Protocol

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

Protocol for: Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med 2021;384:20-30. DOI: 10.1056/NEJMoa2030340

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

PROTOCOL

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TOCILIZUMAB IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA**
PROTOCOL NUMBER:	ML42528
VERSION NUMBER:	1
EUDRACT NUMBER:	2020-001154-22
IND NUMBER:	148225
NCT NUMBER:	To be determined
TEST PRODUCT:	Tocilizumab (RO4877533)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
29-Apr-2020 19:57:07	[redacted]	[redacted]

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PROTOCOL ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TOCILIZUMAB IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA**
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by the CRO.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TOCILIZUMAB IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA**
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PHASE:	Phase III
INDICATION:	COVID-19 pneumonia
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the efficacy and safety of tocilizumab (TCZ) compared with a placebo in combination with SOC in hospitalized patients with COVID-19 pneumonia. To enhance the understanding of the clinical profile of tocilizumab for patients who belong to high-risk and minority populations, an emphasis will be placed on including minority-enrolling sites. Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with standard of care (SOC) for the treatment of COVID-19 pneumonia on the basis of the following endpoint:

- Cumulative proportion of patients requiring mechanical ventilation by Day 28

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status
- Time to clinical failure, defined as the time to death, mechanical ventilation, intensive care unit (ICU) admission, or withdrawal (whichever occurs first)
- Mortality rate by Day 28
- Time to hospital discharge or “ready for discharge” (e.g., awaiting social disposition) as evidenced by, for example, normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Change from baseline in inflammatory markers levels (high sensitivity C-reactive protein [hs-CRP], D-dimer, and ferritin) over time
- Cumulative proportion of patients requiring CPAP or BIPAP by Day 28

Safety Objective

The safety objective for this study is to evaluate the safety of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0
- Incidence of any post-treatment bacterial and/or fungal infection
- Incidence of any post-treatment acute kidney injury (defined by 50% increase of creatinine from baseline)

STUDY DESIGN

Description of the Study

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of TCZ in combination with SOC compared with placebo in combination with SOC in hospitalized adult patients with COVID-19. The Sponsor intends to enroll approximately 379 patients that have been diagnosed with COVID-19 pneumonia and meet the entry criteria.

Patients must be at least 18 years of age with confirmed SARS-CoV-2 (COVID-19) infection per World Health Organization (WHO) criteria, including a positive polymerase chain reaction (PCR) of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have SpO_2 <94% on ambient air and be on SOC, which may include anti-viral treatment, low dose systemic corticosteroids, and supportive care.

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. Patients with active tuberculosis (TB) or suspected active bacterial, fungal, viral, or other infection (besides COVID-19 and well-controlled HIV) will be excluded from the study.

Patients will be screened and randomized within 48 hours of hospital admission. Patients will be randomized at a 2:1 ratio to receive blinded treatment of either TCZ or placebo, respectively. Study treatment must be given within approximately 4 hours after randomization. TCZ and placebo will be given in combination with SOC.

Patients assigned to the TCZ arm will receive one infusion of TCZ 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the placebo arm will receive one infusion of placebo, both in addition to SOC.

If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of 2 screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 7 days after previously signing the consent form. The investigator will record the reasons for screen failure in the screening log.

The study assessments to be conducted include the following: physical examination, vital signs, oxygen saturation, assessment of consciousness, presence and absence of respiratory support, adverse events, concomitant therapies, and clinical laboratory tests.

Patients will be followed up for a total of 60 days after first dose of study medication.

If patients are discharged from the hospital prior to Day 28 or discontinue the study, the Study Completion/Discontinuation assessments are to be conducted prior to discharge or at discontinuation from the study. In addition, if patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. Follow-up visits may be conducted by onsite clinic visits, telephone calls, or home visits. After Day 28, all patients should have a follow-up visit on approximately Day 60 which may be conducted as an onsite clinic visit, telephone call, or home visit for discharged patients.

During the study, standard supportive care will be given according to clinical practice. After study completion, patients should be referred to their regular healthcare provider based on their doctor's decision and as part of standard of care.

Number of Patients

This study aims to enroll approximately 379 hospitalized patients with COVID-19 pneumonia.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form by any patient capable of giving consent, or, when the patient is not capable of giving consent, by his or her legal/authorized representative
- Age ≥18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Hospitalized
- COVID-19 pneumonia confirmed per a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid) and radiographic imaging (CT scan or chest X-ray)
- Able to complete screening within 48 hours of hospital admission
- Blood oxygen saturation (SpO_2) <94% while on ambient air

  If a patient is on supplemental oxygen with SpO_2 ≥94%, but desaturation to <94% on lower supplemental oxygen or ambient air is documented during screening, the inclusion criterion is met.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 90 days after the final dose of study drug. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

  Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 60 days after the final dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria

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

- Known severe allergic reactions to TCZ or other monoclonal antibodies
- Require CPAP, BIPAP, or mechanical ventilation
- Active TB infection or last TB infection within 1 month of randomization
- Suspected active bacterial, fungal, viral, or other infection (besides COVID-19 and well-controlled HIV)
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
- Immunocompromised (besides well-controlled HIV) or on immunosuppressive therapy (except for steroids for COVID), advanced cancer
- Have received oral anti-rejection or immunomodulatory drugs (including TCZ) within the past 3 months
- Participating in another IL-6 antagonist clinical trial or other drug clinical trials (participation in COVID-19 anti-viral trials may be permitted if approved by Medical Monitor)
- ALT or AST >5 x upper limit of normal (ULN) detected within 24 hours at screening (according to local laboratory reference ranges)
- ANC <1000/μL at screening (according to local laboratory reference ranges)
- Platelet count <50,000/μL at screening (according to local laboratory reference ranges)
- Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
- Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (investigational COVID-19 antivirals may be permitted if approved by Medical Monitor)
- Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Any history of diverticulitis or gastrointestinal perforation

The use of remdesivir, hydroxychloroquine, chloroquine, and convalescent plasma, is not an exclusion to participation in this trial, and is left to the discretion of the primary medical team.

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for last follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 2 months after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 8 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

Patients assigned to the active arm will receive one or two doses of tocilizumab (TCZ) via intravenous (IV) infusion at a dose of 8 mg/kg IV to a maximum of 800 mg per dose.

Comparator

Patients assigned to the comparator arm will receive one or two doses of placebo via IV infusion.

Statistical Methods

Primary Analysis

The primary efficacy objective for this study is to evaluate the efficacy of TCZ plus standard of care, compared with placebo plus standard of care using the following endpoint:

- Cumulative proportion of patients requiring mechanical ventilation by Day 28

Time to the first utilization of mechanical ventilation after randomization will be analyzed by the Kaplan Meier analysis, with the cumulative proportion of patients requiring mechanical ventilation estimated at Day 28. Details of the primary endpoint analysis will be included in the Statistical Analysis Plan (SAP).

Determination of Sample Size

The estimated sample size was determined based on the time from randomization to the first utilization of mechanical ventilation by Day 28.

The total modified intent-to-treat (mITT) sample size of 379 patients with a 2:1 randomization of TCZ (n=253) to placebo (n=126) provides approximately 80% power using a Logrank test to detect a 15% difference between treatment groups in time to mechanical ventilation by Day 28 under the following assumptions: cumulative survival (i.e., not requiring mechanical ventilation) rates of 75% in the TCZ group and 60% in placebo group, with 28-day follow-up, using a two-sided 5% alpha, and 10% dropout rate in each arm. Sample size re-estimation may be considered during the study based on updated assumptions of the treatment effect.

Planned Interim Analyses

An Internal Monitoring Committee (IMC) will evaluate safety according to procedures and guidelines detailed in the IMC agreement. The IMC will consist of Sponsor representatives who will not be blinded to study data. Details of the safety reviews will be provided in the SAP.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ARDS	acute respiratory distress syndrome
BIPAP	bilevel positive airway pressure
CAR	chimeric antigen receptor
CDC	Centers for Disease Control
CoV	coronaviruses
CPAP	continuous positive airway pressure
CRP	C-reactive protein
CRS	cytokine-release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
EC	Ethics Committee
eCRF	electronic Case Report Form
ECMO	extracorporeal membrane oxygenation
EDC	electronic data capture
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
GCA	giant cell arteritis
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
hs-CRP	high sensitivity C-reactive protein
ICH	International Council for Harmonisation
ICU	intensive care unit
IL-6	interleukin 6
IL-6R	interleukin-6 receptor
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system
LPLV	last patient, last visit
IV	intravenous
MERS-CoV	Middle East respiratory syndrome
MOD	multiple organ dysfunction
MOF	multi-organ failure
mITT	modified intent-to-treat

Abbreviation	Definition
NCI	National Cancer Institute
PaO_2	partial pressure of oxygen
PCR	polymerase chain reaction
PCT	procalcitonin
pJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetic
PY	patient years
RA	rheumatoid arthritis
RT-PCR	real time polymerase chain reaction
SAP	Statistical Analysis Plan
SARS-CoV	severe acute respiratory syndrome
SC	subcutaneous
sJIA	systemic juvenile idiopathic arthritis
sIL-6R	soluble IL-6R
SOC	standard of care
SpO_2	blood oxygen saturation
SSc	systemic sclerosis
TAK	Takayasu arteritis
TB	tuberculosis
TCZ	tocilizumab
ULN	upper limit of normal
WHO	World Health Organization

1. BACKGROUND

1.1 BACKGROUND ON COVID-19 PNEUMONIA

Coronaviruses (CoV) are positive-stranded RNA viruses, named for the crown-like appearance of their spike glycoproteins on the virus envelope. They are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV).

COVID-19, which is the acronym of "coronavirus disease 2019," is caused by a novel coronavirus strain (SARS-CoV-2) and was newly named on 11 February 2020 by the World Health Organization (WHO). An epidemic of cases with unexplained lower respiratory tract infections was first detected in Wuhan, the largest metropolitan area in China's Hubei province, and was reported to the WHO Country Office in China on December 31, 2019. A pandemic was subsequently declared by the WHO on 11 March 2020.

According to the WHO, as of 12 April 2020 over 1,600,000 cases of COVID-19 were reported in over 200 countries and territories worldwide, with over 105,000 deaths (WHO 2020a). Up to ~20% of infected patients experienced complications related to a severe form of interstitial pneumonia, which may progress to acute respiratory distress syndrome (ARDS) and/or multi-organ failure (MOF) and death (WHO 2020b).

To date, there is no vaccine and no specific antiviral medicine shown to be effective in preventing or treating COVID-19. Most patients with mild cases of disease recover with symptomatic treatment and supportive care. However, patients with more severe illness frequently require hospitalization (WHO 2020b).

Cohort studies of ethnically homogeneous patients in China indicate that male gender, and comorbidities such as diabetes, hypertension, and cardiovascular disease predispose to increased risk of infection and morbidity (Li et al. 2020). The U.S. Centers for Disease Control (CDC) published hospitalization rates and characteristics of patients with COVID-19 suggest minority patients may be disproportionately affected by COVID-19, potentially due to increased frequency of underlying conditions (Garg 2020).

1.2 BACKGROUND ON TOCILIZUMAB

Tocilizumab (TCZ) is a recombinant humanized, anti-human monoclonal antibody of the IgG1 subclass directed against soluble and membrane-bound IL-6R. TCZ binds specifically to both soluble IL-6R (sIL-6R) and membrane-bound IL-6R and has been shown to inhibit both soluble and membrane-bound IL-6R–mediated signaling. IL-6 is a pleiotropic pro inflammatory multifunctional cytokine produced by a variety of cell types and has been shown to be involved in diverse physiological processes such as T-cell activation; induction of acute phase proteins; stimulation of hematopoietic precursor cell growth and differentiation; proliferation of hepatic, dermal, and neural cells; bone

metabolism; lipid metabolism; hepatoprotection; and fibrosis. Elevated tissue and serum levels of IL-6 have been implicated in the disease pathology of several inflammatory and autoimmune disorders including rheumatoid arthritis (RA), Castleman disease, systemic juvenile idiopathic arthritis (sJIA), polyarticular juvenile idiopathic arthritis (pJIA), giant cell arteritis (GCA), Takayasu arteritis (TAK), systemic sclerosis (SSc), and cytokine-release syndrome (CRS). Inhibition of the biological activity of IL-6 or IL-6R has been effective in the treatment of these disorders, including chimeric antigen receptor (CAR) T-cell induced CRS, for which treatment with TCZ has been approved in many countries.

TCZ has intravenous (IV) and subcutaneous (SC) formulations. Some of the above-listed indications (RA, sJIA, and pJIA) have received approval for both the IV and SC formulations, whereas others have received approval exclusively for the IV (Castleman disease and CRS) or the SC (GCA and TAK) formulation.

[redacted]

1.3 TOCILIZUMAB TREATMENT IN CYTOKINE-RELEASE SYNDROME OF CAR-T THERAPY

CRS has been identified as a clinically significant, on-target, off-tumor side effect of the CAR T-cell therapies used for treatment of malignancies. Characteristics of CRS include fever, fatigue, headache, encephalopathy, hypotension, tachycardia, coagulopathy, nausea, capillary leak, and multi-organ dysfunction. The reported incidence of CRS after CAR T-cell therapy ranges from 50% to 100%, with 13% to 48% of patients experiencing the severe or life-threatening form. Serum levels of inflammatory cytokines are elevated, particularly interleukin-6 (IL-6). The severity of symptoms may correlate with the serum cytokine concentrations and the duration of exposure to the inflammatory cytokines.

On August 30, 2017, the U.S. Food and Drug Administration approved tocilizumab (Actemra®) for the treatment of severe or life-threatening CAR T cell-induced CRS in adults and in pediatric patients 2 years of age and older. The approved dose is 8 mg/kg for body weight $\geq$30 kg and 12 mg/kg for body weight $<$30 kg. Up to three additional doses may be given if no improvement of sign/symptoms, and the interval between the subsequent doses should be at least 8 hours.

The approval of TCZ was based on a retrospective analysis of data for patients treated with TCZ who developed CRS after treatment with tisagenlecleucel (Kymriah®) or axicabtagene ciloleucel (Yescarta®) in prospective clinical trials, (Le et al. 2018). Thirty-one out of the 45 patients (69%) from the CTL019 series achieved a response (defined as being afebrile and off vasopressors for at least 24 hours within 14 days of the first dose of TCZ (maximum up to two doses) and without use of additional treatment other than corticosteroids) within 14 days of the first dose of TCZ, and the median time from the first dose to response was 4 days. Eight of the 15 patients (53%) from the axicabtagene ciloleucel series achieved a response, and the median time to response was 4.5 days. The response rates were largely consistent among subgroups such as age group, sex, race, ethnicity, grade of CRS at first dose of TCZ, and duration of CRS prior to treatment with TCZ. There were no reports of adverse reactions attributable to TCZ.

Pharmacokinetic (PK) data were available for 27 patients after the first dose of TCZ and for 8 patients after a second dose of TCZ. Based on 131 PK observations, the geometric mean (% CV) maximum concentration of TCZ in the patients with CAR T cell induced, severe or life-threatening CRS was 99.5 μg/mL (36.8%) after the first infusion and 160.7 μg/mL (113.8%) after the second infusion. The PK modeling analysis showed that patients with CRS had a faster clearance of TCZ than healthy volunteers and other patient populations, and simulations showed that exposure was considered acceptable with up to four doses of TCZ at least 8 hours apart in patients with CRS.

TCZ is also approved for CAR-T induced severe or life-threatening CRS in the European Union and certain other countries.

1.4 REAL WORLD EXPERIENCE WITH TOCILIZUMAB IN COVID-19 PNEUMONIA

Physicians in China initiated the off-label use of TCZ in the treatment of COVID-19 pneumonia. Based on the results of an initial 21-patient retrospective study in which patients with severe or critical COVID-19 pneumonia were treated with TCZ (Submitted, Xu et al. 2020), an investigator-sponsored randomized, controlled trial (n=188) has been initiated in the same population in China, testing the same TCZ dose regimen and is currently ongoing, with approximately 70 patients enrolled. At present, the 21-patient publication (Xu et al. 2020) and case reports of individual patients include the limited available published clinical data the Sponsor is aware of regarding the use of TCZ in the treatment of COVID-19 pneumonia.

On 3 March 2020, TCZ was included in the seventh updated diagnosis and treatment plan for COVID-19 issued by the China National Health Commission as one treatment option for severe or critical forms of COVID-19 pneumonia. The Chinese Center for Disease Control and Prevention defined disease severity according to the following criteria:

- Severe disease: dyspnea, respiratory frequency ≥30/min, blood oxygen saturation (SpO_2) ≤93%, PaO2/FiO_2 ratio (the ratio between the blood pressure of the oxygen [partial pressure of oxygen, PaO_2] and the percentage of oxygen supplied [fraction of inspired oxygen, FiO_2]) <300 mmHg, and/or lung infiltrates >50% within 24 to 48 hours; this occurred in 14% of cases.
- Critical disease: respiratory failure, septic shock, and/or multiple organ dysfunction (MOD) or failure (MOF); this occurred in 5% of cases (Wu et al. 2020).

