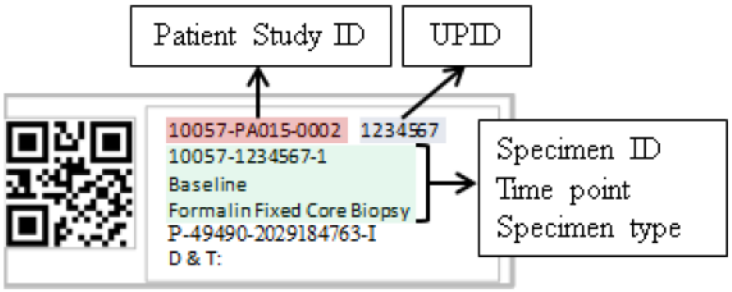
5.3.2.1 Blood Specimen Labels

Include the following on blood specimens (including whole blood):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum)
- Collection date (to be added by hand)

5.3.2.2 Example of Specimen Label

The following image is an example of a tissue specimen label printed on a standard Avery label that is 1" high and 2.625" wide.



The QR code in the above example is for the Specimen ID shown on the second line.
NOTE: The QR code label is currently under development at Theradex as of 31-Aug-2018; therefore, labels generated by the STS for this study may not include a QR code.

The second line item from the end includes four data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. The last alpha-numeric code is protocol specific and is only included if the protocol requires an additional special code classification

The last line on the example label is for the handwritten date and optional time.

5.3.3 Overview of Process at Treating Site

5.3.3.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization, and any prescribed slot

assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

5.3.3.2 Rave Specimen Tracking Process Steps

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, and number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using report in EDC and collect specimen.

- Label specimen containers and write collection date on each label. After collection, store labeled specimens as described in Section 5.4.2.

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form: Enter collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: Select additional specimens to add to an existing shipment referenced by the tracking number.

Step 5: Print shipping list report and prepare to ship.

- Print two copies of the shipping list, one to provide in the box, the other for your own records.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

5.4 Specimen Collection

5.4.1 Blood Collection

5.4.1.1 Collection of Blood in EDTA Tubes for Whole Blood Processing

1. Label EDTA tubes according to the instructions in Section 5.3.2.
2. Collect 7 mL blood in EDTA tube(s) and gently invert tube to mix.
3. Ship on day of collection (whenever possible) according to instructions in Section 5.5.
4. If blood cannot be shipped on the day of collection (e.g., a late scheduled collection), then refrigerate until shipment.

5.4.1.2 Collection of Blood in Sodium Heparin Tubes for Whole Blood Processing

1. Label Sodium Heparin tubes according to the instructions in Section 5.3.2.
2. Collect 7 mL blood in Sodium Heparin tube(s) and gently invert tube to mix.
3. Ship on day of collection (whenever possible) according to instructions in Section 5.5.
4. If blood cannot be shipped on the day of collection (e.g., a late scheduled collection), then refrigerate until shipment.

5.5 Shipping Specimens from Clinical Site to the Biopathology Center (BPC)

5.5.1 General Shipping Information

Fresh blood should be shipped as one shipment at ambient temperature, whenever possible. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container.

5.5.2 Specimen Shipping Instructions

Fresh blood may be shipped on Monday through Friday. Please select "Saturday Delivery" when shipping fresh blood on a Friday.

5.5.2.1 Shipping Blood in Single-Chamber kit

1. Before packaging specimens, verify that each specimen is labeled according to instructions in Section 5.3.2
2. Place the blood collection tube(s) into a zip-lock bag.
3. Place zip-lock bag into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
4. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
5. Place the specimen(s) and a copy of the shipping manifest into a sturdy shipping container. In winter months, please use an insulated container and include extra

insulation, such as bubble wrap, inside the shipping container to prevent specimens from freezing.
6. Close the container and tape shut.
7. Attach a shipping label printed from the Kit Management system (https://ricapps.nationwidechildrens.org/KitManagement) to the top of the shipping container.
8. Attach a Biological Substance Category B sticker to the side of the container.
9. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt

5.5.3 Shipping Address

Ship to the address below. Ship fresh blood specimens the same day of specimen collection. Do not ship specimens the day before a holiday.

Biopathology Center (BPC) at Nationwide Children's Hospital (NCH)
The Research Institute at Nationwide Children's Hospital
700 Children's Drive, WA1340
Columbus, Ohio 43205
PH: (800) 347-2486 FAX: 614-722-2897
Email: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred.