Because body weight measurement is not always feasible in urgent circumstances, the dose regimen used in China is a single fixed dose of 400 mg TCZ IV (which equates to between 4–8 mg/kg based on the body weight range of the Chinese adult population), with the maximum single dose no more than 800 mg. If clinical signs/symptoms do not improve, an additional dose can be administered after 12 hours. The guidance advises that no more than two doses should be given. TCZ treatment is not permitted for people with active infections including TB, bacterial, or fungal.

Results from 21 Patients Treated with Tocilizumab in China

In February 2020, twenty-one patients with severe or critical COVID-19 pneumonia were treated with TCZ IV (400 mg) plus standard of care. The average age of the patients was 56.8 ± 16.5 years, ranging from 25 to 88 years. Seventeen patients (81.0%) were assessed as severe and four (19.0%) as critical. Most patients (85%) presented with lymphopenia. C-reactive protein (CRP) levels were increased in all 20 patients (mean, 75.06 ± 66.80 mg/L). The median procalcitonin (PCT) value was 0.33 ± 0.78 ng/mL, and only two of 20 patients (10.0%) presented with an abnormal value. Mean IL-6 level before TCZ was 132.38 ± 278.54 pg/mL (normal <7 pg/mL).

Standard of care consisted of lopinavir, methylprednisolone, other symptom relievers, and oxygen therapy as recommended by the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Sixth Edition). All 21 patients had received routine standard of care treatment for a week before deteriorating with sustained fever, hypoxemia, and chest CT image worsening.

Eighteen patients (85.7%) received TCZ once, and three patients (14.3%) had a second dose due to fever within 12 hours. According to the authors, after TCZ treatment, fever returned to normal and all other symptoms improved remarkably. Fifteen of the 20 patients (75.0%) had lowered their oxygen intake and one patient needed no oxygen therapy. CT scans showed significant remission of opacities in both lungs in 19/20 patients (90.5%) after treatment with TCZ. The percentage of lymphocytes in peripheral blood, which was decreased in 85.0% of patients (17/20) before treatment

(mean, 15.52±8.89%), returned to normal in 52.6% of patients (10/19) on the fifth day after treatment. Abnormally elevated CRP decreased significantly in 84.2% patients (16/19). No adverse drug reactions and no subsequent pulmonary infections were reported.

Nineteen patients (90.5%) were discharged at the time of the report, including two critical patients. There were no deaths among the 21 treated patients.

The study authors concluded that TCZ is an effective treatment for patients with severe COVID-19 (Submitted, Xu et al. 2020).

Results from Individual Case Reports

Michot et al. (2020) reported a 42-year-old with history of renal cell carcinoma hospitalized for COVID-19 pneumonia and treated with 5 days of lopinavir-ritonavir treated and 2 doses of tocilizumab (8 mg/kg IV) following rapid respiratory decompensation. The patient experienced clinical improvement with discontinuation of supplemental oxygen 4 days later and fully recovered. No adverse drug reactions were reported.

Ferrey et al. (2020) reported a 56-year-old with end stage renal disease hospitalized for bilateral interstitial pneumonia secondary to COVID-19 who developed acute respiratory distress syndrome. The patient was treated with hydroxychloroquine, tocilizumab, and broad spectrum antibiotics along with supportive care. At the time of publication, the patient remained in critical condition without report of adverse drug reactions.

Cellina et al. (2020) reported a 64 year old male with confirmed COVID-19 infection and dyspnea who had favorable changes in computed tomography (CT) results following 2 doses of tocilizumab (8 mg/kg) 12 hours apart. The patient's clinical condition improved and was able to be weaned off the ventilator. No adverse drug reactions were reported.

Results from Patients in Special Populations

De Luna et al. (2020) reported a 45-year-old male with sickle cell disease who developed rapid and severe COVID-19 pneumonia. He was treated with amoxicillin-clavulanic acid and hydroxychloroquine but clinical condition continued to deteriorate with increased oxygen requirement. He was treated with 1 dose of tocilizumab (8 mg/kg) and was reported to have clear improvement in general condition. The patient was discharged 2 days later. No adverse drug reactions were reported.

Zhang et al. (2020) reported a 60-year-old male with multiple myeloma in Wuhan, China who developed shortness of breath and was started on methylprednisolone. CT chest was positive for ground glass opacities and RT-PCR confirmed COVID-19 infection. He was treated with umifenovir without clinical improvement. Clinical improvement noted

following 1 dose of tocilizumab (8 mg/kg) with gradual decline in IL-6. The patient was later discharged from the hospital. No adverse drug reactions were reported.

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

There are currently no drugs licensed for the treatment of patients with COVID-19. Given the results of studies outlined above, TCZ, along with standard of care (SOC) treatment, could provide efficacy, offering the potential to treat COVID-19 in hospitalized populations more effectively than current SOC alone. Extensive safety data have previously been generated on the use of TCZ in other indications. Therefore, a placebo-controlled study in combination with SOC to assess safety and efficacy of TCZ in hospitalized patients with COVID-19 pneumonia is justified to address the high unmet need and burden of disease in this severely ill population.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of TCZ compared with a placebo in combination with SOC in hospitalized patients with COVID-19 pneumonia. To enhance the understanding of the clinical profile of tocilizumab for patients who belong to high-risk and minority populations, an emphasis will be placed on including minority-enrolling sites.

Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoint:

- Cumulative proportion of patients requiring mechanical ventilation by Day 28

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status
- Time to clinical failure, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first)
- Mortality rate by Day 28
- Time to hospital discharge or “ready for discharge” (e.g., awaiting social disposition) as evidenced by, for example, normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen

2.1.3 Exploratory Efficacy Objectives

The exploratory efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Change from baseline in inflammatory markers levels (hs-CRP, D-dimer, and ferritin) over time
- Cumulative proportion of patients requiring CPAP or BIPAP by Day 28

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0
- Incidence of any post-treatment bacterial and/or fungal infection
- Incidence of any post-treatment acute kidney injury (defined by 50% increase of creatinine from baseline)

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of TCZ in combination with SOC compared with placebo in combination with SOC in hospitalized adult patients with COVID-19. The Sponsor intends to enroll approximately 379 patients that have been diagnosed with COVID-19 pneumonia and meet the entry criteria.

Patients must be at least 18 years of age with confirmed SARS-CoV-2 (COVID-19) infection per WHO criteria, including a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have SpO_2 <94% on ambient air and be on SOC, which may include anti-viral treatment, low dose systemic corticosteroids, and supportive care.

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. Patients with active tuberculosis (TB) or suspected active bacterial, fungal, viral, or other infection (besides COVID-19 and well-controlled HIV) will be excluded from the study.

Patients will be screened and randomized within 48 hours of hospital admission. Patients will be randomized at a 2:1 ratio to receive blinded treatment of either TCZ or

placebo, respectively. Study treatment must be given within approximately 4 hours after randomization. TCZ and placebo will be given in combination with SOC.

Patients assigned to the TCZ arm will receive one infusion of TCZ 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the placebo arm will receive one infusion of placebo (see Section 4.3), both in addition to SOC.

If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of 2 screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 7 days after previously signing the consent form. The investigator will record the reasons for screen failure in the screening log in Section 4.5.1.

The study assessments to be conducted include the following: physical examination, vital signs, oxygen saturation, assessment of consciousness, presence and absence of respiratory support, adverse events, concomitant therapies, and clinical laboratory tests. Please see Appendix 1 and Appendix 2 for details concerning the timing of these assessments.

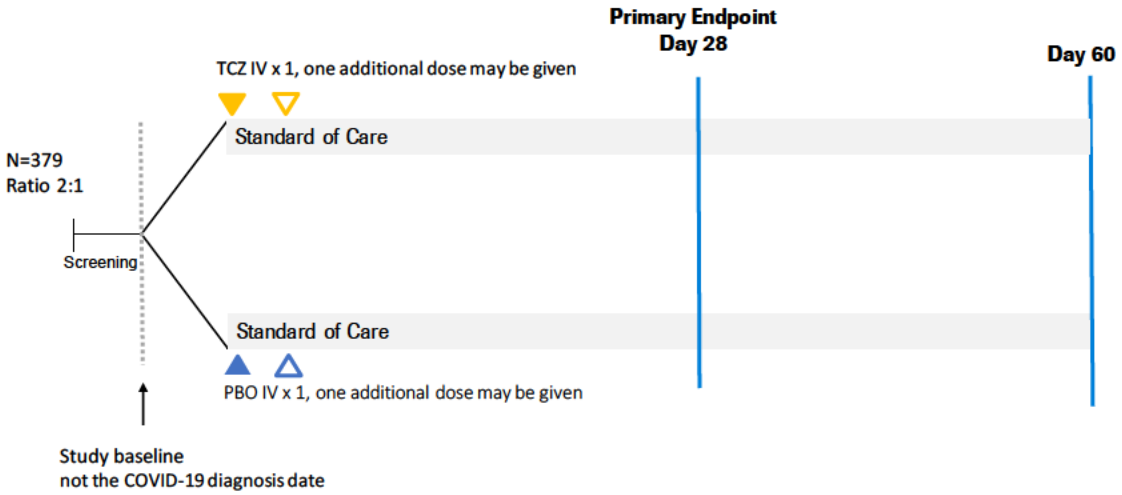
Patients will be followed up for a total of 60 days after first dose of study medication.

If patients are discharged from the hospital prior to Day 28 or discontinue the study, the Study Completion/Discontinuation assessments are to be conducted prior to discharge or at discontinuation from the study. In addition, if patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. Follow-up visits may be conducted by onsite clinic visits, telephone calls, or home visits. After Day 28, all patients should have a follow-up visit on approximately Day 60 which may be conducted as an onsite clinic visit, telephone call, or home visit for discharged patients.

During the study, standard supportive care will be given according to clinical practice. After study completion, patients should be referred to their regular healthcare provider based on their doctor's decision and as part of standard of care.

Figure 1 presents an overview of the study design. Schedules of activities are provided in Appendix 1 and Appendix 2.

Figure 1 Study Schema



IV = intravenous; PBO = placebo; TCZ = tocilizumab.
Note: Patients will be screened and randomized within 48 hours of hospital admission. Study treatment must be given within approximately 4 hours after randomization.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for last follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 2 months after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 8 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Tocilizumab Dose and Schedule

At baseline, patients assigned to the TCZ arm will receive one infusion of TCZ 8 mg/kg IV, with a maximum dose of 800 mg. If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of TCZ 8 mg/kg IV can be given, 8–24 hours after the initial infusion.

The TCZ dose regimen chosen in this study for adult patients is consistent with the approved TCZ dose for patients experiencing CRS induced by CAR-T cell therapy who weigh ≥30 kg. Further, based on the off-label experience from China (one additional dose if fever is not improved within 12 hours) and the fact that up to three additional infusions of TCZ (with at least 8 hours in between infusions) are allowed for CAR-T

induced CRS, the proposed additional one infusion if clinical signs/symptoms worsen or do not improve is justified.

Patients will be followed-up for a period of 60 days from randomization. This period is supported by historical data from studies performed in healthy subjects and patients with RA (study LRO300 and LRO301) where the mean apparent half-life was determined by non-compartmental analysis and ranged from 7 to 8 days following a single dose of 10 mg/kg IV or multiple doses of 8 mg/kg IV Q4W. Moreover, modeling of free sIL6R levels over time, as the principal marker of target engagement, showed that soluble receptors returned to their maximum level after 4 weeks following a single administration of 8 mg/kg IV, demonstrating the absence of drug binding and therefore of drug effect after 4 weeks (Gibiansky and Frey 2012).

3.3.2 Rationale for Patient Population

Based on the current knowledge of COVID-19, approximately 80% of patients infected with SARS-CoV-2 (COVID-19) experience mild disease and can recover at home and require only simple symptomatic relief. However, approximately 20% require hospitalization due to more severe disease. A study of 138 hospitalized patients with COVID-19 published on 7 February 2020 found that 26% of patients admitted to hospital required transfer to the intensive care unit (ICU) and 4.3% died; however, given that a number of patients were still hospitalized at the time of this report, this number may be an underestimate (Wang et al. 2020). A previous study had found that out of 41 admitted hospital patients, 13 (32%) were admitted to an ICU and six (15%) died (Huang et al. 2020). A more recent study with 1099 patients indicated that 16% of patients developed a severe form of disease, 5% were admitted to an ICU, 2.3% underwent invasive mechanical ventilation, and 1.4% died (Guan et al. 2020).

Given the significant unmet need in hospitalized high-risk and/or minority patient populations with COVID-19 pneumonia, and based on the emerging evidence for TCZ use in patients with COVID-19 pneumonia, this study is designed to evaluate the efficacy and safety of TCZ in this population. Morbidity and mortality are particularly high for elderly patients and those with comorbidities. This study will include both these groups, with no upper age limit.

3.3.3 Rationale for Control Group

The study will compare the efficacy and safety of TCZ IV compared with placebo in combination with SOC. Despite the lack of targeted treatments for COVID-19, SOC for patients with COVID-19 pneumonia generally includes supportive care and may include available anti-viral agents and low-dose systemic corticosteroids as dictated by local treatment guidelines. Therefore, SOC plus placebo treatment is appropriate as a control in this study.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study aims to enroll approximately 379 hospitalized patients with COVID-19 pneumonia.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form by any patient capable of giving consent, or, when the patient is not capable of giving consent, by his or her legal/authorized representative
- Age ≥18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Hospitalized
- COVID-19 pneumonia confirmed per a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid) and radiographic imaging (CT scan or chest X-ray)
- Able to complete screening within 48 hours of hospital admission
- SpO_2 <94% while on ambient air

  If a patient is on supplemental oxygen with SpO2 ≥94%, but desaturation to <94% on lower supplemental oxygen or ambient air is documented during screening, the inclusion criterion is met.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 90 days after the final dose of study drug. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

  Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.

If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 60 days after the final dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.2 Exclusion Criteria

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

- Known severe allergic reactions to TCZ or other monoclonal antibodies
- Require CPAP, BIPAP, or mechanical ventilation
- Active TB infection or last TB infection within 1 month of randomization
- Suspected active bacterial, fungal, viral, or other infection (besides COVID-19 and well-controlled HIV)
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
- Immunocompromised (besides well-controlled HIV) or on immunosuppressive therapy (except for steroids for COVID), advanced cancer
- Have received oral anti-rejection or immunomodulatory drugs (including TCZ) within the past 3 months
- Participating in another IL-6 antagonist clinical trial or other drug clinical trials (participation in COVID-19 anti-viral trials may be permitted if approved by Medical Monitor)
- ALT or AST $>$5 x upper limit of normal (ULN) detected within 24 hours at screening (according to local laboratory reference ranges)
- ANC $<$1000/μL at screening (according to local laboratory reference ranges)
- Platelet count $<$50,000/μL at screening (according to local laboratory reference ranges)
- Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination

- Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (investigational COVID-19 antivirals may be permitted if approved by Medical Monitor)
- Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Any history of diverticulitis or GI perforation

The use of remdesivir, hydroxychloroquine, chloroquine, and convalescent plasma, is not an exclusion to participation in this trial, and is left to the discretion of the primary medical team.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, double-blind, placebo-controlled study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS).

Patients will be randomly assigned to one of two treatment arms: TCZ in combination with SOC or placebo in combination with SOC. Randomization will occur in a 2:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. The randomization will be stratified by age (i.e., ≤60 and >60 years of age).

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study, with the exception of the study pharmacist. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial and members of the internal Monitoring Committee (IMC). These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and IMC members.

Genentech monitors, project statisticians, and the project team will be blinded from study results, with the exception of the IMC members. Study centers may be unblinded after the final study results are reported.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior

to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMP) for this study are tocilizumab IV and its placebo as the comparator.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Tocilizumab and Placebo

TCZ will be supplied by the Sponsor as a sterile IV injection for reconstitution in 20-mL glass vials with a 10 mL fill (200 mg/10 mL of TCZ) or with a 20 mL fill (400 mg/20 mL of TCZ). An appropriate number of vials (depending on the patient's body weight) of TCZ will be assigned to each patient for the infusion. The amount of solution that is withdrawn from each vial will depend on the patient's allocated dose. For information on the formulation and handling of TCZ, see the TCZ pharmacy manual and Tocilizumab Investigator's Brochure.

Placebo will be supplied by the investigative site in the form of a 0.9% sodium chloride (normal saline) bag.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

4.3.2.1 Tocilizumab and Placebo

TCZ/placebo will be administered by IV infusion at doses of 8 mg/kg. The maximum dose of TCZ that will be administered is 800 mg. The dose of TCZ infusion will be calculated on the basis of body weight measured prior to infusion (see Appendix 1). One additional infusion of blinded treatment of TCZ or placebo can be given 8–24 hours after the initial infusion.

TCZ/placebo must be administered under close supervision of the investigator in a setting where medications and resuscitation facilities are available. Patients should be monitored for at least 2 hours after the TCZ infusion is completed.

The TCZ/placebo vials will be stored at a temperature of 2°C–8°C. The infusion bag of TCZ/placebo should be diluted to 100 mL infusion bag using aseptic technique. The fully diluted TCZ/placebo solutions for infusion using 0.9% Sodium Chloride Injection, USP may be stored at 2° to 8°C (36° to 46°F) or at room temperature for up to 24 hours and should be protected from light.

If stored at 2° to 8°C (36° to 46°F), the infusion bag should be allowed to return to room temperature before administration. The TCZ will be administered at room temperature by controlled infusion into a vein over a 1-hour period. In exceptional cases this time may be extended to up to 6 hours. The infusion speed must be 10 mL/hr for 15 minutes and then increased to 130 mL/hr to complete the dosing in 1 hour. The entire 100 mL content of the infusion bag must be administered. A total of 20 mL of normal saline will be administered following the infusion of study medication to flush the remaining study drug through the intravenous set.

Refer to the Tocilizumab Investigator's Brochure for further instructions regarding recommended storage conditions and packaging configuration.

4.3.3 Investigational Medicinal Product Handling and Accountability

The IMP (TCZ/placebo) required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive TCZ/placebo, and only authorized staff may supply or administer TCZ/placebo.

TCZ/placebo will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the

Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the TCZ/placebo Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Tocilizumab

Since the TCZ treatment is not intended for continued therapy, the Sponsor does not have any plans to provide TCZ or any other study treatments to patients who have completed the study.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements, investigational anti-viral agents, blood products) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

All patients will receive standard of care per local practice for the treatment of COVID-19 pneumonia. The standard of care may include anti-viral treatment, low-dose systemic corticosteroids, and supportive care.

Chloroquine or hydroxychloroquine is permitted as part of local practice. The recommended maximum dose of chloroquine is 400 mg twice a day.

Clinical management guidelines from WHO recommend against the use of corticosteroids in patients with COVID-19 pneumonia. However, country- and region-specific guidelines recommend considering corticosteroids in some COVID-19 patients. This protocol allows the use of low-dose steroids as part of local SOC. If steroids are given, the Sponsor recommends a dose of no more than 1 mg/kg methylprednisolone or equivalent for no more than 5 days.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience

infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists (e.g., famotidine, ranitidine), or equivalent medications per local standard practice. Serious infusion associated events manifested by, for example, dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

4.4.2 Cautionary Therapy

4.4.2.1 Medications Given with Precaution due to Effects Related to CYP Enzymes

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., IL-6) during chronic inflammation. Therefore, for molecules that antagonize cytokine activity, such as TCZ, it is expected that the formation of CYP450 enzymes could be normalized. When starting TCZ therapy, patients taking medications that are individually dose adjusted and metabolized by means of CYP450, CYP3A4, CYP1A2, or CYP2C9 (e.g., atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporin, or benzodiazepines) are recommended to be monitored as doses may need to be adjusted to maintain their therapeutic effect.

The above list of medications is not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Treatment with any investigational agent (except for SARS-CoV-2 [COVID-19] anti-viral agents with approval of Medical Monitor), cell-depleting therapies, biologic agents (e.g., tumor necrosis factor antagonists or IL-6/IL-6R therapies including sarilumab, siltuximab), Janus kinase inhibitors (e.g., tofacitinib, baricitinib), alkylating agents (e.g., chlorambucil, cyclophosphamide), thalidomide, IV gamma globulin, anti-thymocyte globulin, and azathioprine during the study
- Bone marrow transplantation with total lymphoid irradiation during the study
- Plasmapheresis or extracorporeal photopheresis during the study
- Immunization with a live or attenuated vaccine for the duration of the patient's study participation.

4.5 STUDY ASSESSMENTS

The sequence of assessments at each visit will be standardized as follows (at visits required in the schedules of assessments).

1. Efficacy assessments: clinical status, clinical signs and symptoms, oxygen saturation
2. Safety assessments: vital signs, review of adverse events, concomitant medications
3. Laboratory samples: on days when study drug is administered, all samples (including safety) must be taken within 4 hours prior to study drug treatment.
4. IV infusion of TCZ/placebo (only at baseline and an additional dose if needed)
5. Safety assessments; vital signs post TCZ (if applicable)

Schedules of assessments are found in Appendix 1 and Appendix 2.

If patients are discharged from the hospital prior to Day 28 or discontinue the study, the Study Completion/Discontinuation assessments are to be conducted prior to discharge or at discontinuation from the study. In addition, if patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. Follow-up visits may be conducted by onsite clinic visits, telephone calls, or home visits. After Day 28, all patients should have a follow-up visit on approximately Day 60 which may be conducted as an onsite clinic visit, telephone call, or home visit for discharged patients.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). In the pandemic situation where access to hospitals is limited, if allowed, verbal consent can be obtained from the patient's legally authorized representative and must be documented by the investigator or the authorized designee. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. Physical examination, blood tests, and other assessments conducted after arrival at the hospital, but before the informed consent is signed, can be used as screening assessments. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, home oxygen use, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to first dose of study drug will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, self-reported race/ethnicity, smoking history, and patient characteristics.

4.5.3 Physical Examinations

A complete physical examination, performed at screening, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, , respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions electronic Case Report Form (eCRF).

Limited, symptom-directed physical examinations may be performed at unscheduled postbaseline visits as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

In addition, patient body weight will be measured at screening (see Appendix 1). If it is not feasible to weigh bed-bound patients, historical body weight may be used.

Physical examination, blood tests, and other assessments conducted after arrival at the hospital, but before the informed consent is signed, can be used as screening assessments.

4.5.4 Vital Signs and Oxygen Saturation

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure, and body temperature. Peripheral oxygen saturation should also be measured at the same time as the vitals. For patients requiring supplemental oxygen, the oxygen flow rate (L/min) and/or FiO_2 should be recorded.

Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Ventilation Requirement

Assessment of ventilation usage (non-invasive or mechanical) should be recorded once daily with ordinal scale determination based upon the following categories:

- No supplemental oxygen
- Supplemental oxygen (nasal cannula, face mask)
- Non-invasive ventilation or high-flow oxygen (high-flow nasal cannula, CPAP, BiPAP)
- Intubation and mechanical ventilation

4.5.6 Laboratory and Other Biological Samples

Samples for the following laboratory tests will be measured by study site's local laboratory:

- Partial pressure of oxygen (PaO_2, if arterial blood gases are performed during screening or follow-up)
- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total bilirubin, ALP, ALT, AST
- hs-CRP, D-dimer, and ferritin (if hs-CRP is not available, a CRP can be conducted; D-dimer if available locally)
- Pregnancy test

  All women of childbearing potential will have a pregnancy test at screening (urine or serum). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- SARS-CoV-2 (COVID-19) PCR (screening): nasopharyngeal swab or other respiratory specimen, blood, urine, stool, other bodily fluid

4.5.7 Liver Function Monitoring

Patients should be assessed for liver function prior to each dose of TCZ or placebo. On Day 1, the assessment is mandatory. On Day 1, the local laboratory full blood chemistry panel required as part of screening can be used for this assessment or prior blood results if tests conducted within 24 hours prior to screening. Results must be reviewed by the investigator before dose administration. Dosing will occur only if the clinical assessment and local laboratory liver chemistry panel values are acceptable.

4.5.8 Chest X-Rays and CT Scan

Either a chest CT scan or a chest X-ray are acceptable to determine eligibility and for follow up. During the study, follow-up CT scans or chest X-rays will be performed per the schedule of assessments.

Chest X-ray/CT scan findings should be recorded on the appropriate eCRF. If additional chest X-rays/CT scans are taken per local practice, this information should be provided in the eCRF.

4.5.9 Electrocardiograms

Single ECG recordings will be obtained at screening, as outlined in the schedule of activities (see Appendix 1) and may be obtained thereafter as needed per investigator's discretion.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

4.5.10 Ordinal Scale Determination

Assessment of clinical status using a 7-category ordinal scale will be recorded at baseline on Day 1 and then again once daily every morning (between approximately 8 am and 12 pm) while hospitalized. The ordinal scale categories are as follows:

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

Patients who are ready to be discharged but are still hospitalized (e.g., due to non-medical or administrative reasons) will be assigned an ordinal scale category of 1. Patients in a non-ICU hospital ward who are eligible for ICU care based on clinical presentation but are awaiting ICU care will be assigned an ordinal scale category of 4. Patients in an ICU for administrative or non-medical reasons who are ready for a

non-ICU hospital ward will be assigned an ordinal scale category of 2 (if not requiring supplemental oxygen), 3 (if requiring supplemental oxygen), or 4 (if requiring non-invasive ventilation or high-flow oxygen).

In general, patients with oxygen saturation consistently ≤90% should be considered for escalation to a higher clinical status category, while patients with oxygen saturation consistently ≥96% should be considered for de-escalation to a lower category. Patients on supplemental oxygen should be evaluated at least daily and considered for reduction or discontinuation of oxygen support. Actual changes in level of support will be at the discretion of the clinician(s) treating the patient based on the patient's overall condition and may be dictated by other clinical and non-clinical considerations.

Normal body temperature is defined as oral, rectal, axillary, temporal, or tympanic temperature 36.1–38.0°C. Normal respiratory rate is defined as 12–20 breaths per minute.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Any event that meets stopping criteria defined in Section 5.1.1
- Severe allergic reaction to TCZ

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment will not be replaced.

Patients who discontinue from the study treatment should continue in the study and complete all assessments through Day 60.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure

- Adverse event
- Loss to follow-up

Every effort should be made to obtain information on patients lost to follow up but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with TCZ in clinical studies and post-marketing experience. The important safety risks for TCZ are outlined below. Please refer to the Tocilizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the

nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events and laboratory abnormalities, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Tocilizumab

This section highlights the main risks for this study population and following 1–2 doses of TCZ. For a complete list of all identified or potential risks of TCZ therapy, please refer to the current version of the TCZ Investigator's Brochure.

5.1.1.1 Hypersensitivity Reactions, Including Anaphylaxis

An infusion reaction is defined as any adverse event that occurs during or within 24 hours after the infusion. This may include hypersensitivity or anaphylactic reactions. Stevens-Johnson syndrome has been reported during treatment with TCZ in the post-marketing setting. Signs of a possible hypersensitivity reaction include, but are not limited to, the following:

- Fever, chills, pruritus, urticaria, angioedema, and skin rash
- Cardiopulmonary reactions, including chest pain, dyspnea, hypotension, or hypertension

TCZ infusions will be administered to patients at the site under close supervision. Health care professionals administering TCZ infusions should be trained in the appropriate procedures for TCZ administration, should be able to recognize the symptoms associated with potential hypersensitivity reactions, including anaphylaxis, and should have the appropriate medication available for immediate use in case of hypersensitivity reaction such as anaphylaxis during or after administration of TCZ. The patient should be treated according to the standard of care for management of the hypersensitivity reaction.

If a patient has symptoms of serious hypersensitivity reactions, such as anaphylaxis, or requires an interruption of the study drug because of symptoms of hypersensitivity including anaphylaxis, administration of TCZ must be discontinued permanently.

5.1.1.2 Serious Infections and Opportunistic Infections

Physicians should exercise caution when considering the use of TCZ in patients with increased risk of infection, such as a history of recurring infections or with underlying conditions (e.g., diabetes mellitus) which may predispose patients to serious infections and opportunistic infections such as TB and viral reactivations (e.g., hepatitis B virus).

Vigilance for timely detection of serious infection is recommended for patients receiving biologic agents, as signs and symptoms of acute inflammation may be lessened because of suppression of the acute-phase reaction. The effects of TCZ on hs-CRP and neutrophils, and the signs and symptoms of infection, should be considered when evaluating a patient for a potential infection. It is recommended that neutropenic patients (ANC $<1000/\mu L$) undergo weekly surveillance blood cultures during the study.

If a patient develops a serious infection, administration of TCZ should be discontinued.

5.1.1.3 Gastrointestinal Perforations

Symptomatic diverticulosis, diverticulitis, or chronic ulcerative lower GI disease, such as Crohn disease, ulcerative colitis, or other chronic lower GI conditions, might predispose patients to GI perforations. Timely diagnosis and appropriate treatment may reduce the potential for complications of diverticular disease and thus reduce the risk of GI perforations.

Discontinuation of TCZ is required for patients who develop GI perforations.

5.1.1.4 Hematologic Abnormalities

Decreases in neutrophil counts, platelet counts, and fibrinogen levels have been observed following treatment with TCZ for labelled indications. Treatment-related neutropenia was not associated with serious infection in clinical trials in any indication and no association between decreases in platelet counts and serious bleeding events has been observed.

5.1.1.5 Demyelinating Disorders

The effect of treatment with TCZ on demyelinating disorders is not known; events have been reported rarely. Physicians should exercise caution when considering the use of TCZ in patients with preexisting or recent-onset demyelinating disorders.

Patients should be closely monitored for signs and symptoms potentially indicative of central demyelinating disorders.

5.1.1.6 Elevated Liver Enzymes

In clinical trials, mild and moderate elevations of hepatic transaminases have been observed with TCZ treatment.

Recommended TCZ dose modifications for elevated liver enzymes in these populations are not applicable to this study due to single-dose therapy (with possible additional infusion) with TCZ or placebo.

Patients who develop elevated liver function tests during the study must have repeat tests performed as clinically indicated until levels return to baseline, even if they withdraw from the study. If the specialist deems a liver biopsy necessary, the prepared histologic slides will be requested by the Sponsor for central review by a third party, and the biopsy report should be forwarded to the Sponsor.

5.1.1.7 CYP450 Enzyme Normalization

The expression of hepatic cytochrome P450 (CYP450) enzymes is suppressed by cytokines, such as IL-6, that stimulate chronic inflammation. TCZ normalizes expression of these enzymes. The effect of TCZ on CYP450 enzymes (except CYP2C19 and

CYP2D6) is clinically relevant for CYP450 substrates with a narrow therapeutic index and/or when the dose is individually adjusted.

When starting or stopping therapy with TCZ, patients taking medicinal products which are individually dose adjusted and are metabolized via CYP450 CYP3A4, CYP1A2, CYP2B6, or CYP2C9 (e.g., atorvastatin, calcium-channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, cyclosporine, or benzodiazepines) should be monitored as doses of these products may need to be adjusted to maintain their therapeutic effect.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, 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.

- Serious and/or medically significant infections
- Myocardial infarction or acute coronary syndrome
- GI perforations
- Malignancies
- Anaphylaxis or hypersensitivity reactions
- Stroke
- Serious and/or medically significant bleeding events
- Serious and/or medically significant hepatic events
- Demyelinating disorders

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported during the 60-day follow-up period.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of nondirective questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 1 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no"

accordingly. The following guidance should be taken into consideration (see also Table 2):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 2 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon rechallenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event

report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms

- Results in a change in study treatment (e.g., treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., treatment interruption or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (>3 × ULN) in combination with either an elevated total bilirubin (>2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- 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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of COVID-19 pneumonia.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of COVID-19 pneumonia, "COVID-19 pneumonia progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of COVID-19 Pneumonia

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events (with the exception of death due to COVID-19 pneumonia progression as described in Section 5.3.5.7). These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.11 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For TCZ (or placebo), adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with TCZ (or placebo), regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one

entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board (IRB)/Ethics Community (EC).

5.4.1 Medical Monitors and Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], M.D.

Mobile Telephone No.: [redacted]

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported during the 60-day follow-up period. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 3 months after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 60 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately

(i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 60 days after study initiation), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
Tocilizumab	Tocilizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

A IMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

All efficacy outcomes will be analyzed in the modified intent-to-treat (mITT) population. The mITT population is defined as all patients randomized in the study that received any amount of study medication, with patients grouped according to the treatment assignment at randomization.

Safety analyses will be performed on the safety evaluable population, which consists of all patients who receive any amount of study medication. In all safety analyses, patients will be grouped according to the treatment that the patients actually received rather than the treatment assigned at randomization.

Detailed specifications of the statistical methods will be described in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

The estimated sample size was determined based on the time from randomization to the first utilization of mechanical ventilation by Day 28.

The total mITT sample size of 379 patients with a 2:1 randomization of TCZ (n=253) to placebo (n=126) provides approximately 80% power using a Logrank test to detect a 15% difference between treatment groups in time to mechanical ventilation by Day 28 under the following assumptions: cumulative survival (i.e., not requiring mechanical ventilation) rates of 75% in the TCZ group and 60% in placebo group, with 28-day follow-up, using a two-sided 5% alpha, and 10% dropout rate in each arm. Sample size re-estimation may be considered during the study based on updated assumptions of the treatment effect.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who are randomized, enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized.

Eligibility criteria and other major protocol deviations will be listed and summarized by treatment group.

6.3 TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented by treatment group and will be presented for the mITT and may, in addition, be presented for the safety population.

Medical history data, including surgery and procedures, and baseline conditions, will be summarized descriptively by treatment group using the safety population.

Previous and concomitant treatments will be summarized descriptively by treatment group.

Exposure to study drug will be summarized, including number of doses. A listing of patients by treatment group, detailing dosing of study drug will be prepared.