5.5.4 Contact Information for Assistance

For all queries, please use the contact information below:

Biopathology Center (BPC) at Nationwide Children's Hospital (NCH)
The Research Institute at Nationwide Children's Hospital
700 Children's Drive, WA1340
Columbus, Ohio 43205
PH: (800) 347-2486 FAX: 614-722-2897
Email: BPCBank@nationwidechildrens.org

5.6 Biomarker Plan

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Blood-based Biomarkers							
1	MSD V-plex (a combination of a Proinflammatory Panel 10 -plex and 2 plex and 1-plex)	INF gamma, IL-10, IL-12p70, IL-13, IL-1beta, IL-2, IL-4, IL-6, IL-8, TNF-alpha, GM-CSF, IL-15, MIP-1a CLIA: N	Exploratory Evaluation of Cytokine Storm-induced hypoxic pneumonitis, prospective research	Serum from Blood in Sodium Heparin Tubes and EDTA Tubes	Baseline Every 12 hours for four collections 72 hours after initial treatment 7 days after initial treatment if still hospitalized	O	Frederick National Labs John Inglefield jon.inglefield@nih.gov
2	SARS-CoV-2 Viral Load	TBD CLIA N	Exploratory	Serum from Blood in Sodium Heparin Tubes and EDTA Tubes	Baseline Every 12 hours for four collections 72 hours after initial treatment 7 days after initial treatment if still hospitalized	O	TBD

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
3	Tocilizumab pharmacokinetics	TBD CLIA: N	Exploratory Determination of tocilizumab PK profile for exposure/response analysis	Serum from Blood in Sodium Heparin Tubes	Baseline Every 12 hours for four collections 72 hours after initial treatment 7 days after initial treatment if still hospitalized	O	TBD

5.7 Exploratory/Ancillary Correlative Studies

5.7.1 MSD V-plex (a combination of a Proinflammatory Panel 10 -plex and 2 plex and 1-plex)

5.7.1.1 Specimen(s) Receipt and Processing at the Biopathology Center

Whole blood in Sodium Heparin and EDTA tubes will be processed into serum, aliquoted and frozen prior to storage prior to sending to the laboratory for analysis.

5.7.1.2 Site(s) Performing Correlative Study

The MSD V-plex panel will be run at the Frederick National Labs under the direction of John Inglefield and others to be named.

5.7.2 SARS-CoV-2 Viral Load

5.7.2.1 Specimen(s) Receipt and Processing at the Biopathology Center

Whole blood in Sodium Heparin and EDTA tubes will be processed into serum, aliquoted and frozen prior to storage prior to sending to the laboratory for analysis.

5.7.2.2 Site(s) Performing Correlative Study

The SARS-CoV-2 viral load will be run at a Laboratory to be determined.

5.7.3 Tocilizumab Pharmacokinetics

5.7.3.1 Specimen(s) Receipt and Processing at the Biopathology Center

Whole blood in Sodium Heparin tubes will be processed into serum, aliquoted and frozen prior to storage prior to sending to the laboratory for analysis.

5.7.3.2 Site(s) Performing Correlative Study

The tocilizumab pharmacokinetics will be run at a Laboratory to be determined.

6. TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered on an inpatient basis. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7.

Dosing:

- Subjects will receive a first dose of tocilizumab as described in the table below.
    - A single dose should not exceed 800 mg regardless of weight.
    - Patients who are not intubated or will not be imminently intubated will start at a lower dose as per Table 1, with the potential to dose-escalate on subsequent dosing
    - Data provided by Genentech confirms sIL-6 saturation at 4 mg/kg though the duration is slightly less than for the 8 mg/kg. For those not requiring mechanical ventilation, this lower dose is closer to what was used in the Wuhan report. For those under 30 kg in weight, the 6 mg/kg is extrapolated to be equivalent to 4 mg/kg in heavier/larger patients. Otherwise the doses are as per the tocilizumab package insert for adults and children.
- Response to a first dose of tocilizumab should be assessed prior to proceeding with subsequent dosing
    - It may take up to 6 hours following the completion of the infusion to see response to tocilizumab. Usually the first signs are with resolution or improvement in fevers.
- A second dose of tocilizumab may be given between 8 hours and 7 days following completion of the first infusion. A second infusion could be considered for the following reasons:
    - Sustained or recurrent fever **OR**
    - No decrease or not more than a 1-category improvement on the 7-category ordinal scale (only stabilization or partial improvement following first dose) **OR**
    - A ≥1-category worsening on the 7-category ordinal scale from nadir

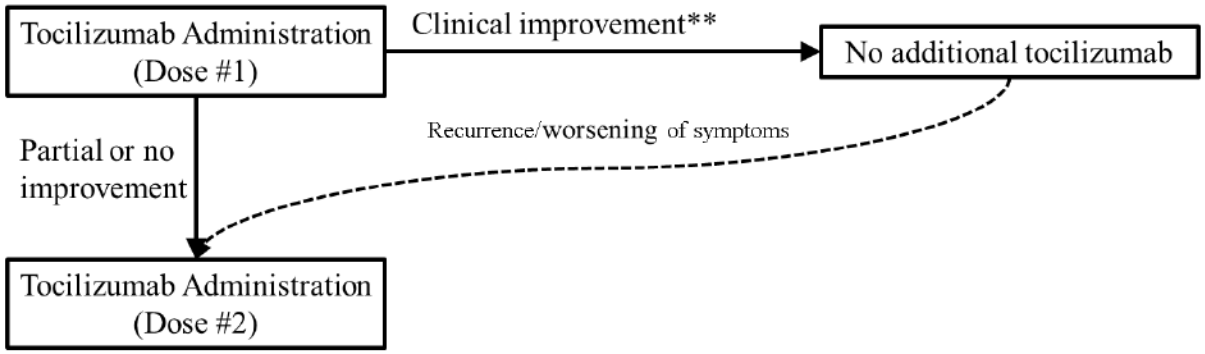
(only Ordinal Scales 3-6 are eligible for initial dose of tocilizumab)