6.4 EFFICACY ANALYSES

All efficacy analyses will use the mITT population.

Descriptive subgroup analyses to evaluate the consistency of results across pre-specified subgroups may also be conducted.

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of TCZ plus SOC compared with placebo plus SOC using the following endpoint:

- Cumulative proportion of patients requiring mechanical ventilation by Day 28

Time to the first utilization of mechanical ventilation after randomization will be analyzed by the Kaplan Meier analysis, with the cumulative proportion of patients requiring mechanical ventilation estimated at Day 28. Details of the primary endpoint analysis will be included in the SAP.

6.4.2 Secondary Efficacy Endpoints

Time to event secondary endpoints will be compared between the TCZ group and the placebo group using the log-rank test. The Kaplan-Meier plot, median time to response, and their 95% CIs, and a p-value will be presented.

- Time to improvement in ordinal clinical status

Defined as time from randomization to the time when at least a 2-category improvement in the 7-category ordinal scale is observed. Assessment of patient status using an ordinal scale will be recorded at baseline and once daily in the morning (between approximately 8 am and 12 pm) while hospitalized. The ordinal scale categories are as follows:

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

- Time to clinical failure

  Defined as the time to first occurrence on study of death, mechanical ventilation, ICU admission or withdrawal, whichever occurs first.

- Difference in mortality rate at Day 28 will be compared using the Fisher's exact test. The difference in proportions for the treatment group comparison will be presented, together with a 95% CI using an exact method.

- Time to hospital discharge or "ready for discharge"

  "Ready for discharge" defined as normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen.

Comparison of clinical status according to the 7-category ordinal scale may also be analyzed using a proportional odds model at Day 28.

6.4.3 Exploratory Efficacy Endpoints

Inflammatory markers, hs-CRP, D-dimer, and ferritin, will be summarized descriptively using means, standard deviations, medians, and ranges. Absolute value and change from baseline will be provided over time by treatment group.

The time to first requiring CPAP or BIPAP after randomization will be analyzed by the Kaplan Meier analysis, with the cumulative proportion of patients requiring CPAP or BIPAP estimated at Day 28.

Additional exploratory efficacy endpoints may be explored and details will be provided in the SAP.

6.5 INTERIM ANALYSES

An IMC will evaluate safety according to procedures and guidelines detailed in the IMC agreement. The IMC will consist of Sponsor representatives who will not be blinded to study data. Details of the safety reviews will be provided in the SAP.

6.6 SAFETY ANALYSES

Safety assessments will be performed on the safety evaluable population, which consists of all patients who receive any amount of study medication. In all safety analyses, patients will be grouped according to the treatment that the patients actually received rather than the treatment assigned at randomization.

Safety will be assessed through descriptive summaries of treatment emergent adverse events (nature, frequency, severity, and causality). Adverse events will also be listed.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0 scale

The proportion of patients with any post-treatment bacterial and/or fungal infection and acute kidney injury will be summarized, respectively.

A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of study drug.

Separate summaries will be generated for serious adverse events, deaths, adverse events leading to discontinuation of study drug, and adverse events of special interest.

Adverse events will be summarized by MedDRA term, appropriate thesaurus level, and toxicity grade.

Descriptive summaries of laboratory values and change from baseline throughout the study will be tabulated by treatment arm. For selected parameters, changes from the proportion of patients experiencing clinically significant changes relative to baseline will be summarized by treatment arm.

Values, along with change from baseline, will be summarized using descriptive statistics for each vital sign parameter.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of

eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Due to the pandemic situation, access to hospitals is restricted; therefore, only remote data monitoring will be performed for this study. Study monitors will perform ongoing remote data review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate and complete. Sites will be asked to implement a QC step of a second person reviewing the data entry in the eCRF where possible.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be

entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the

greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative or where allowed, HCP consent on behalf of the patient before his or her participation in the study. Due to the pandemic situation and restricted hospital access, where allowed, verbal consent may be given by the patient’s legally authorized representative and this must be documented by the investigator or authorized designee. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or

revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC (national or regional) by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate

authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted remotely by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Genentech, Inc. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 20 sites will participate to enroll approximately 379 patients. Enrollment will occur through an IxRS. Target enrollment may be changed if a sample size re-estimation is performed (see Section 6.1).

Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected either from local laboratories or from The Roche Integrated Global Textbook Ranges, as appropriate.

An IMC will be employed to monitor and evaluate patient safety throughout the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities: Days 1 and 2

	Screening [a, b]	Baseline		
Study Day	–2 to 0	1		2
Time Post Initial Treatment (Assessment Window)		0 Pre-dose (approx. –4 hrs)	15 min After end of infusion (approx. +1 hr)	24 hrs (±12 hrs)
Informed consent	x			
Inclusion/exclusion criteria	x	x		
Demographic data	x			
Randomization		x		
Medical history	x			
Complete physical examination [c, d]	x			
Weight	x			
COVID-19 diagnosis [e]	x			
Chest X-ray/CT scan [d, f]	x			
ECG	x			
Pregnancy test [d, g]	x			
PaO_2/FiO_2 [d, h]	x (optional)	← Optional →		
SpO_2 [d, i]	x			x
Vital signs [d, i]	x	x	x	x
Ordinal scoring (including ventilation requirement) [j]		x		x
Adverse events [k]		x		x
Concomitant medications [l]		x		x
Hematology [d, m]	x			x

Appendix 1: Schedule of Activities: Days 1 and 2

	Screening [a, b]	Baseline		
Study Day	−2 to 0	1		2
Time Post Initial Treatment (Assessment Window)		0 Pre-dose (approx. −4 hrs)	15 min After end of infusion (approx. +1 hr)	24 hrs (±12 hrs)
Chemistry [d, n]	x			x
hs-CRP, D-dimer, and ferritin (CRP if hs-CRP not available locally; D-dimer if available via local laboratory) [d]	x			
Study drug administration [o]		x		

CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; eCRF=electronic case report form; hs-CRP=high sensitivity C-reactive protein; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0; PaO_2/FiO_2=arterial oxygen partial pressure/fraction of inspired oxygen; SpO_2=peripheral capillary oxygen saturation.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Results from standard-of-care tests or examinations performed prior to obtaining informed consent and within 48 hours before randomization may be used; such tests do not need to be repeated for screening.

[b] Informed consent must be documented before any study-specific screening procedure is performed.

[c] A complete physical examination, performed at screening and per the investigator's discretion during the study, includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities identified during the study should be reported as adverse events.

[d] Physical examination, blood tests, and other assessments conducted after arrival at the hospital, but before the informed consent is signed, can be used as screening assessments.

[e] COVID-19 test (SARS-CoV2 PCR) to confirm diagnosis should be performed at or before screening (if testing is conducted before screening, documentation must be available).

[f] Screening chest X-ray or CT scans should be performed within 48 hours prior to randomization. If additional chest X-rays/CT scans are taken per local practice during the study, this information should be provided in the eCRF.

[g] For women of childbearing potential, including those who have had a tubal ligation, positive urine test results will be confirmed with a serum pregnancy test. Study drug infusion must not be administered unless the serum pregnancy test result is negative.

[h] If arterial blood gases are measured.

[i] All vital sign measurements (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressures, and body temperature) and oxygen saturation should be recorded together once daily while the patient remains hospitalized. If measured more than once daily, the worst values (highest temperature, respiratory rate, and heart rate; lowest blood pressure, oxygen saturation, and consciousness level) during that period should be recorded on the eCRF.

[j] Assessment of clinical status using the ordinal scale, which includes change in ventilation usage (non-invasive or mechanical), should be recorded at baseline on Day 1 then again daily every morning (between approximately 8 am and 12 pm) for patients who remain hospitalized.

[kj] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 60 days after the final dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[l] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit.

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).

[n] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total bilirubin, ALP, ALT, AST.

[o] The initial study drug infusion should be given within approximately 4 hours of randomization. If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion.

Appendix 2
Schedule of Activities: Day 3–Study Completion

	Days 3–28 [a]																									Study Completion/ Discontinuation [i]
Study Day	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 [i]	
Vital signs [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PaO_2/FiO_2 [c]	← Optional →																										(optional)
SpO_2 [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ordinal scoring [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [e]	←																									→	x
Concomitant medications [f]	←																									→	x
Hematology [g]																										x	x
Chemistry [h]																										x	x
CRP, D-dimer, and ferritin (CRP if hs-CRP not available locally; D-dimer if available via local laboratory)																										x	x

CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; eCRF=electronic case report form; hs-CRP=high sensitivity C-reactive protein; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0; $PaO_2/FiO2$=arterial oxygen partial pressure/fraction of inspired oxygen; SpO_2=peripheral capillary oxygen saturation.

[a] If patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. Follow-up visits may be conducted by onsite clinic visits, telephone calls, or home visits.

[b] All vital sign measurements (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressures, and body temperature) and oxygen saturation should be recorded together once daily while the patient remains hospitalized. If measured more than once daily, the worst values (highest temperature, respiratory rate, and heart rate; lowest blood pressure, oxygen saturation, and consciousness level) during that period should be recorded on the eCRF.

[c] If arterial blood gases are measured.

Appendix 2: Schedule of Activities: Day 3–Study Completion

[d] Assessment of clinical status using the ordinal scale should be recorded at baseline on Day 1 then again daily for patients who remain hospitalized.

[e] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 60 days after the final dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[f] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit.

[g] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).

[h] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total bilirubin, ALP, ALT, AST.

[i] If patients are discharged from the hospital prior to Day 28 or discontinue the study, the Study Completion/Discontinuation assessments are to be conducted prior to discharge or at discontinuation from the study. In addition, if patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. The Day 60 follow up may be conducted by an onsite clinic visit, telephone call, or home visit for discharged patients. Day 60 follow up is required to collect adverse events only.

PROTOCOL

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TOCILIZUMAB IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA**
PROTOCOL NUMBER:	ML42528
VERSION NUMBER:	2
EUDRACT NUMBER:	2020-001154-22
IND NUMBER:	148225
NCT NUMBER:	NCT04372186
TEST PRODUCT:	Tocilizumab (RO4877533)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.
DATE FINAL:	See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
02-Jun-2020 16:35:43	[redacted]	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
1	29 April 2020

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol ML42528 has been amended primarily in response to feedback [redacted]; however, other revisions were made for the reasons stated below. Changes to the protocol, along with a rationale for each change, are summarized below:

- The endpoint for the primary efficacy objective was revised to include death based upon feedback received [redacted] (Sections 2.1.1, 6.1, 6.4.1).
- A preference for high sensitivity C-reactive protein (hs-CRP) was removed as it was determined that only CRP testing was available at a majority of sites (Sections 2.1.3, 4.5.6, 5.1.1.2, 6.4.3, Appendices 1 and 2).
- Clarification was added that pre-dose assessments must be repeated and reviewed before an additional infusion of blinded treatment of tocilizumab or placebo is administered (Section 3, Appendix 1).
- The screening period was increased from 48 hours to 96 hours based on investigator feedback to facilitate patient enrollment (Sections 3.1, 4.1.1, and Appendix 1).
- Revisions were made to clarify that informed consent does not necessarily need to be a form signed by the patient since the inclusion criteria and Section 8.2 allow for verbal consent by the patient's legally authorized representative (Section 4.1.1).
- Text was added to clarify that the placebo is not supplied by the Sponsor (Section 4.3.1.1).
- The prohibited therapies were expanded to include "open-label tocilizumab" for clarity (Section 4.4.3).
- The analysis of the primary efficacy endpoint was revised to include death, since death was added to the primary efficacy objective, and to add stratification by age group to enhance the accuracy of the analysis (Section 6.4.1).
- The analysis for the secondary efficacy endpoint "mortality rate at Day 28" was revised to change the method from the Fisher's exact test to the Cochran-Mantel-Haenszel test and to add stratification by age group to apply the appropriate analysis (Section 6.4.2).
- The estimated number of sites anticipated to participate in this study was increased from 20 to 40 based on the shifting epidemiology of the pandemic (Section 9.5).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF TOCILIZUMAB IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA**
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TEST PRODUCT:	Tocilizumab (RO4877533)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	Genentech, Inc.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by the CRO.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF TOCILIZUMAB IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA**
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VERSION NUMBER:	2
EUDRACT NUMBER:	2020-001154-22
IND NUMBER:	148225
NCT NUMBER:	NCT04372186
TEST PRODUCT:	Tocilizumab (RO4877533)
PHASE:	Phase III
INDICATION:	COVID-19 pneumonia
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the efficacy and safety of tocilizumab (TCZ) compared with a placebo in combination with SOC in hospitalized patients with COVID-19 pneumonia. To enhance the understanding of the clinical profile of tocilizumab for patients who belong to high-risk and minority populations, an emphasis will be placed on including minority-enrolling sites. Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with standard of care (SOC) for the treatment of COVID-19 pneumonia on the basis of the following endpoint:

- Cumulative proportion of patients *with death or* requiring mechanical ventilation by Day 28

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status
- Time to clinical failure, defined as the time to death, mechanical ventilation, intensive care unit (ICU) admission, or withdrawal (whichever occurs first)
- Mortality rate by Day 28
- Time to hospital discharge or “ready for discharge” (e.g., awaiting social disposition) as evidenced by, for example, normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Change from baseline in inflammatory markers levels (high sensitivity C-reactive protein [hs-CRP]/*C-reactive protein [CRP]*, D-dimer, and ferritin) over time
- Cumulative proportion of patients requiring CPAP or BIPAP by Day 28

Safety Objective

The safety objective for this study is to evaluate the safety of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0
- Incidence of any post-treatment bacterial and/or fungal infection
- Incidence of any post-treatment acute kidney injury (defined by 50% increase of creatinine from baseline)

STUDY DESIGN

Description of the Study

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of TCZ in combination with SOC compared with placebo in combination with SOC in hospitalized adult patients with COVID-19. The Sponsor intends to enroll approximately 379 patients that have been diagnosed with COVID-19 pneumonia and meet the entry criteria.

Patients must be at least 18 years of age with confirmed SARS-CoV-2 (COVID-19) infection per World Health Organization (WHO) criteria, including a positive polymerase chain reaction (PCR) of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have SpO_2 <94% on ambient air and be on SOC, which may include anti-viral treatment, low dose systemic corticosteroids, and supportive care.

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. Patients with active tuberculosis (TB) or suspected active bacterial, fungal, viral, or other infection (besides COVID-19 and well-controlled HIV) will be excluded from the study.

Patients will be screened and randomized within *96* hours of hospital admission. Patients will be randomized at a 2:1 ratio to receive blinded treatment of either TCZ or placebo, respectively. Study treatment must be given within approximately 4 hours after randomization. TCZ and placebo will be given in combination with SOC.

Patients assigned to the TCZ arm will receive one infusion of TCZ 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the placebo arm will receive one infusion of placebo, both in addition to SOC.

If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion. *Note: Pre-dose assessments must be repeated and reviewed before an additional infusion of blinded treatment of TCZ or placebo is administered*

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity *within 96 hours of hospital admission* (for a total of 2 screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 7 days after previously signing the consent form. The investigator will record the reasons for screen failure in the screening log.

The study assessments to be conducted include the following: physical examination, vital signs, oxygen saturation, assessment of consciousness, presence and absence of respiratory support, adverse events, concomitant therapies, and clinical laboratory tests.

Patients will be followed up for a total of 60 days after first dose of study medication.

If patients are discharged from the hospital prior to Day 28 or discontinue the study, the Study Completion/Discontinuation assessments are to be conducted prior to discharge or at discontinuation from the study. In addition, if patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. Follow-up visits may be conducted by onsite clinic visits, telephone calls, or home visits. After Day 28, all patients should have a follow-up visit on approximately Day 60 which may be conducted as an onsite clinic visit, telephone call, or home visit for discharged patients.

During the study, standard supportive care will be given according to clinical practice. After study completion, patients should be referred to their regular healthcare provider based on their doctor's decision and as part of standard of care.

Number of Patients

This study aims to enroll approximately 379 hospitalized patients with COVID-19 pneumonia.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- *Documented i*nformed *c*onsent by any patient capable of giving consent, or, when the patient is not capable of giving consent, by his or her legal/authorized representative
- Age ≥18 years at time of *providing* Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Hospitalized
- COVID-19 pneumonia confirmed per a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid) and radiographic imaging (CT scan or chest X-ray)
- Able to complete screening within *96* hours of hospital admission
- Blood oxygen saturation (SpO_2) <94% while on ambient air

  If a patient is on supplemental oxygen with SpO_2 ≥94%, but desaturation to <94% on lower supplemental oxygen or ambient air is documented during screening, the inclusion criterion is met.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 90 days after the final dose of study drug. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

  Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 60 days after the final dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria

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

- Known severe allergic reactions to TCZ or other monoclonal antibodies
- Require CPAP, BIPAP, or mechanical ventilation
- Active TB infection or last TB infection within 1 month of randomization
- Suspected active bacterial, fungal, viral, or other infection (besides COVID-19 and well-controlled HIV)
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
- Immunocompromised (besides well-controlled HIV) or on immunosuppressive therapy (except for steroids for COVID), advanced cancer
- Have received oral anti-rejection or immunomodulatory drugs (including TCZ) within the past 3 months
- Participating in another IL-6 antagonist clinical trial or other drug clinical trials (participation in COVID-19 anti-viral trials may be permitted if approved by Medical Monitor)
- ALT or AST >5 x upper limit of normal (ULN) detected within 24 hours at screening (according to local laboratory reference ranges)
- ANC <1000/μL at screening (according to local laboratory reference ranges)
- Platelet count <50,000/μL at screening (according to local laboratory reference ranges)
- Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
- Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (investigational COVID-19 antivirals may be permitted if approved by Medical Monitor)
- Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Any history of diverticulitis or gastrointestinal perforation

The use of remdesivir, hydroxychloroquine, chloroquine, and convalescent plasma, is not an exclusion to participation in this trial, and is left to the discretion of the primary medical team.

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for last follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 2 months after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 8 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

Patients assigned to the active arm will receive one or two doses of tocilizumab (TCZ) via intravenous (IV) infusion at a dose of 8 mg/kg IV to a maximum of 800 mg per dose.

Comparator

Patients assigned to the comparator arm will receive one or two doses of placebo via IV infusion.

Statistical Methods

Primary Analysis

The primary efficacy objective for this study is to evaluate the efficacy of TCZ plus standard of care, compared with placebo plus standard of care using the following endpoint:

- Cumulative proportion of patients *with death or* requiring mechanical ventilation by Day 28

Time to *death or* the first utilization of mechanical ventilation after randomization will be *compared between the TCZ group and the placebo group using the stratified log-rank test with age group (age ≤60, age >60 years) as the stratification factor. T*he cumulative proportion of patients *with death or* requiring mechanical ventilation at Day 28 *will be estimated using the Kaplan-Meier method*.

Details of the primary endpoint analysis will be included in the Statistical Analysis Plan (SAP).

Determination of Sample Size

The estimated sample size was determined based on the time from randomization to the first utilization of mechanical ventilation by Day 28.

The total modified intent-to-treat (mITT) sample size of 379 patients with a 2:1 randomization of TCZ (n=253) to placebo (n=126) provides approximately 80% power using a Logrank test to detect a 15% difference between treatment groups in time to *death or* mechanical ventilation by Day 28 under the following assumptions: cumulative survival (i.e., *alive and* not requiring mechanical ventilation) rates of 75% in the TCZ group and 60% in placebo group, with 28-day follow-up, using a two-sided 5% alpha, and 10% dropout rate in each arm. Sample size re-estimation may be considered during the study based on updated assumptions of the treatment effect.

Planned Interim Analyses

An Internal Monitoring Committee (IMC) will evaluate safety according to procedures and guidelines detailed in the IMC agreement. The IMC will consist of Sponsor representatives who will not be blinded to study data. Details of the safety reviews will be provided in the SAP.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ARDS	acute respiratory distress syndrome
BIPAP	bilevel positive airway pressure
CAR	chimeric antigen receptor
CDC	Centers for Disease Control
CoV	coronaviruses
CPAP	continuous positive airway pressure
CRP	C-reactive protein
CRS	cytokine-release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
EC	Ethics Committee
eCRF	electronic Case Report Form
ECMO	extracorporeal membrane oxygenation
EDC	electronic data capture
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
GCA	giant cell arteritis
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
hs-CRP	high sensitivity C-reactive protein
ICH	International Council for Harmonisation
ICU	intensive care unit
IL-6	interleukin 6
IL-6R	interleukin-6 receptor
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system
LPLV	last patient, last visit
IV	intravenous
MERS-CoV	Middle East respiratory syndrome
MOD	multiple organ dysfunction
MOF	multi-organ failure
mITT	modified intent-to-treat

Abbreviation	Definition
NCI	National Cancer Institute
PaO_2	partial pressure of oxygen
PCR	polymerase chain reaction
PCT	procalcitonin
pJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetic
PY	patient years
RA	rheumatoid arthritis
RT-PCR	real time polymerase chain reaction
SAP	Statistical Analysis Plan
SARS-CoV	severe acute respiratory syndrome
SC	subcutaneous
sJIA	systemic juvenile idiopathic arthritis
sIL-6R	soluble IL-6R
SOC	standard of care
SpO_2	blood oxygen saturation
SSc	systemic sclerosis
TAK	Takayasu arteritis
TB	tuberculosis
TCZ	tocilizumab
ULN	upper limit of normal
WHO	World Health Organization

1. BACKGROUND

1.1 BACKGROUND ON COVID-19 PNEUMONIA

Coronaviruses (CoV) are positive-stranded RNA viruses, named for the crown-like appearance of their spike glycoproteins on the virus envelope. They are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV).

COVID-19, which is the acronym of "coronavirus disease 2019," is caused by a novel coronavirus strain (SARS-CoV-2) and was newly named on 11 February 2020 by the World Health Organization (WHO). An epidemic of cases with unexplained lower respiratory tract infections was first detected in Wuhan, the largest metropolitan area in China's Hubei province, and was reported to the WHO Country Office in China on December 31, 2019. A pandemic was subsequently declared by the WHO on 11 March 2020.

According to the WHO, as of 12 April 2020 over 1,600,000 cases of COVID-19 were reported in over 200 countries and territories worldwide, with over 105,000 deaths (WHO 2020a). Up to ~20% of infected patients experienced complications related to a severe form of interstitial pneumonia, which may progress to acute respiratory distress syndrome (ARDS) and/or multi-organ failure (MOF) and death (WHO 2020b).

To date, there is no vaccine and no specific antiviral medicine shown to be effective in preventing or treating COVID-19. Most patients with mild cases of disease recover with symptomatic treatment and supportive care. However, patients with more severe illness frequently require hospitalization (WHO 2020b).

Cohort studies of ethnically homogeneous patients in China indicate that male gender, and comorbidities such as diabetes, hypertension, and cardiovascular disease predispose to increased risk of infection and morbidity (Li et al. 2020). The U.S. Centers for Disease Control (CDC) published hospitalization rates and characteristics of patients with COVID-19 suggest minority patients may be disproportionately affected by COVID-19, potentially due to increased frequency of underlying conditions (Garg 2020).

1.2 BACKGROUND ON TOCILIZUMAB

Tocilizumab (TCZ) is a recombinant humanized, anti-human monoclonal antibody of the IgG1 subclass directed against soluble and membrane-bound IL-6R. TCZ binds specifically to both soluble IL-6R (sIL-6R) and membrane-bound IL-6R and has been shown to inhibit both soluble and membrane-bound IL-6R–mediated signaling. IL-6 is a pleiotropic pro inflammatory multifunctional cytokine produced by a variety of cell types and has been shown to be involved in diverse physiological processes such as T-cell activation; induction of acute phase proteins; stimulation of hematopoietic precursor cell growth and differentiation; proliferation of hepatic, dermal, and neural cells; bone

metabolism; lipid metabolism; hepatoprotection; and fibrosis. Elevated tissue and serum levels of IL-6 have been implicated in the disease pathology of several inflammatory and autoimmune disorders including rheumatoid arthritis (RA), Castleman disease, systemic juvenile idiopathic arthritis (sJIA), polyarticular juvenile idiopathic arthritis (pJIA), giant cell arteritis (GCA), Takayasu arteritis (TAK), systemic sclerosis (SSc), and cytokine-release syndrome (CRS). Inhibition of the biological activity of IL-6 or IL-6R has been effective in the treatment of these disorders, including chimeric antigen receptor (CAR) T-cell induced CRS, for which treatment with TCZ has been approved in many countries.

TCZ has intravenous (IV) and subcutaneous (SC) formulations. Some of the above-listed indications (RA, sJIA, and pJIA) have received approval for both the IV and SC formulations, whereas others have received approval exclusively for the IV (Castleman disease and CRS) or the SC (GCA and TAK) formulation.

[redacted]

1.3 TOCILIZUMAB TREATMENT IN CYTOKINE-RELEASE SYNDROME OF CAR-T THERAPY

CRS has been identified as a clinically significant, on-target, off-tumor side effect of the CAR T-cell therapies used for treatment of malignancies. Characteristics of CRS include fever, fatigue, headache, encephalopathy, hypotension, tachycardia, coagulopathy, nausea, capillary leak, and multi-organ dysfunction. The reported incidence of CRS after CAR T-cell therapy ranges from 50% to 100%, with 13% to 48% of patients experiencing the severe or life-threatening form. Serum levels of inflammatory cytokines are elevated, particularly interleukin-6 (IL-6). The severity of symptoms may correlate with the serum cytokine concentrations and the duration of exposure to the inflammatory cytokines.

On August 30, 2017, the U.S. Food and Drug Administration approved tocilizumab (Actemra®) for the treatment of severe or life-threatening CAR T cell-induced CRS in adults and in pediatric patients 2 years of age and older. The approved dose is 8 mg/kg for body weight ≥30 kg and 12 mg/kg for body weight <30 kg. Up to three additional doses may be given if no improvement of sign/symptoms, and the interval between the subsequent doses should be at least 8 hours.

The approval of TCZ was based on a retrospective analysis of data for patients treated with TCZ who developed CRS after treatment with tisagenlecleucel (Kymriah®) or axicabtagene ciloleucel (Yescarta®) in prospective clinical trials, (Le et al. 2018). Thirty-one out of the 45 patients (69%) from the CTL019 series achieved a response (defined as being afebrile and off vasopressors for at least 24 hours within 14 days of the first dose of TCZ (maximum up to two doses) and without use of additional treatment other than corticosteroids) within 14 days of the first dose of TCZ, and the median time from the first dose to response was 4 days. Eight of the 15 patients (53%) from the axicabtagene ciloleucel series achieved a response, and the median time to response was 4.5 days. The response rates were largely consistent among subgroups such as age group, sex, race, ethnicity, grade of CRS at first dose of TCZ, and duration of CRS prior to treatment with TCZ. There were no reports of adverse reactions attributable to TCZ.

Pharmacokinetic (PK) data were available for 27 patients after the first dose of TCZ and for 8 patients after a second dose of TCZ. Based on 131 PK observations, the geometric mean (% CV) maximum concentration of TCZ in the patients with CAR T cell induced, severe or life-threatening CRS was 99.5 μg/mL (36.8%) after the first infusion and 160.7 μg/mL (113.8%) after the second infusion. The PK modeling analysis showed that patients with CRS had a faster clearance of TCZ than healthy volunteers and other patient populations, and simulations showed that exposure was considered acceptable with up to four doses of TCZ at least 8 hours apart in patients with CRS.

TCZ is also approved for CAR-T induced severe or life-threatening CRS in the European Union and certain other countries.

1.4 REAL WORLD EXPERIENCE WITH TOCILIZUMAB IN COVID-19 PNEUMONIA

Physicians in China initiated the off-label use of TCZ in the treatment of COVID-19 pneumonia. Based on the results of an initial 21-patient retrospective study in which patients with severe or critical COVID-19 pneumonia were treated with TCZ (Submitted, Xu et al. 2020), an investigator-sponsored randomized, controlled trial (n=188) has been initiated in the same population in China, testing the same TCZ dose regimen and is currently ongoing, with approximately 70 patients enrolled. At present, the 21-patient publication (Xu et al. 2020) and case reports of individual patients include the limited available published clinical data the Sponsor is aware of regarding the use of TCZ in the treatment of COVID-19 pneumonia.

On 3 March 2020, TCZ was included in the seventh updated diagnosis and treatment plan for COVID-19 issued by the China National Health Commission as one treatment option for severe or critical forms of COVID-19 pneumonia. The Chinese Center for

Disease Control and Prevention defined disease severity according to the following criteria:

- Severe disease: dyspnea, respiratory frequency ≥30/min, blood oxygen saturation (SpO_2) ≤93%, PaO2/FiO_2 ratio (the ratio between the blood pressure of the oxygen [partial pressure of oxygen, PaO_2] and the percentage of oxygen supplied [fraction of inspired oxygen, FiO_2]) <300 mmHg, and/or lung infiltrates >50% within 24 to 48 hours; this occurred in 14% of cases.
- Critical disease: respiratory failure, septic shock, and/or multiple organ dysfunction (MOD) or failure (MOF); this occurred in 5% of cases (Wu et al. 2020).

Because body weight measurement is not always feasible in urgent circumstances, the dose regimen used in China is a single fixed dose of 400 mg TCZ IV (which equates to between 4–8 mg/kg based on the body weight range of the Chinese adult population), with the maximum single dose no more than 800 mg. If clinical signs/symptoms do not improve, an additional dose can be administered after 12 hours. The guidance advises that no more than two doses should be given. TCZ treatment is not permitted for people with active infections including TB, bacterial, or fungal.

Results from 21 Patients Treated with Tocilizumab in China

In February 2020, twenty-one patients with severe or critical COVID-19 pneumonia were treated with TCZ IV (400 mg) plus standard of care. The average age of the patients was 56.8 ± 16.5 years, ranging from 25 to 88 years. Seventeen patients (81.0%) were assessed as severe and four (19.0%) as critical. Most patients (85%) presented with lymphopenia. C-reactive protein (CRP) levels were increased in all 20 patients (mean, 75.06 ± 66.80 mg/L). The median procalcitonin (PCT) value was 0.33 ± 0.78 ng/mL, and only two of 20 patients (10.0%) presented with an abnormal value. Mean IL-6 level before TCZ was 132.38 ± 278.54 pg/mL (normal <7 pg/mL).

Standard of care consisted of lopinavir, methylprednisolone, other symptom relievers, and oxygen therapy as recommended by the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Sixth Edition). All 21 patients had received routine standard of care treatment for a week before deteriorating with sustained fever, hypoxemia, and chest CT image worsening.

Eighteen patients (85.7%) received TCZ once, and three patients (14.3%) had a second dose due to fever within 12 hours. According to the authors, after TCZ treatment, fever returned to normal and all other symptoms improved remarkably. Fifteen of the 20 patients (75.0%) had lowered their oxygen intake and one patient needed no oxygen therapy. CT scans showed significant remission of opacities in both lungs in 19/20 patients (90.5%) after treatment with TCZ. The percentage of lymphocytes in peripheral blood, which was decreased in 85.0% of patients (17/20) before treatment (mean, 15.52±8.89%), returned to normal in 52.6% of patients (10/19) on the fifth day after treatment. Abnormally elevated CRP decreased significantly in 84.2% patients

(16/19). No adverse drug reactions and no subsequent pulmonary infections were reported.

Nineteen patients (90.5%) were discharged at the time of the report, including two critical patients. There were no deaths among the 21 treated patients.

The study authors concluded that TCZ is an effective treatment for patients with severe COVID-19 (Submitted, Xu et al. 2020).

Results from Individual Case Reports

Michot et al. (2020) reported a 42-year-old with history of renal cell carcinoma hospitalized for COVID-19 pneumonia and treated with 5 days of lopinavir-ritonavir treated and 2 doses of tocilizumab (8 mg/kg IV) following rapid respiratory decompensation. The patient experienced clinical improvement with discontinuation of supplemental oxygen 4 days later and fully recovered. No adverse drug reactions were reported.

Ferrey et al. (2020) reported a 56-year-old with end stage renal disease hospitalized for bilateral interstitial pneumonia secondary to COVID-19 who developed acute respiratory distress syndrome. The patient was treated with hydroxychloroquine, tocilizumab, and broad spectrum antibiotics along with supportive care. At the time of publication, the patient remained in critical condition without report of adverse drug reactions.

Cellina et al. (2020) reported a 64 year old male with confirmed COVID-19 infection and dyspnea who had favorable changes in computed tomography (CT) results following 2 doses of tocilizumab (8 mg/kg) 12 hours apart. The patient's clinical condition improved and was able to be weaned off the ventilator. No adverse drug reactions were reported.

Results from Patients in Special Populations

De Luna et al. (2020) reported a 45-year-old male with sickle cell disease who developed rapid and severe COVID-19 pneumonia. He was treated with amoxicillin-clavulanic acid and hydroxychloroquine but clinical condition continued to deteriorate with increased oxygen requirement. He was treated with 1 dose of tocilizumab (8 mg/kg) and was reported to have clear improvement in general condition. The patient was discharged 2 days later. No adverse drug reactions were reported.

Zhang et al. (2020) reported a 60-year-old male with multiple myeloma in Wuhan, China who developed shortness of breath and was started on methylprednisolone. CT chest was positive for ground glass opacities and RT-PCR confirmed COVID-19 infection. He was treated with umifenovir without clinical improvement. Clinical improvement noted following 1 dose of tocilizumab (8 mg/kg) with gradual decline in IL-6. The patient was later discharged from the hospital. No adverse drug reactions were reported.