For those at or above 30 kg (≥):			
Cohort	**Clinical Status Description**	**Dosing for Initial Dose**	**Dosing for Second Dose***
A1	**3-4** (Not on mechanical ventilation at time of registration and no immediate plan for intubation)	4 mg/kg	8 mg/kg **(ordinal scale 2 may receive if clinically indicated)***
B1	**5-6** (On mechanical ventilation at time of enrollment or imminent intubation indicated)	8 mg/kg	8 mg/kg
For those below 30 kg (<):			
Cohort	**Clinical Status Description**	**Dosing for Initial Dose**	**Dosing for Second Dose***
A2	**3-4** (Not on mechanical ventilation at time of registration and no immediate plan for intubation)	6 mg/kg	12 mg/kg **(ordinal scale 2 may receive if clinically indicated)***
B2	**5-6** (On mechanical ventilation at time of enrollment or imminent intubation indicated)	12 mg/kg	12 mg/kg

- Maximal administrated dose, for a single dose: **800 mg regardless of weight**
- Optimal response to tocilizumab may not be seen until 5-6 hours after completion of the initial infusion and will typically manifest with resolution of/improvement in fever prior to other clinical signs

*A second dose may be given if there is sustained or recurrent fever, no decrease or not more than a 1-category improvement on the 7-category ordinal scale (only stabilization or partial improvement following first dose), or a ≥1-category worsening on the 7-category ordinal scale from nadir. The second dose **may be given between 8 hours and 7 days from completion of the first dose**. In many cases a second dose may not be necessary to achieve optimal benefit.

6.2 Treatment Schema



**Optimal response to tocilizumab may not be seen until 5-6 hours after completion of the initial infusion and will typically manifest with resolution of/improvement in fever prior to other clinical signs

Subjects with no objective improvement after 2 doses are unlikely to benefit from further administration of tocilizumab and alternative therapies should be considered.

6.3 Concomitant Medications/Therapy

6.3.1 Concurrent Therapy

Subjects will receive concurrent standard of care therapy at the discretion of the treating team. Corticosteroids may be used as clinically indicated in the treatment of SARS/ARDS.

Concurrent cancer therapy can be continued at the discretion of the treating team, with the following exclusion:

- Initiation of myelosuppressive chemotherapy for patients in remission (*e.g.*, adjuvant chemotherapy for breast cancer, AML consolidation) is prohibited while on study until clinical recovery (attainment of 1 or 2 on the 7-category ordinal scale)

Patients receiving steroids as part of cancer therapy can continue to receive steroids, but if a delay in steroids can be implemented that is preferable.

Treatment with any concurrent investigational agent is prohibited, except for:

- Investigational SARS-CoV-2 (COVID-19) anti-viral agents
- Convalescent serum
- Any investigational anti-cancer therapy aimed at treating the underlying disease

Treatment with any additional investigational agent directed at pulmonary complications of COVID-19 is prohibited through 14 days after the last dose of tocilizumab for those who remain on study, with exception for treatment that may be considered life-saving.

6.3.2 Infection Prophylaxis

Infection prophylaxis with antimicrobial therapy should be initiated as per the institutional clinical practice guidelines. Given the risk of viral reactivation with use of tocilizumab, patients with a known history of viral infection should be on appropriate antiviral prophylaxis as feasible. Intravenous immunoglobulin may be utilized as clinically indicated. Surveillance blood and fungal cultures must be performed per institutional guidance in neutropenic patients.

6.3.3 Hematologic Support

Growth factor support (*e.g.*, GCSF/filgrastim) may be used as clinically indicated in the setting of severe infection.

Using daily CBCs as a guide, the patient will receive platelets and packed red blood cells (PRBCs) as needed. Attempts will be made to keep hemoglobin >8.0 gm/dL, and platelet count >10,000/mm^3 (for afebrile patients) and >20,000/mm^3 (for febrile patients). All blood products should be irradiated. Leukocyte filters should be utilized for all blood and platelet transfusions to decrease sensitization to transfused WBCs and decrease the risk of CMV infection.

In patients with symptomatic coagulopathy, attempts will be made to keep platelets >50,000/mm^3 and fibrinogen above the lower limit of normal.

6.3.4 Clinical Trials or Alternative COVID-19 Directed therapies

Patients may be concurrently enrolled on alterative clinical trials or be receiving alternative COVID-19 directed therapies, including anti-virals, azithromycin, convalescent plasma, or anti-malarials amongst others. Patients may NOT be enrolled on concurrent trials with IL-6 directed therapy or be receiving other IL-6 directed therapies. It is requested that if patients are on other clinical trials, those trials should be checked for specific prohibition of tocilizumab therapy. In the case where the other clinical trial in which the patient is participating prohibits tocilizumab therapy, treating physicians should make a decision based on best judgment whether to enroll the patient on this trial.