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

There are currently no drugs licensed for the treatment of patients with COVID-19. Given the results of studies outlined above, TCZ, along with standard of care (SOC) treatment, could provide efficacy, offering the potential to treat COVID-19 in hospitalized populations more effectively than current SOC alone. Extensive safety data have previously been generated on the use of TCZ in other indications. Therefore, a placebo-controlled study in combination with SOC to assess safety and efficacy of TCZ in hospitalized patients with COVID-19 pneumonia is justified to address the high unmet need and burden of disease in this severely ill population.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of TCZ compared with a placebo in combination with SOC in hospitalized patients with COVID-19 pneumonia. To enhance the understanding of the clinical profile of tocilizumab for patients who belong to high-risk and minority populations, an emphasis will be placed on including minority-enrolling sites.

Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoint:

- Cumulative proportion of patients *with death or* requiring mechanical ventilation by Day 28

2.1.2 Secondary Efficacy Objectives

The secondary efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status
- Time to clinical failure, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first)
- Mortality rate by Day 28
- Time to hospital discharge or “ready for discharge” (e.g., awaiting social disposition) as evidenced by, for example, normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen

2.1.3 Exploratory Efficacy Objectives

The exploratory efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Change from baseline in inflammatory markers levels (hs-CRP/CRP, D-dimer, and ferritin) over time
- Cumulative proportion of patients requiring CPAP or BIPAP by Day 28

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0
- Incidence of any post-treatment bacterial and/or fungal infection
- Incidence of any post-treatment acute kidney injury (defined by 50% increase of creatinine from baseline)

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of TCZ in combination with SOC compared with placebo in combination with SOC in hospitalized adult patients with COVID-19. The Sponsor intends to enroll approximately 379 patients that have been diagnosed with COVID-19 pneumonia and meet the entry criteria.

Patients must be at least 18 years of age with confirmed SARS-CoV-2 (COVID-19) infection per WHO criteria, including a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have SpO_2 <94% on ambient air and be on SOC, which may include anti-viral treatment, low dose systemic corticosteroids, and supportive care.

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. Patients with active tuberculosis (TB) or suspected active bacterial, fungal, viral, or other infection (besides COVID-19 and well-controlled HIV) will be excluded from the study.

Patients will be screened and randomized within 96 hours of hospital admission. Patients will be randomized at a 2:1 ratio to receive blinded treatment of either TCZ or

placebo, respectively. Study treatment must be given within approximately 4 hours after randomization. TCZ and placebo will be given in combination with SOC.

Patients assigned to the TCZ arm will receive one infusion of TCZ 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the placebo arm will receive one infusion of placebo (see Section 4.3), both in addition to SOC.

If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion. *Note: Pre-dose assessments must be repeated and reviewed before an additional infusion of blinded treatment of TCZ or placebo is administered.*

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity *within 96 hours of hospital admission* (for a total of 2 screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 7 days after previously signing the consent form. The investigator will record the reasons for screen failure in the screening log in Section 4.5.1.

The study assessments to be conducted include the following: physical examination, vital signs, oxygen saturation, assessment of consciousness, presence and absence of respiratory support, adverse events, concomitant therapies, and clinical laboratory tests. Please see Appendix 1 and Appendix 2 for details concerning the timing of these assessments.

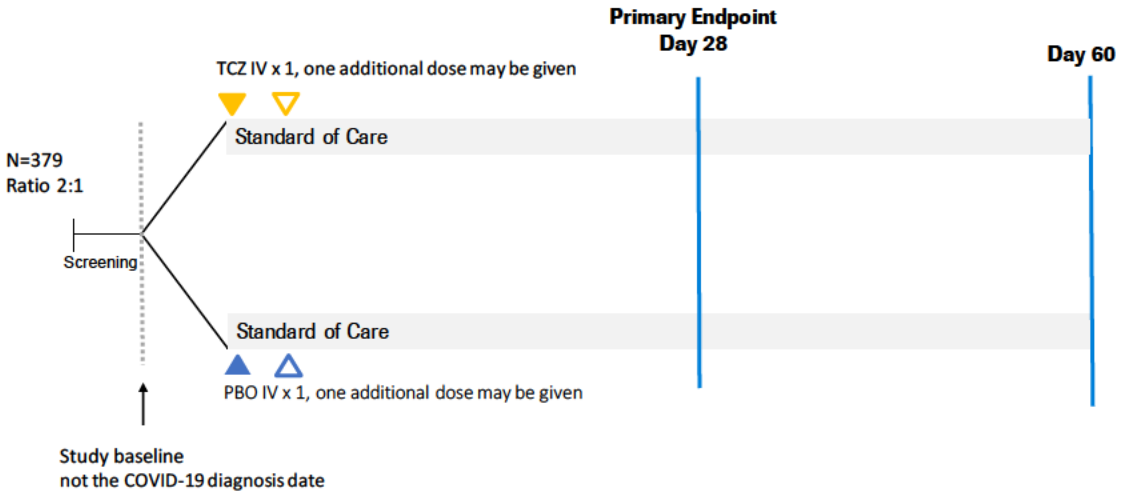
Patients will be followed up for a total of 60 days after first dose of study medication.

If patients are discharged from the hospital prior to Day 28 or discontinue the study, the Study Completion/Discontinuation assessments are to be conducted prior to discharge or at discontinuation from the study. In addition, if patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. Follow-up visits may be conducted by onsite clinic visits, telephone calls, or home visits. After Day 28, all patients should have a follow-up visit on approximately Day 60 which may be conducted as an onsite clinic visit, telephone call, or home visit for discharged patients.

During the study, standard supportive care will be given according to clinical practice. After study completion, patients should be referred to their regular healthcare provider based on their doctor's decision and as part of standard of care.

Figure 1 presents an overview of the study design. Schedules of activities are provided in Appendix 1 and Appendix 2.

Figure 1 Study Schema



IV = intravenous; PBO = placebo; TCZ = tocilizumab.
Note: Patients will be screened and randomized within 96 hours of hospital admission. Study treatment must be given within approximately 4 hours after randomization.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for last follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 2 months after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 8 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Tocilizumab Dose and Schedule

At baseline, patients assigned to the TCZ arm will receive one infusion of TCZ 8 mg/kg IV, with a maximum dose of 800 mg. If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of TCZ 8 mg/kg IV can be given, 8–24 hours after the initial infusion.

The TCZ dose regimen chosen in this study for adult patients is consistent with the approved TCZ dose for patients experiencing CRS induced by CAR-T cell therapy who weigh ≥30 kg. Further, based on the off-label experience from China (one additional dose if fever is not improved within 12 hours) and the fact that up to three additional infusions of TCZ (with at least 8 hours in between infusions) are allowed for CAR-T

induced CRS, the proposed additional one infusion if clinical signs/symptoms worsen or do not improve is justified.

Patients will be followed-up for a period of 60 days from randomization. This period is supported by historical data from studies performed in healthy subjects and patients with RA (study LRO300 and LRO301) where the mean apparent half-life was determined by non-compartmental analysis and ranged from 7 to 8 days following a single dose of 10 mg/kg IV or multiple doses of 8 mg/kg IV Q4W. Moreover, modeling of free sIL6R levels over time, as the principal marker of target engagement, showed that soluble receptors returned to their maximum level after 4 weeks following a single administration of 8 mg/kg IV, demonstrating the absence of drug binding and therefore of drug effect after 4 weeks (Gibiansky and Frey 2012).

3.3.2 Rationale for Patient Population

Based on the current knowledge of COVID-19, approximately 80% of patients infected with SARS-CoV-2 (COVID-19) experience mild disease and can recover at home and require only simple symptomatic relief. However, approximately 20% require hospitalization due to more severe disease. A study of 138 hospitalized patients with COVID-19 published on 7 February 2020 found that 26% of patients admitted to hospital required transfer to the intensive care unit (ICU) and 4.3% died; however, given that a number of patients were still hospitalized at the time of this report, this number may be an underestimate (Wang et al. 2020). A previous study had found that out of 41 admitted hospital patients, 13 (32%) were admitted to an ICU and six (15%) died (Huang et al. 2020). A more recent study with 1099 patients indicated that 16% of patients developed a severe form of disease, 5% were admitted to an ICU, 2.3% underwent invasive mechanical ventilation, and 1.4% died (Guan et al. 2020).

Given the significant unmet need in hospitalized high-risk and/or minority patient populations with COVID-19 pneumonia, and based on the emerging evidence for TCZ use in patients with COVID-19 pneumonia, this study is designed to evaluate the efficacy and safety of TCZ in this population. Morbidity and mortality are particularly high for elderly patients and those with comorbidities. This study will include both these groups, with no upper age limit.

3.3.3 Rationale for Control Group

The study will compare the efficacy and safety of TCZ IV compared with placebo in combination with SOC. Despite the lack of targeted treatments for COVID-19, SOC for patients with COVID-19 pneumonia generally includes supportive care and may include available anti-viral agents and low-dose systemic corticosteroids as dictated by local treatment guidelines. Therefore, SOC plus placebo treatment is appropriate as a control in this study.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study aims to enroll approximately 379 hospitalized patients with COVID-19 pneumonia.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- *Documented i*nformed *c*onsent by any patient capable of giving consent, or, when the patient is not capable of giving consent, by his or her legal/authorized representative
- Age ≥18 years at time of *providing i*nformed *c*onsent
- Ability to comply with the study protocol, in the investigator's judgment
- Hospitalized
- COVID-19 pneumonia confirmed per a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid) and radiographic imaging (CT scan or chest X-ray)
- Able to complete screening within *96* hours of hospital admission
- SpO_2 <94% while on ambient air

  If a patient is on supplemental oxygen with SpO_2 ≥94%, but desaturation to <94% on lower supplemental oxygen or ambient air is documented during screening, the inclusion criterion is met.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 90 days after the final dose of study drug. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

  Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation

methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 60 days after the final dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.2 Exclusion Criteria

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

- Known severe allergic reactions to TCZ or other monoclonal antibodies
- Require CPAP, BIPAP, or mechanical ventilation
- Active TB infection or last TB infection within 1 month of randomization
- Suspected active bacterial, fungal, viral, or other infection (besides COVID-19 and well-controlled HIV)
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
- Immunocompromised (besides well-controlled HIV) or on immunosuppressive therapy (except for steroids for COVID), advanced cancer
- Have received oral anti-rejection or immunomodulatory drugs (including TCZ) within the past 3 months
- Participating in another IL-6 antagonist clinical trial or other drug clinical trials (participation in COVID-19 anti-viral trials may be permitted if approved by Medical Monitor)
- ALT or AST >5 x upper limit of normal (ULN) detected within 24 hours at screening (according to local laboratory reference ranges)
- ANC <1000/μL at screening (according to local laboratory reference ranges)
- Platelet count <50,000/μL at screening (according to local laboratory reference ranges)
- Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination

- Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (investigational COVID-19 antivirals may be permitted if approved by Medical Monitor)
- Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Any history of diverticulitis or GI perforation

The use of remdesivir, hydroxychloroquine, chloroquine, and convalescent plasma, is not an exclusion to participation in this trial, and is left to the discretion of the primary medical team.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, double-blind, placebo-controlled study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS).

Patients will be randomly assigned to one of two treatment arms: TCZ in combination with SOC or placebo in combination with SOC. Randomization will occur in a 2:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. The randomization will be stratified by age (i.e., ≤60 and >60 years of age).

4.2.2 Blinding

Study site personnel and patients will be blinded to treatment assignment during the study, with the exception of the study pharmacist. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial and members of the internal Monitoring Committee (IMC). These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, IxRS service provider, and IMC members.

Genentech monitors, project statisticians, and the project team will be blinded from study results, with the exception of the IMC members. Study centers may be unblinded after the final study results are reported.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior

to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMP) for this study are tocilizumab IV and its placebo as the comparator.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Tocilizumab and Placebo

TCZ will be supplied by the Sponsor as a sterile IV injection for reconstitution in 20-mL glass vials with a 10 mL fill (200 mg/10 mL of TCZ) or with a 20 mL fill (400 mg / 20 mL of TCZ). An appropriate number of vials (depending on the patient's body weight) of TCZ will be assigned to each patient for the infusion. The amount of solution that is withdrawn from each vial will depend on the patient's allocated dose. For information on the formulation and handling of TCZ, see the TCZ pharmacy manual and Tocilizumab Investigator's Brochure.

Placebo will be supplied by the investigative site in the form of a 0.9% sodium chloride (normal saline) bag. *Placebo is not supplied by the Sponsor; please refer to the pharmacy manual for instructions on the preparation of the placebo.*

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

4.3.2.1 Tocilizumab and Placebo

TCZ/placebo will be administered by IV infusion at doses of 8 mg/kg. The maximum dose of TCZ that will be administered is 800 mg. The dose of TCZ infusion will be calculated on the basis of body weight measured prior to infusion (see Appendix 1). One additional infusion of blinded treatment of TCZ or placebo can be given 8–24 hours after the initial infusion.

TCZ/placebo must be administered under close supervision of the investigator in a setting where medications and resuscitation facilities are available. Patients should be monitored for at least 2 hours after the TCZ infusion is completed.

The TCZ/placebo vials will be stored at a temperature of 2°C–8°C. The infusion bag of TCZ/placebo should be diluted to 100 mL infusion bag using aseptic technique. The fully diluted TCZ/placebo solutions for infusion using 0.9% Sodium Chloride Injection, USP may be stored at 2° to 8°C (36° to 46°F) or at room temperature for up to 24 hours and should be protected from light.

If stored at 2° to 8°C (36° to 46°F), the infusion bag should be allowed to return to room temperature before administration. The TCZ/*placebo* will be administered at room temperature by controlled infusion into a vein over a 1-hour period. In exceptional cases this time may be extended to up to 6 hours. The infusion speed must be 10 mL/hr for 15 minutes and then increased to 130 mL/hr to complete the dosing in 1 hour. The entire 100 mL content of the infusion bag must be administered. A total of 20 mL of normal saline will be administered following the infusion of study medication to flush the remaining study drug through the intravenous set.

Refer to the Tocilizumab Investigator's Brochure for further instructions regarding recommended storage conditions and packaging configuration.

4.3.3 Investigational Medicinal Product Handling and Accountability

The IMP (TCZ/placebo) required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive TCZ/placebo, and only authorized staff may supply or administer TCZ/placebo.

TCZ/placebo will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the

Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the TCZ/placebo Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Tocilizumab

Since the TCZ treatment is not intended for continued therapy, the Sponsor does not have any plans to provide TCZ or any other study treatments to patients who have completed the study.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements, investigational anti-viral agents, blood products) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

All patients will receive standard of care per local practice for the treatment of COVID-19 pneumonia. The standard of care may include anti-viral treatment, low-dose systemic corticosteroids, and supportive care.

Chloroquine or hydroxychloroquine is permitted as part of local practice. The recommended maximum dose of chloroquine is 400 mg twice a day.

Clinical management guidelines from WHO recommend against the use of corticosteroids in patients with COVID-19 pneumonia. However, country- and region-specific guidelines recommend considering corticosteroids in some COVID-19 patients. This protocol allows the use of low-dose steroids as part of local SOC. If steroids are given, the Sponsor recommends a dose of no more than 1 mg/kg methylprednisolone or equivalent for no more than 5 days.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience

infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists (e.g., famotidine, ranitidine), or equivalent medications per local standard practice. Serious infusion associated events manifested by, for example, dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

4.4.2 Cautionary Therapy

4.4.2.1 Medications Given with Precaution due to Effects Related to CYP Enzymes

The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., IL-6) during chronic inflammation. Therefore, for molecules that antagonize cytokine activity, such as TCZ, it is expected that the formation of CYP450 enzymes could be normalized. When starting TCZ therapy, patients taking medications that are individually dose adjusted and metabolized by means of CYP450, CYP3A4, CYP1A2, or CYP2C9 (e.g., atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporin, or benzodiazepines) are recommended to be monitored as doses may need to be adjusted to maintain their therapeutic effect.

The above list of medications is not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Treatment with any investigational agent (except for SARS-CoV-2 [COVID-19] anti-viral agents with approval of Medical Monitor), cell-depleting therapies, biologic agents (e.g., tumor necrosis factor antagonists or IL-6/IL-6R therapies including sarilumab, siltuximab), Janus kinase inhibitors (e.g., tofacitinib, baricitinib), alkylating agents (e.g., chlorambucil, cyclophosphamide), thalidomide, IV gamma globulin, anti-thymocyte globulin, and azathioprine during the study
- *Open-label tocilizumab*
- Bone marrow transplantation with total lymphoid irradiation during the study
- Plasmapheresis or extracorporeal photopheresis during the study
- Immunization with a live or attenuated vaccine for the duration of the patient's study participation.

4.5 STUDY ASSESSMENTS

The sequence of assessments at each visit will be standardized as follows (at visits required in the schedules of assessments).

1. Efficacy assessments: clinical status, clinical signs and symptoms, oxygen saturation
2. Safety assessments: vital signs, review of adverse events, concomitant medications
3. Laboratory samples: on days when study drug is administered, all samples (including safety) must be taken within 4 hours prior to study drug treatment.
4. IV infusion of TCZ/placebo (only at baseline and an additional dose, if needed)
5. Safety assessments; vital signs post TCZ (if applicable)

Schedules of assessments are found in Appendix 1 and Appendix 2.

If patients are discharged from the hospital prior to Day 28 or discontinue the study, the Study Completion/Discontinuation assessments are to be conducted prior to discharge or at discontinuation from the study. In addition, if patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. Follow-up visits may be conducted by onsite clinic visits, telephone calls, or home visits. After Day 28, all patients should have a follow-up visit on approximately Day 60 which may be conducted as an onsite clinic visit, telephone call, or home visit for discharged patients.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). In the pandemic situation where access to hospitals is limited, if allowed, verbal consent can be obtained from the patient's legally authorized representative and must be documented by the investigator or the authorized designee. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. Physical examination, blood tests, and other assessments conducted after arrival at the hospital, but before the informed consent is signed, can be used as screening assessments. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, home oxygen use, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to first dose of study drug will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, self-reported race/ethnicity, smoking history, and patient characteristics.

4.5.3 Physical Examinations

A complete physical examination, performed at screening, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions electronic Case Report Form (eCRF).

Limited, symptom-directed physical examinations may be performed at unscheduled postbaseline visits as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

In addition, patient body weight will be measured at screening (see Appendix 1). If it is not feasible to weigh bed-bound patients, historical body weight may be used.

Physical examination, blood tests, and other assessments conducted after arrival at the hospital, but before the informed consent is signed, can be used as screening assessments.

4.5.4 Vital Signs and Oxygen Saturation

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure, and body temperature. Peripheral oxygen saturation should also be measured at the same time as the vitals. For patients requiring supplemental oxygen, the oxygen flow rate (L/min) and/or FiO_2 should be recorded.

Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.5 Ventilation Requirement

Assessment of ventilation usage (non-invasive or mechanical) should be recorded once daily with ordinal scale determination based upon the following categories:

- No supplemental oxygen
- Supplemental oxygen (nasal cannula, face mask)
- Non-invasive ventilation or high-flow oxygen (high-flow nasal cannula, CPAP, BiPAP)
- Intubation and mechanical ventilation

4.5.6 Laboratory and Other Biological Samples

Samples for the following laboratory tests will be measured by study site's local laboratory:

- Partial pressure of oxygen (PaO_2, if arterial blood gases are performed during screening or follow-up)
- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes)
- Chemistry panel (serum or plasma): bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total bilirubin, ALP, ALT, AST
- hs-CRP*/CRP*, D-dimer *(if available locally)*, and ferritin
- Pregnancy test

  All women of childbearing potential will have a pregnancy test at screening (urine or serum). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- SARS-CoV-2 (COVID-19) PCR (screening): nasopharyngeal swab or other respiratory specimen, blood, urine, stool, other bodily fluid

4.5.7 Liver Function Monitoring

Patients should be assessed for liver function prior to each dose of TCZ or placebo. On Day 1, the assessment is mandatory. On Day 1, the local laboratory full blood chemistry panel required as part of screening can be used for this assessment or prior blood results if tests conducted within 24 hours prior to screening. Results must be reviewed by the investigator before dose administration. Dosing will occur only if the clinical assessment and local laboratory liver chemistry panel values are acceptable.

4.5.8 Chest X-Rays and CT Scans

Either a chest CT scan or a chest X-ray are acceptable to determine eligibility and for follow up. During the study, follow-up CT scans or chest X-rays will be performed per the schedule of assessments.

Chest X-ray/CT scan findings should be recorded on the appropriate eCRF. If additional chest X-rays/CT scans are taken per local practice, this information should be provided in the eCRF.

4.5.9 Electrocardiograms

Single ECG recordings will be obtained at screening, as outlined in the schedule of activities (see Appendix 1) and may be obtained thereafter as needed per investigator's discretion.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

4.5.10 Ordinal Scale Determination

Assessment of clinical status using a 7-category ordinal scale will be recorded at baseline on Day 1 and then again once daily every morning (between approximately 8 am and 12 pm) while hospitalized. The ordinal scale categories are as follows:

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

Patients who are ready to be discharged but are still hospitalized (e.g., due to non-medical or administrative reasons) will be assigned an ordinal scale category of 1. Patients in a non-ICU hospital ward who are eligible for ICU care based on clinical presentation but are awaiting ICU care will be assigned an ordinal scale category of 4. Patients in an ICU for administrative or non-medical reasons who are ready for a

non-ICU hospital ward will be assigned an ordinal scale category of 2 (if not requiring supplemental oxygen), 3 (if requiring supplemental oxygen), or 4 (if requiring non-invasive ventilation or high-flow oxygen).

In general, patients with oxygen saturation consistently ≤90% should be considered for escalation to a higher clinical status category, while patients with oxygen saturation consistently ≥96% should be considered for de-escalation to a lower category. Patients on supplemental oxygen should be evaluated at least daily and considered for reduction or discontinuation of oxygen support. Actual changes in level of support will be at the discretion of the clinician(s) treating the patient based on the patient's overall condition and may be dictated by other clinical and non-clinical considerations.

Normal body temperature is defined as oral, rectal, axillary, temporal, or tympanic temperature 36.1–38.0°C. Normal respiratory rate is defined as 12–20 breaths per minute.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Any event that meets stopping criteria defined in Section 5.1.1
- Severe allergic reaction to TCZ

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment will not be replaced.

Patients who discontinue from the study treatment should continue in the study and complete all assessments through Day 60.

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure

- Adverse event
- Loss to follow-up

Every effort should be made to obtain information on patients lost to follow up but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with TCZ in clinical studies and post-marketing experience. The important safety risks for TCZ are outlined below. Please refer to the Tocilizumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including

assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events and laboratory abnormalities, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Tocilizumab

This section highlights the main risks for this study population and following 1–2 doses of TCZ. For a complete list of all identified or potential risks of TCZ therapy, please refer to the current version of the TCZ Investigator's Brochure.

5.1.1.1 Hypersensitivity Reactions, Including Anaphylaxis

An infusion reaction is defined as any adverse event that occurs during or within 24 hours after the infusion. This may include hypersensitivity or anaphylactic reactions. Stevens-Johnson syndrome has been reported during treatment with TCZ in the post-marketing setting. Signs of a possible hypersensitivity reaction include, but are not limited to, the following:

- Fever, chills, pruritus, urticaria, angioedema, and skin rash
- Cardiopulmonary reactions, including chest pain, dyspnea, hypotension, or hypertension

TCZ infusions will be administered to patients at the site under close supervision. Health care professionals administering TCZ infusions should be trained in the appropriate procedures for TCZ administration, should be able to recognize the symptoms associated with potential hypersensitivity reactions, including anaphylaxis, and should have the appropriate medication available for immediate use in case of hypersensitivity reaction such as anaphylaxis during or after administration of TCZ. The patient should be treated according to the standard of care for management of the hypersensitivity reaction.

If a patient has symptoms of serious hypersensitivity reactions, such as anaphylaxis, or requires an interruption of the study drug because of symptoms of hypersensitivity including anaphylaxis, administration of TCZ must be discontinued permanently.

5.1.1.2 Serious Infections and Opportunistic Infections

Physicians should exercise caution when considering the use of TCZ in patients with increased risk of infection, such as a history of recurring infections or with underlying conditions (e.g., diabetes mellitus) which may predispose patients to serious infections and opportunistic infections such as TB and viral reactivations (e.g., hepatitis B virus).

Vigilance for timely detection of serious infection is recommended for patients receiving biologic agents, as signs and symptoms of acute inflammation may be lessened because of suppression of the acute-phase reaction. The effects of TCZ on hs-CRP/CRP and neutrophils, and the signs and symptoms of infection, should be considered when evaluating a patient for a potential infection. It is recommended that

neutropenic patients (ANC <1000/μL) undergo weekly surveillance blood cultures during the study.

If a patient develops a serious infection, administration of TCZ should be discontinued.

5.1.1.3 Gastrointestinal Perforations

Symptomatic diverticulosis, diverticulitis, or chronic ulcerative lower GI disease, such as Crohn disease, ulcerative colitis, or other chronic lower GI conditions, might predispose patients to GI perforations. Timely diagnosis and appropriate treatment may reduce the potential for complications of diverticular disease and thus reduce the risk of GI perforations.

Discontinuation of TCZ is required for patients who develop GI perforations.

5.1.1.4 Hematologic Abnormalities

Decreases in neutrophil counts, platelet counts, and fibrinogen levels have been observed following treatment with TCZ for labelled indications. Treatment-related neutropenia was not associated with serious infection in clinical trials in any indication and no association between decreases in platelet counts and serious bleeding events has been observed.

5.1.1.5 Demyelinating Disorders

The effect of treatment with TCZ on demyelinating disorders is not known; events have been reported rarely. Physicians should exercise caution when considering the use of TCZ in patients with preexisting or recent-onset demyelinating disorders.

Patients should be closely monitored for signs and symptoms potentially indicative of central demyelinating disorders.

5.1.1.6 Elevated Liver Enzymes

In clinical trials, mild and moderate elevations of hepatic transaminases have been observed with TCZ treatment.

Recommended TCZ dose modifications for elevated liver enzymes in these populations are not applicable to this study due to single-dose therapy (with possible additional infusion) with TCZ or placebo.

Patients who develop elevated liver function tests during the study must have repeat tests performed as clinically indicated until levels return to baseline, even if they withdraw from the study. If the specialist deems a liver biopsy necessary, the prepared histologic slides will be requested by the Sponsor for central review by a third party, and the biopsy report should be forwarded to the Sponsor.

5.1.1.7 CYP450 Enzyme Normalization

The expression of hepatic cytochrome P450 (CYP450) enzymes is suppressed by cytokines, such as IL-6, that stimulate chronic inflammation. TCZ normalizes expression of these enzymes. The effect of TCZ on CYP450 enzymes (except CYP2C19 and CYP2D6) is clinically relevant for CYP450 substrates with a narrow therapeutic index and/or when the dose is individually adjusted.

When starting or stopping therapy with TCZ, patients taking medicinal products which are individually dose adjusted and are metabolized via CYP450 CYP3A4, CYP1A2, CYP2B6, or CYP2C9 (e.g., atorvastatin, calcium-channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, cyclosporine, or benzodiazepines) should be monitored as doses of these products may need to be adjusted to maintain their therapeutic effect.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug

- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see

Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study drug, 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.
- Serious and/or medically significant infections
- Myocardial infarction or acute coronary syndrome
- GI perforations
- Malignancies
- Anaphylaxis or hypersensitivity reactions
- Stroke
- Serious and/or medically significant bleeding events
- Serious and/or medically significant hepatic events
- Demyelinating disorders

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported during the 60-day follow-up period.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of nondirective questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 1 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 2):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 2 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon rechallenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs

and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., treatment interruption or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (>3 × ULN) in combination with either an elevated total bilirubin (>2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- 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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of COVID-19 pneumonia.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression of COVID-19 pneumonia, "COVID-19 pneumonia progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of COVID-19 Pneumonia

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events (with the exception of death due to COVID-19 pneumonia progression as described in Section 5.3.5.7). These data will be captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.11 Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For TCZ (or placebo), adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with TCZ (or placebo), regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one

entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board (IRB)/Ethics Community (EC).

5.4.1 Medical Monitors and Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], M.D.

Mobile Telephone No.: [redacted]

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported during the 60-day follow-up period. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 3 months after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 60 days after the final dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately

(i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 60 days after study initiation), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
Tocilizumab	Tocilizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An IMC will monitor the incidence of the above-listed anticipated events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

All efficacy outcomes will be analyzed in the modified intent-to-treat (mITT) population. The mITT population is defined as all patients randomized in the study that received any amount of study medication, with patients grouped according to the treatment assignment at randomization.

Safety analyses will be performed on the safety evaluable population, which consists of all patients who receive any amount of study medication. In all safety analyses, patients will be grouped according to the treatment that the patients actually received rather than the treatment assigned at randomization.

Detailed specifications of the statistical methods will be described in the Statistical Analysis Plan (SAP).

6.1 DETERMINATION OF SAMPLE SIZE

The estimated sample size was determined based on the time from randomization to the first utilization of mechanical ventilation by Day 28.

The total mITT sample size of 379 patients with a 2:1 randomization of TCZ (n=253) to placebo (n=126) provides approximately 80% power using a Logrank test to detect a 15% difference between treatment groups in time to *death or* mechanical ventilation by Day 28 under the following assumptions: cumulative survival (i.e., *alive and* not requiring mechanical ventilation) rates of 75% in the TCZ group and 60% in placebo group, with 28-day follow-up, using a two-sided 5% alpha, and 10% dropout rate in each arm. Sample size re-estimation may be considered during the study based on updated assumptions of the treatment effect.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who are randomized, enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized.

Eligibility criteria and other major protocol deviations will be listed and summarized by treatment group.

6.3 TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented by treatment group and will be presented for the mITT and may, in addition, be presented for the safety population.

Medical history data, including surgery and procedures, and baseline conditions, will be summarized descriptively by treatment group using the safety population.

Previous and concomitant treatments will be summarized descriptively by treatment group.

Exposure to study drug will be summarized, including number of doses. A listing of patients by treatment group, detailing dosing of study drug will be prepared.

6.4 EFFICACY ANALYSES

All efficacy analyses will use the mITT population.

Descriptive subgroup analyses to evaluate the consistency of results across pre-specified subgroups may also be conducted.

6.4.1 Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of TCZ plus SOC compared with placebo plus SOC using the following endpoint:

- Cumulative proportion of patients *with death or* requiring mechanical ventilation by Day 28

Time to *death or* the first utilization of mechanical ventilation after randomization will be *compared between the TCZ group and the placebo group using the stratified log-rank test with age group (age ≤60, age >60 years) as the stratification factor. T*he cumulative proportion of patients *with death or* requiring mechanical ventilation at Day 28 *will be estimated using the Kaplan-Meier method*.

Details of the primary endpoint analysis will be included in the SAP.

6.4.2 Secondary Efficacy Endpoints

Time to event secondary endpoints will be compared between the TCZ group and the placebo group using the *stratified* log-rank test. The Kaplan-Meier plot, median time to response, and their 95% CIs, and a p-value will be presented.

- Time to improvement in ordinal clinical status

  Defined as time from randomization to the time when at least a 2-category improvement in the 7-category ordinal scale is observed. Assessment of patient status using an ordinal scale will be recorded at baseline and once daily in the

morning (between approximately 8 am and 12 pm) while hospitalized. The ordinal scale categories are as follows:

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

- Time to clinical failure

  Defined as the time to first occurrence on study of death, mechanical ventilation, ICU admission, or withdrawal, whichever occurs first.

- *Mortality rate at Day 28*

  Difference in mortality rate at Day 28 will be compared using the *Cochran-Mantel-Haenszel test statistic stratified by age group (age ≤60, age >60 years)*. The difference in proportions *and its 95% CI* for the treatment group comparison will be presented.

- Time to hospital discharge or "ready for discharge"

  "Ready for discharge" defined as normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen.

Comparison of clinical status according to the 7-category ordinal scale may also be analyzed using a proportional odds model at Day 28.

6.4.3 Exploratory Efficacy Endpoints

Inflammatory markers, hs-CRP*/CRP*, D-dimer, and ferritin, will be summarized descriptively using means, standard deviations, medians, and ranges. Absolute value and change from baseline will be provided over time by treatment group.

The time to first requiring CPAP or BIPAP after randomization will be analyzed by the Kaplan Meier analysis, with the cumulative proportion of patients requiring CPAP or BIPAP estimated at Day 28.

Additional exploratory efficacy endpoints may be explored and details will be provided in the SAP.

6.5 INTERIM ANALYSES

An IMC will evaluate safety according to procedures and guidelines detailed in the IMC agreement. The IMC will consist of Sponsor representatives who will not be blinded to study data. Details of the safety reviews will be provided in the SAP.

6.6 SAFETY ANALYSES

Safety assessments will be performed on the safety evaluable population, which consists of all patients who receive any amount of study medication. In all safety analyses, patients will be grouped according to the treatment that the patients actually received rather than the treatment assigned at randomization.

Safety will be assessed through descriptive summaries of treatment emergent adverse events (nature, frequency, severity, and causality). Adverse events will also be listed.

All verbatim adverse event terms will be mapped to MedDRA thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0 scale

The proportion of patients with any post-treatment bacterial and/or fungal infection and acute kidney injury will be summarized, respectively.

A treatment-emergent adverse event is defined as any new adverse event reported or any worsening of an existing condition on or after the first dose of study drug.

Separate summaries will be generated for serious adverse events, deaths, adverse events leading to discontinuation of study drug, and adverse events of special interest.

Adverse events will be summarized by MedDRA term, appropriate thesaurus level, and toxicity grade.

Descriptive summaries of laboratory values and change from baseline throughout the study will be tabulated by treatment arm. For selected parameters, changes from the proportion of patients experiencing clinically significant changes relative to baseline will be summarized by treatment arm.

Values, along with change from baseline, will be summarized using descriptive statistics for each vital sign parameter.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Due to the pandemic situation, access to hospitals is restricted; therefore, only remote data monitoring will be performed for this study. Study monitors will perform ongoing remote data review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate and complete. Sites will be asked to implement a QC step of a second person reviewing the data entry in the eCRF where possible.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S.