6.3.5 CYP450 Substrates

Cytochrome P450 enzymes in the liver are down-regulated by infection and inflammation stimuli

including cytokines such as IL-6. Inhibition of IL-6 signaling in patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab, leading to increased metabolism of drugs that are CYP450 substrates. *In vitro* studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Its effect on CYP2C8 or transporters is unknown. *In vivo* studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure one week following a single dose of tocilizumab, respectively. The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of tocilizumab, in patients being treated with these types of medicinal products, perform therapeutic monitoring of effect (*e.g.*, warfarin) or drug concentration (*e.g.*, cyclosporine or theophylline) and the individual dose of the medicinal product adjusted as needed. Exercise caution when co-administering tocilizumab with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, *e.g.*, oral contraceptives, lovastatin, atorvastatin, *etc*. The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.

6.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for up to 2 doses of tocilizumab or until one of the following criteria applies:

- COVID-19 disease progression using the Clinical Status Scale
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

6.5 Duration of Follow-Up

Patients will be followed for at least 60 days after tocilizumab infusion; attempts to follow up for up to a year will be made. Any follow-ups occurring after discharge from hospitalization may

occur via telephone if all toxicities have resolved. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 Dosing Delays

- Dosing should be held if subjects develop a new serious infection following tocilizumab (not including SARS-CoV-2) and not resumed until the infection is under control
- Consider monitoring in the event neurotoxicity (*e.g.*, new seizures, delirium) and potential delay in dosing. Consider initiation of corticosteroids for the treatment of neurotoxicity
- Patients with hypersensitivity reactions to the first dose of tocilizumab should not receive a second dose.

7.2 Dosing Modifications

- No dose adjustment is required in patients with mild or moderate renal impairment. The safety and efficacy have not been well studied in those with hepatic impairment.

8. PHARMACEUTICAL INFORMATION

8.1.1 Tocilizumab (NSC 820013)

Other Names: Actemra

Classification: monoclonal antibody inhibitor of IL-6 receptor

Mode of Action:

Tocilizumab binds specifically to both soluble IL-6R (sIL-6R) and membrane-bound IL-6R
(mIL-6R) and has been shown to inhibit sIL-6R and mIL-6R□mediated signaling.

Description:

Tocilizumab is a recombinant humanized, anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) sub-class directed against the soluble and membrane-bound interleukin 6 receptor (IL-6R).

How Supplied:

Tocilizumab is supplied by Genentech and distributed by the Pharmaceutical Management Branch, CTEP, DCTD, NCI as a preservative-free, sterile, clear, colorless to pale yellow solution in 80 mg / 4 mL, 200 mg / 10 mL, and 400 mg / 20 mL vials for further dilution prior to intravenous infusion. In addition to tocilizumab, each vial contains, disodium phosphate dodecahydrate/sodium dihydrogen phosphate dihydrate buffered solution,

polysorbate 80, sucrose, and Water for Injection to adjust the concentration to 20 mg/mL.

Preparation:

Patient < 30 kg: prepare infusion using a 50 mL infusion bag or bottle
Patient ≥ 30 kg: prepare infusion using a 100 mL infusion bag or bottle

1. Withdraw a volume of 0.9% or 0.45% Sodium Chloride Injection, USP, equal to the volume of the tocilizumab injection required for the patient's dose from the infusion bag.
2. Withdraw the amount of tocilizumab for intravenous infusion from the vial(s) and add slowly into the 0.9% or 0.45% Sodium Chloride Injection, USP infusion bag or bottle. To mix the solution, gently invert the bag to avoid foaming.

Storage:

Store intact vials refrigerated at 2ºC to 8ºC (36°F to 46°F). Do not freeze. Protect the vials from light by storage in the original package.

If a storage temperature excursion is identified, promptly return tocilizumab to 2ºC to 8ºC (36°F to 46°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability:

Refer to the package label for expiration.

Diluted tocilizumab solutions for infusion using **0.9% Sodium Chloride Injection**, USP may be stored at 2° to 8°C (36° to 46°F) or room temperature for up to 24 hours and should be protected from light. If not used immediately following preparation, store prepared infusion bags in the refrigerator.

Diluted tocilizumab solutions for infusion using **0.45% Sodium Chloride Injection**, USP may be stored at 2° to 8°C (36° to 46°F) for up to 24 hours or room temperature for up to 4 hours and should be protected from light. If not used immediately following preparation, store prepared infusion bags in the refrigerator.

Diluted tocilizumab solutions are compatible with polypropylene, polyethylene and polyvinyl chloride infusion bags and polypropylene, polyethylene and glass infusion bottles.

CAUTION: The single-use dosage form contains no antibacterial preservatives. Therefore, any unused product remaining in the vial after the dose has been prepared must be discarded.

Route of Administration: intravenous

Method of Administration:

- Allow the diluted tocilizumab solution to reach room temperature prior to infusion.
- Administer intravenously over 60 minutes. Do not administer as an intravenous push or bolus.

- Tocilizumab should not be infused concomitantly in the same intravenous line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of tocilizumab with other drugs.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulates and discolorations are noted, the product should not be used.

Potential Drug Interactions:

Cytochrome P450s in the liver are down-regulated by infection and inflammation stimuli including cytokines such as IL-6. Inhibition of IL-6 signaling in patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab, leading to increased metabolism of drugs that are CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Its effect on CYP2C8 or transporters is unknown. In vivo studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure one week following a single dose of tocilizumab, respectively. The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of tocilizumab, in patients being treated with these types of medicinal products, perform therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) and the individual dose of the medicinal product adjusted as needed. Exercise caution when co-administering tocilizumab with CYP3A4 substrate drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy. Avoid concomitant use with live vaccines.

Patient Care Implications:

Male and female patients receiving tocilizumab should maintain adequate contraceptive measures during and for a minimum of 28 days after the last dose of tocilizumab.

Availability

Tocilizumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Tocilizumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.5).

8.1.2 Agent Ordering and Agent Accountability

8.1.2.1 NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The

eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

The CTEP Pharmaceutical Management Branch (PMB) will provide direction as to when sites can order PMB-supplied agents.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.2.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.3 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This is an interventional study to evaluate clinical outcomes of tocilizumab in severe COVID-19 disease and to describe resource utilization of intensive health care resources on a patient level basis.

The primary endpoint of this study is the clinical outcome of patients administered at least one dose of tocilizumab as evaluated per the 7-category disease severity ordinal scale presented in the Schema.

9.2 Sample Size/Accrual Rate

The accrual rate to this trial is expected to be brisk owing to the rapid acceleration of COVID-19 cases. The trial will treat up to approximately 217 patients. Efforts to enroll around 20 pediatric patients to this trial will be made. Efforts to include institutions that serve pediatric cancer populations with COVID-19 among children have been prioritized. The investigators will monitor enrollment of pediatric patients and inclusion of additional pediatric sites will be undertaken as feasible. There are two cohorts: cohort A (not on mechanical ventilation and no imminent risk of requiring it); cohort B (on or at imminent risk of mechanical ventilation).

Accrual will be tracked, and outcomes evaluated both cumulatively and also by the following age stratification: Stratum 1) 2 years-14 years; Stratum 2)15-39 years; Stratum 3) 40-64 years; Stratum 4) 65 years and over.

There will be no accrual halt while the data from the initial patients is collected and gathered. There will be repeated assessment of clinical outcomes after every 20 additional patients per cohort are enrolled to provide ongoing safety monitoring. Accrual will be halted if there is evidence of harm due to tocilizumab. Evidence of harm will be evaluated to include the following:

- Increase in rare but serious adverse events associated with tocilizumab administration such as evidence that anaphylaxis is occurring in more than 15% of patients.
- In Cohort A, if more than 25% of patients die within 48 hours, the protocol team will evaluate the cases to determine whether enrollment should be paused.
- Cohort B is expected to have a potentially high death rate from COVID-19 disease. The protocol team will monitor the deaths to evaluate according to underlying cancer type (hematologic, thoracic, other solid tumors), whether the underlying cause of death is related to the study treatment rather than to the cancer type, and severity of COVID-19 disease.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	5	5	0	0	**10**
Asian	4	3	0	0	**7**
Native Hawaiian or Other Pacific Islander	2	1	0	0	**3**
Black or African American	20	18	6	6	**50**
White	75	51	13	6	**145**
More Than One Race	1	1	0	0	**2**
Total	**107**	**79**	**19**	**12**	**217**

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9.3 Stratification Factors

Stratum 1) 2 years-14 years; Stratum 2)15-39 years; Stratum 3) 40-64 years; Stratum 4) 65 years and over.

9.4 Toxicity Reporting and Exclusions

9.4.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first infusion with tocilizumab.

9.4.2 Clinical Outcome Evaluation

Patients will be evaluated and scored for severity of COVID-19 illness at baseline and once daily following the first administration of tocilizumab until discharge from the hospital or Day 60, whichever is first. For the purposes of this protocol, a response will be defined as a point reduction in symptoms as assessed by the Clinical Status Ordinal at baseline and after tocilizumab administration.

Based on the response criteria outlined in Sections 9.4.2.1 and 9.4.2.2 below, subjects meeting the definition of either complete or partial response as their best response by Day 14 following tocilizumab administration will be considered as having benefitted from tocilizumab.

Response determinations will be made daily over the course of hospitalization. The time to achieve the best response, as well as the number of doses received to achieve the best response, will be captured for each treated patient.

A final clinical status response determination will also be provided at the time the patient is either: 1) alive and discharged from the hospital; 2) has died or 3) meets off-study criteria.

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations. Each patient will be assigned to one of the following cohorts:

- **Cohort A** –not on mechanical ventilation at time of registration and no immediate plan for intubation
- **Cohort B**—On mechanical ventilation at time of registration or imminent intubation indicated

9.4.2.1 Clinical Outcome evaluation Cohort A (NOT on mechanical ventilation)

- Complete response: reduction in severe symptoms such that they are not life-threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise) and can be discharged from hospital
- Partial response improvement in clinical status score by at least one point but requires continued hospitalization
- Progressive disease: Clinical score changes to a 5 or 6 (see Schema for the Clinical Ordinal Scale)
- Death

9.4.2.2 Clinical Outcome evaluation Cohort B (on mechanical ventilation)

- Complete response: reduction in severe symptoms such that they are not life-threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise) and can be discharged from hospital
- Ventilator Complete Response: Removal from mechanical ventilation and discharge from ICU/ICU eligibility
- Partial response: Discharged from ICU but requires continued hospitalization
- Ventilator Partial Response: Removal from mechanical ventilation and but require non-invasive ventilation or high flow O2 continued ICU support/remains ICU eligible
- Progressive disease: No decrease in supportive care deemed possible
- Death

Subjects who have progressive disease (no decrease in supportive care deemed possible) or death from COVID-19 will be considered as a Treatment failure

9.4.3 Population for Analysis

All of the patients who met the eligibility criteria and are infused with at least one dose of tocilizumab will be included in the clinical outcome analysis. Thus, an incorrect treatment schedule or drug administration will not result in exclusion from the analysis of the response rate. Treatment failure will be defined by any progressive disease or death as per the response criteria in section 12.1 and 12.2. For those subjects who are enrolled but not infused, reasons for non-infusion will be captured as feasible.

9.5 Data Collection

Data will be collected during the treatment of these patients as well as during their follow-up in order to gain additional information concerning the efficacy and adverse events of tocilizumab in this population. The primary indicator of efficacy will be the frequency of response, length of time from level of care to step down level of care, and survival. Because long term outcomes are of interest, follow-up of patients until death is important.

Additionally, intubation and cause of death will also be captured in support of the trial objectives. See Appendix A for a list of collections that should be recorded in the Case Report Form (CRF).

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

AE monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

Due to the narrow safety profile of tocilizumab compared to the adverse events expected from the underlying condition of the patients, collection of adverse event data will be limited to:

- Grade 5 adverse events (deaths)
- Grade 1-5 adverse events of special interested listed in Section 10.3.4
- Additional serious or life-threatening infection (other than COVID-19)
- Any other grade 3-4 adverse events considered related to tocilizumab per routine and serious reporting guidelines in Sections 10.3.3 and 10.4

10.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

10.1.1 CAEPR for Tocilizumab (Actemra®, RO4877533, NSC 820013)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting

Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification *Frequency is provided based on 8726 patients*. Below is the CAEPR for Tocilizumab (RO487753).

> **NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.0, April 14, 2020[1]

Adverse Events with Possible Relationship to Tocilizumab (RO4877533) (CTCAE 5.0 Term) [n=8726]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
		Gastrointestinal disorders - Other (gastrointestinal perforations)	
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (Hepatoxicity)[2]	
IMMUNE DISORDERS			
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[3]		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
	Neutrophil count decreased		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Hepatoxocity includes drug induced liver injury (DILI), acute liver failure, hepatitis, and jaundice

[3]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on tocilizumab (RO487753) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that tocilizumab (RO487753) caused the adverse event:

ENDOCRINE DISORDERS - Hypothyroidism
GASTROINTESTINAL DISORDERS - Abdominal pain; Gastric ulcer; Gastritis; Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Injection site reaction
IMMUNE SYSTEM DISORDERS- Allergic reaction
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Infusion related reaction
INVESTIGATIONS - Blood bilirubin increased; Cholesterol high; Fibrinogen decreased; Platelet count decreased; Weight gain; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypertriglyceridemia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Dizziness; Headache

RENAL AND URINARY DISORDERS - Renal and urinary disorders - Other, specify (nephrolithiasis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Pruritus; Rash maculo-papular; Urticaria; Stevens-Johnson Syndrome
VASCULAR DISORDERS - Hypertension

Note: Tocilizumab (RO487753) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section 10.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

Adverse event (AE) monitoring and reporting for this trial is limited to grade 4 and 5 events that have an attribution of Probable or Definite to tocilizumab.

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

10.3 Expedited Adverse Event Reporting

10.3.1 Rave-CTEP-AERS Integration

The Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-

AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query-free (fields added to the form during study build do not need to be query-free for the integration call with CTEP-AERS to be a success).

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents > Education and Promotion, and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

10.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

10.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality as long as the death occurred within 30 days after the last administration of the investigational agent. Attribution to treatment or other cause must be provided.

Death due to **progressive disease from COVID-19** should be reported as **Grade 5** "Infections and Infestations, Other, **COVID-19 Disease progression."** Evidence that the death was a manifestation of underlying COVID-19 disease (*e.g.*, radiological changes suggesting clinical deterioration associated with a disease process) should be submitted.

Death due to **progressive disease of cancer** should be reported as **Grade 5** "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, as per the below table (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Relatedness	Grade 1 – 3 Timeframes	Grade 4 Timeframes	Grade 5 Timeframes
Unrelated Unlikely	Not required	Not required	24-Hour + 5 Calendar Days
Possible Probable Definite	Not required	24-Hour + 5 Calendar Days	24-Hour + 5 Calendar Days
Expedited AE reporting timelines are defined as: "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.			
Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: **Expedited 24-hour notification followed by complete report within 5 calendar days for:** All Grade 4 and Grade 5 AEs			

10.3.4 Adverse Events of Special Interest

At the request of the pharmaceutical collaborator, the following events are of special interest, and both routine and expedited reporting will be collected on this trial.

Tocilizumab Events of Special Interest are:

- Serious and/or medically significant infections (excluding COVID-19)
- Myocardial infarction/Acute coronary syndrome
- Medically significant bleeding events
- Gastrointestinal perforations
- Malignancies (excluding existing malignancy type)
- Anaphylaxis/Hypersensitivity reactions
- Demyelinating disorders
- Stroke
- Cases of potential drug-induced liver injury (DILI) 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 × ULN in combination with total bilirubin > 2 × ULN
    - Treatment-emergent ALT or AST > 3 × 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

10.4 Routine Adverse Event Reporting

Adverse Events **must** be reported in routine study data submissions as follows:

- Adverse Events of Special Interest per section 10.3.4 regardless of relatedness: grades 1-5
- Other routine adverse events **related to tocilizumab**: grades 3-4
- All grade 5 adverse events regardless of relatedness

Reminder: AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

11. STUDY CALENDAR

Routine evaluations for the hospitalized patients can be used for the baseline studies

	Baseline	Day 1	Every 12 Hours four times following first dose of tocilizumab	Every 24 Hours until hospital discharge	72 hours after initial dose	7 days after initial dose[e]	Off Treatment[a]
Tocilizumab		A, B					
Informed consent	X						
Demographics	X						
Medical history	X						
Concurrent meds	X	X----------X[f]					
Physical exam	X						
Vital signs	X			X[g]			
Height	X						
Weight	X						
BSA	X						
BMI	X						
Performance status	X						
COVID-19 testing	X						
Oxygen Saturation	X			X[g]			
CBC w/diff, plts	X		X[g]	X			X[g]

Serum chemistry[b]	X						
PT, PTT, INR,	X[g]		X[g]				X[g]
fibrinogen, D-dimer	X[g]		X[g]				X[g]
Ferratin	X[g]		X[g]				X[g]
C-reactive Protein	X[g]		X[g]				X[g]
SMA20	X[g]		X[g]				X[g]
Adverse event evaluation	X	X----------X					
Chest X-Ray (AP and lateral) (as clinically indicated)[d]	X						
Pregnancy test[c]	X						
Blood collection in Sodium Heparin tube for cytokine release syndrome analysis and SARS-CoV-2 viral load[d]	X[d]		X[d]		X[d]	X[d]	
Blood collection in Sodium Heparin tube for tocilizumab PK analysis	X[d]		X[d]		X[d]	X[d]	
Blood collection in EDTA tube for and SARS-CoV-2 viral load[d]	X[d]		X[d]		X[d]	X[d]	

A, B: Tocilizumab: Dose as assigned by Cohort; IV. A second dose may be given between 8 hours and 7 days after the completion of the first infusion, if there is sustained or recurrent fever, no decrease or not more than a 1-category improvement on the 7-category ordinal scale (only stabilization or partial improvement following first dose), or a ≥1-category worsening on the 7-category ordinal scale from nadir.

a: Off-treatment evaluation. Vital status to be assessed at Day 14, Day 30 and Day 60 after last dose of tocilizumab.

b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

c: Pregnancy test for women of childbearing potential at the discretion of the patient and physician.

d: Optional. For pediatric patients, all blood collections are optional. Baseline and 72 hour specimens should be prioritized for collection. For the every 12 hour collection schedule, pediatric patients should only have two collections
e: If the patient is still hospitalized
f: For patients in the ICU, daily medication recording is not necessary. Collect only yes or no for the duration of the ICU stay: was on vasopressors, was on antibiotics, was on antiviral; was on anticoagulant.
g: Optional. The clinical care blood draws will be captured from the routine blood draws at most for the times indicated. Since these can be very ill patients, they may have clinical blood draws much more frequently than listed here.

12. MEASUREMENT OF EFFECT

Refer to the disease response criteria in Section 9.4.2 for metrics of measuring the effect of tocilizumab administration on disease severity.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

13.2 Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account, and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
    - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type,
    - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR, and

- To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs. Enrollments credited to an NCTN Network Group including COG and NCORP will have the cases included as part of the Network Groups routine audits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission.

13.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave

Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

13.4 CTEP Multicenter Guidelines

N/A

13.5 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

14. REFERENCES

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APPENDIX A SUMMARY TABLE FOR PATIENT DEMOGRAPHICS AND LABORATORY VALUES TO BE RECORDED ON THE CRF

Medical history: (Mandatory)
Cancer diagnosis (solid tumor, leukemia, lymphoma, autoimmune, bone marrow transplant, Solid organ transplant, immunosuppressed)
Cancer stage if known
Age (Stratum: 1) 2 years-14 years; Stratum 2)15-39 years; Stratum 3) 40-64 years; Stratum 4) 65 years and over.
Newly diagnosis vs relapsed/refractory
Active therapy vs completed therapy
Type of recent prior therapy (chemotherapy, small molecule, radiotherapy, immunotherapy, other)
Transfer from a "group" facility, nursing home, rehab, other
Self-Identified Gender (male, female, non-binary)
Race Ethnicity (use standard tables)

Health history (Optional):
Known contact
Smoking
Obese
Chronic lung disease (COPD, Asthma, obstructive sleep apnea, interstitial lung disease, cystic fibrosis, pulmonary hypertension)
Chronic heart disease (CAD, CHF, atrial arrythmia, ventricular arrythmia)
Hypertension
Diabetes mellitus (a1C)

Concomitant medications: (Optional)
Concurrent trial enrollment and treatment (Optional)
Antihypertensives
Anti-hyperglycemics
Anti-HIV drugs
Diuretics
Statin
Brohchodilators
Anticoagulants
Antibiotics
Immunosuppressants
Supplements, including vitamins

Include any COVID-19 directed therapy (Mandatory)
Steroids
Anticoagulants
HIV protease inhibitors
Hydroxychloroquine
Chloroquine

Remdesivir
Tocilizumab
Sarilumab
Other

Presenting symptoms: (Mandatory)
Requirement for non-invasive O_2 supplementation
Requirement for mechanical ventilation in the Emergency Department

Monitoring and recorded in the CRF: (Mandatory at baseline and where indicated; Requested as indicated)
Vital Signs (HR, RR, BP and temperature, **at baseline and daily**; OR per ICU or non-ICU routine
Baseline Height, weight, BSA, BMI
O2 saturation, at baseline and every 24 hours until discharge from hospital
O2 requirement, at baseline and every 24 hours until discharge from hospital
Intubated (yes/no), at baseline and every 24 hours until discharge from hospital
Collection and reporting of all grade 3-5 events attributed to tocilizumab

Labs:
At baseline: (Mandatory)
CBC with differential
ALT/AST

Optional:
PT, PTT, INR, fibrinogen, D-dimer
Ferritin
C-reactive protein
SMA20 (monitor Mg and K frequently as clinically indicated)
Green top sodium heparin tube (for cytokine release syndrome, SARS-CoV-2 viral load, and tocilizumab PK evaluations)
Purple top EDTA tube (for cytokine release syndrome evaluation and SARS-CoV-2 viral load)

Every 12 hours for four collections after first dose of tocilizumab**: (Optional)**
CBC with differential
PT, PTT, INR, fibrinogen, D-dimer
Ferritin
C-reactive protein
SMA20

Every 12 hours for four collections after first dose of tocilizumab **: (Optional research blood collections)**
Green top sodium heparin tube (for cytokine release syndrome SARS-CoV-2 viral load, and tocilizumab PK evaluations)
Purple top EDTA tube (for cytokine release syndrome evaluation and SARS-CoV-2 viral load)

Every 24 hours until discharge from hospital**: (Mandatory)**
CBC with differential

72 Hours after initial dose of tocilizumab: (Optional research blood collections)
Green top sodium heparin tube (for cytokine release syndrome SARS-CoV-2 viral load, and tocilizumab PK evaluations)
Purple top EDTA tube(for cytokine release syndrome evaluation, and SARS-CoV-2 viral load)

7 Days after initial dose of tocilizumab (if still hospitalized): (Optional research blood collections)
Green top sodium heparin tube (for cytokine release syndrome, SARS-CoV-2 viral load, and tocilizumab PK evaluations)
Purple top EDTA tube (for cytokine release syndrome evaluation, and SARS-CoV-2 viral load)

Optional

Off treatment:
CBC with differential
PT, PTT, INR, fibrinogen, D-dimer
Ferritin
C-reactive protein
SMA20

Optional

Imaging Report: (Descriptive or Radiology Reading/Report)
Baseline
CXR, AP and lateral (Unchanged, Worsened, Improved)
As clinically indicated

Treatment with tocilizumab: (Mandatory). Use 24 hour clock
Date and time of first dose of tocilizumab and amount administered
Did fever resolve within 6 hours of tocilizumab administration?
Did respiratory support decrease within 6 hours of tocilizumab administration?
Date and time of second dose of tocilizumab and amount administered?
Did fever resolve within 6 hours of 2nd dose of tocilizumab administration?
Did respiratory support decrease within 6 hours of tocilizumab administration?
NO tocilizumab administered

Clinical outcome Evaluation:
Response evaluation Cohort A (NOT on mechanical ventilation)

- Complete response: reduction in severe symptoms such that they are not life-threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise) and can be discharged from hospital
- Partial response: Improvement in clinical status score by at least one point but requires continued hospitalization

- Progressive disease: Clinical score changes to a 5 or 6 (see Schema for the Clinical Ordinal Scale)
- Death

Subjects who have progressive disease (no decrease in supportive care deemed possible) or death from COVID-19 will be considered as a Treatment failure

Clinical outcome evaluation Cohort B (on mechanical ventilation)

- Complete response: reduction in severe symptoms such that they are not life-threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise) and can be discharged from hospital
- Ventilator Complete Response: Removal from mechanical ventilation and discharge from ICU/ICU eligibility
- Partial response: Discharged from ICU but requires continued hospitalization
- Ventilator Partial Response: Removal from mechanical ventilation and but require non-invasive ventilation or high flow O2 continued ICU support/remains ICU eligible
- Progressive disease: No decrease in supportive care deemed possible
- Death

Subjects who have progressive disease (no decrease in supportive care deemed possible) or death from COVID-19 will be considered as a Treatment failure