Investigational New Drug (IND) Application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative or where allowed, HCP consent on behalf of the patient before his or her participation in the study. **Due to the pandemic situation and restricted hospital access, where allowed, verbal consent may be given by the patient's legally authorized representative and this must be documented by the investigator or authorized designee.** The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC (national or regional) by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data, which may include data on genomic variants, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC

policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted remotely by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by Genentech, Inc. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 40 sites will participate to enroll approximately 379 patients. Enrollment will occur through an IxRS. Target enrollment may be changed if a sample size re-estimation is performed (see Section 6.1).

Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected either from local laboratories or from The Roche Integrated Global Textbook Ranges, as appropriate.

An IMC will be employed to monitor and evaluate patient safety throughout the study.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared

with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities: Days 1 and 2

	Screening [a, b]	Baseline		
Study Day	-4 to 0	1		2
Time Post Initial Treatment (Assessment Window)		0 min Pre-dose (approx. –4 hrs)	15 min After end of infusion (approx. +1 hr)	24 hrs (±12 hrs)
Informed consent	x			
Inclusion/exclusion criteria	x	x		
Demographic data	x			
Randomization		x		
Medical history	x			
Complete physical examination [c, d]	x			
Weight	x			
COVID-19 diagnosis [e]	x			
Chest X-ray/CT scan [d, f]	x			
ECG	x			
Pregnancy test [d, g]	x			
PaO_2/FiO_2 [d, h]	x (optional)	← Optional →		
SpO_2 [d, i]	x	x	x	x
Vital signs [d, i]	x	x	x	x
Ordinal scoring (including ventilation requirement) [j]		x		x
Adverse events [k]		x		x
Concomitant medications [l]		x		x
Hematology [d, m]	x			x

Appendix 1: Schedule of Activities: Days 1 and 2

	Screening [a, b]	Baseline		
Study Day	–4 to 0	1		2
Time Post Initial Treatment (Assessment Window)		0 *min* Pre-dose (approx. –4 hrs)	15 min After end of infusion (approx. +1 hr)	24 hrs (±12 hrs)
Chemistry [d, n]	x			x
hs-CRP/*CRP*, D-dimer *(if available via local laboratory)*, and ferritin [d]	x			
Study drug administration [o]		x		

ALP=alkaline phosphatase; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; eCRF=electronic case report form; hr(s)=hour(s); hs-CRP=high sensitivity C-reactive protein; min=minutes; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0; PaO_2/FiO_2=arterial oxygen partial pressure/fraction of inspired oxygen; SpO_2=peripheral capillary oxygen saturation; TCZ=tocilizumab.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Results from standard-of-care tests or examinations performed prior to obtaining informed consent and within *96* hours before randomization may be used; such tests do not need to be repeated for screening.

[b] Informed consent must be documented before any study-specific screening procedure is performed.

[c] A complete physical examination, performed at screening and per the investigator's discretion during the study, includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities identified during the study should be reported as adverse events.

[d] Physical examination, blood tests, and other assessments conducted after arrival at the hospital, but before the informed consent is signed, can be used as screening assessments.

[e] COVID-19 test (SARS-CoV2 PCR) to confirm diagnosis should be performed at or before screening (if testing is conducted before screening, documentation must be available).

[f] Screening chest X-ray or CT scans should be performed within *96* hours prior to randomization. If additional chest X-rays/CT scans are taken per local practice during the study, this information should be provided in the eCRF.

[g] For women of childbearing potential, including those who have had a tubal ligation, positive urine test results will be confirmed with a serum pregnancy test. Study drug infusion must not be administered unless the serum pregnancy test result is negative.

[h] If arterial blood gases are measured.

[i] All vital sign measurements (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressures, and body temperature) and oxygen saturation should be recorded together once daily while the patient remains hospitalized. If measured more than once daily, the worst values (highest temperature, respiratory rate, and heart rate; lowest blood pressure, oxygen saturation, and consciousness level) during that period should be recorded on the eCRF.

[j] Assessment of clinical status using the ordinal scale, which includes change in ventilation usage (non-invasive or mechanical), should be recorded at baseline on Day 1 then again daily every morning (between approximately 8 am and 12 pm) for patients who remain hospitalized.

[k] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 60 days after the final dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[l] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit.

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).

[n] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total bilirubin, ALP, ALT, and AST.

[o] The initial study drug infusion should be given within approximately 4 hours of randomization. If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion. *Note: Pre-dose assessments must be repeated and reviewed before an additional infusion of blinded treatment of TCZ or placebo is administered.*

Appendix 2
Schedule of Activities: Day 3–Study Completion

	Days 3–28 [a]																								Study Completion/ Discontinuation [i]
Study Day	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 [i]	
Vital signs [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PaO_2/FiO_2 [c]	← Optional →																										(optional)
SpO_2 [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ordinal scoring [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [e]	←																									→	x
Concomitant medications [f]	←																									→	x
Hematology [g]																										x	x
Chemistry [h]																										x	x
hs-CRP/*CRP*, D-dimer *(if available via local laboratory)*, and ferritin																										x	x

ALP=alkaline phosphatase; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; eCRF=electronic case report form; hs-CRP=high sensitivity C-reactive protein; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0; $PaO_2/FiO2$=arterial oxygen partial pressure/fraction of inspired oxygen; SpO_2=peripheral capillary oxygen saturation.

[a] If patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. Follow-up visits may be conducted by onsite clinic visits, telephone calls, or home visits.

[b] All vital sign measurements (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressures, and body temperature) and oxygen saturation should be recorded together once daily while the patient remains hospitalized. If measured more than once daily, the worst values (highest temperature, respiratory rate, and heart rate; lowest blood pressure, oxygen saturation, and consciousness level) during that period should be recorded on the eCRF.

[c] If arterial blood gases are measured.

[d] Assessment of clinical status using the ordinal scale should be recorded at baseline on Day 1 then again daily for patients who remain hospitalized.

[e] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 60 days after the final dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[f] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit.

[g] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).

[h] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total bilirubin, ALP, ALT, and AST.

[i] If patients are discharged from the hospital prior to Day 28 or discontinue the study, the Study Completion/Discontinuation assessments are to be conducted prior to discharge or at discontinuation from the study. In addition, if patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. The Day 60 follow up may be conducted by an onsite clinic visit, telephone call, or home visit for discharged patients. Day 60 follow up is required to collect adverse events only.

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol ML42528 has been amended primarily in response to feedback [redacted]; however, other revisions were made for the reasons stated below. Changes to the protocol, along with a rationale for each change, are summarized below:

- The endpoint for the primary efficacy objective was revised to include death based upon feedback received [redacted] (Sections 2.1.1, 6.1, 6.4.1).
- A preference for high sensitivity C-reactive protein (hs-CRP) was removed as it was determined that only CRP testing was available at a majority of sites (Sections 2.1.3, 4.5.6, 5.1.1.2, 6.4.3, Appendices 1 and 2).
- Clarification was added that pre-dose assessments must be repeated and reviewed before an additional infusion of blinded treatment of tocilizumab or placebo is administered (Section 3, Appendix 1).
- The screening period was increased from 48 hours to 96 hours based on investigator feedback to facilitate patient enrollment (Sections 3.1, 4.1.1, and Appendix 1).
- Revisions were made to clarify that informed consent does not necessarily need to be a form signed by the patient since the inclusion criteria and Section 8.2 allow for verbal consent by the patient's legally authorized representative (Section 4.1.1).
- Text was added to clarify that the placebo is not supplied by the Sponsor (Section 4.3.1.1).
- The prohibited therapies were expanded to include "open-label tocilizumab" for clarity (Section 4.4.3).
- The analysis of the primary efficacy endpoint was revised to include death, since death was added to the primary efficacy objective, and to add stratification by age group to enhance the accuracy of the analysis (Section 6.4.1).
- The analysis for the secondary efficacy endpoint "mortality rate at Day 28" was revised to change the method from the Fisher's exact test to the Cochran-Mantel-Haenszel test and to add stratification by age group to apply the appropriate analysis (Section 6.4.2).
- The estimated number of sites anticipated to participate in this study was increased from 20 to 40 based on the shifting epidemiology of the pandemic (Section 9.5).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

STATISTICAL ANALYSIS PLAN

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TOCILIZUMAB IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA**
PROTOCOL NUMBER:	ML42528
STUDY DRUG:	Tocilizumab (RO4877533)
VERSION NUMBER:	1.0
IND NUMBER:	148225
EUDRACT NUMBER:	2020-001154-22
SPONSOR:	Genentech, Inc.
PLAN PREPARED BY:	[redacted]
DATE FINAL:	See electronic date stamp below

STATISTICAL ANALYSIS PLAN APPROVAL

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ARDS	acute respiratory distress syndrome
BIPAP	bilevel positive airway pressure
CoV	coronaviruses
CPAP	continuous positive airway pressure
CRP	C-reactive protein
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic Case Report Form
ECMO	extracorporeal membrane oxygenation
FiO_2	fraction of inspired oxygen
hs-CRP	high sensitivity C-reactive protein
ICU	intensive care unit
IL-6	interleukin 6
IL-6R	interleukin-6 receptor
IMC	Internal Monitoring Committee
IxRS	interactive voice or web-based response system
LPLV	last patient, last visit
mITT	modified intent-to-treat
NCI	National Cancer Institute
PaO_2	partial pressure of oxygen
PCR	polymerase chain reaction
SAP	Statistical Analysis Plan
SARS-CoV	severe acute respiratory syndrome
SOC	standard of care
SpO_2	blood oxygen saturation
TB	tuberculosis
TCZ	tocilizumab
ULN	upper limit of normal
WHO	World Health Organization

1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for the clinical efficacy and clinical safety for Study ML42528.

There are currently no drugs approved for the treatment of patients with SAS-CoV-2 (COVID-19). Given the results of studies (Xu et al. 2020), tocilizumab (TCZ), along with standard of care (SOC) treatment, could provide efficacy, offering the potential to treat COVID-19 in hospitalized populations more effectively than current SOC alone. Extensive safety data have previously been generated on the use of TCZ in other indications. Therefore, a placebo-controlled study in combination with SOC to assess safety and efficacy of TCZ in hospitalized patients with COVID-19 pneumonia is justified to address the high unmet need.

2. STUDY DESIGN

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of TCZ in combination with SOC compared with placebo in combination with SOC in hospitalized adult patients with COVID-19. The Sponsor intends to enroll approximately 379 patients that have been diagnosed with COVID-19 pneumonia and meet the entry criteria.

Patients must be at least 18 years of age with confirmed SARS-CoV-2 (COVID-19) infection per WHO criteria, including a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have SpO2<94% on ambient air and be on SOC, which may include anti-viral treatment, low dose systemic corticosteroids, and supportive care.

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. Patients with active tuberculosis (TB) or suspected active bacterial, fungal, viral, or other infection (besides COVID-19 and well-controlled HIV) will be excluded from the study.

Patients will be screened and randomized within 96 hours of hospital admission. Patients will be randomized at a 2:1 ratio to receive blinded treatment of either TCZ or placebo, respectively. Study treatment must be given within approximately 4 hours after randomization. TCZ and placebo will be given in combination with SOC.

Patients assigned to the TCZ arm will receive one infusion of TCZ 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the placebo arm will receive one infusion of placebo, both in addition to SOC.

If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status),

one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion. Note: Pre-dose assessments must be repeated and reviewed before an additional infusion of blinded treatment of TCZ or placebo is administered

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity within 96 hours of hospital admission (for a total of 2 screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 7 days after previously signing the consent form. The investigator will record the reasons for screen failure in the screening log.

The study assessments to be conducted include the following: physical examination, vital signs, oxygen saturation, assessment of consciousness, presence and absence of respiratory support, adverse events, concomitant therapies, and clinical laboratory tests. Please see Appendix 2 and Appendix 3 for details concerning the timing of these assessments.

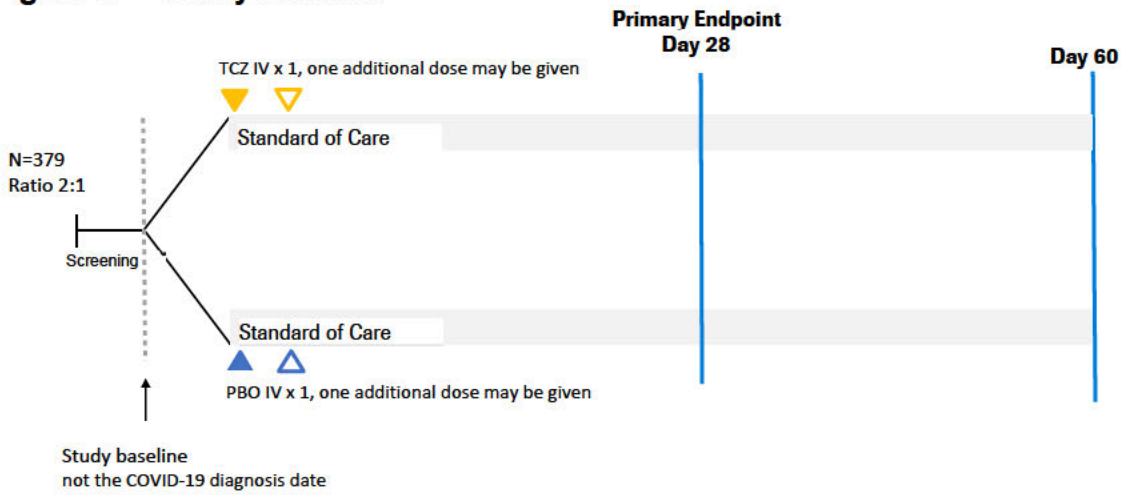
Patients will be followed up for a total of 60 days after first dose of study medication.

If patients are discharged from the hospital prior to Day 28 or discontinue the study, the Study Completion/Discontinuation assessments are to be conducted prior to discharge or at discontinuation from the study. In addition, if patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. Follow-up visits may be conducted by onsite clinic visits, telephone calls, or home visits. After Day 28, all patients should have a follow-up visit on approximately Day 60 which may be conducted as an onsite clinic visit, telephone call, or home visit for discharged patients.

During the study, standard supportive care will be given according to clinical practice. After study completion, patients should be referred to their regular healthcare provider based on their doctor's decision and as part of standard of care.

Figure 1 presents an overview of the study design. Schedules of activities are provided in Appendix 2 and Appendix 3.

Figure 1 Study Schema



IV=intravenous; PBO=placebo; TCZ=tocilizumab.
Note: Patients will be screened and randomized within 96 hours of hospital admission. Study treatment must be given within approximately 4 hours after randomization.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix .

2.2 ENDPOINTS

2.2.1 Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoint:

- Cumulative proportion of patients with death or requiring mechanical ventilation by Day 28

2.2.2 Secondary Efficacy Endpoints

The secondary efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status
- Time to clinical failure, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first)
- Mortality rate by Day 28
- Time to hospital discharge or "ready for discharge" (e.g., awaiting social disposition) as evidenced by, for example, normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen

- 7-category ordinal scale at Day 28

2.2.3 Exploratory Efficacy Endpoint

The exploratory efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Change from baseline in inflammatory markers levels (hs-CRP/CRP, D-dimer, and ferritin) over time

- Time to first requiring CPAP or BIPAP

2.2.4 Safety Endpoint

The safety objective for this study is to evaluate the safety of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0
- Incidence of any post-treatment bacterial and/or fungal infection
- Incidence of any post-treatment acute kidney injury (defined by 50% increase of creatinine from baseline)

2.3 DETERMINATION OF SAMPLE SIZE

The estimated sample size of 379 patients with a 2:1 randomization of TCZ (n=253) to placebo (n=126) provides approximately 80% power using a Logrank test to detect a 15% difference between treatment groups in time to death or mechanical ventilation by Day 28 under the following assumptions: cumulative survival (i.e., alive and not requiring mechanical ventilation) rates of 75% in the TCZ group and 60% in placebo group by Day 28, using a two-sided 5% alpha, and 10% dropout rate in each arm. Sample size re-estimation may be considered during the study based on updated assumptions of the treatment effect.

2.4 ANALYSIS TIMING

No interim efficacy analyses have been planned. Safety data will be reviewed by the an Internal Monitoring Committee (IMC) during the study. The IMC will consist of Sponsor representatives who will not be blinded to study data. The planned safety interim review will occur when the first 30 patients have completed the Day 14 study visit. There will be further IMC meetings when approximately half of the targeted number of patients (i.e., n=189) have been enrolled; but all interim analyses are subject to change depending on enrollment and as appropriate. For details of the IMC reviews, please see Section 3.2.

For the above interim review, only patients whose study schedules have reached the designated visit (i.e., Day 14) or who have been discharged or discontinued from the study by the time of data cut will be included.

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for last follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 2 months after the last patient is enrolled. The total length of the study is expected to be approximately 8 months. Analysis of data from all patients will be performed when all patients have completed or discontinued the study, all data from the study are in the database, and the database is locked.

3. STUDY CONDUCT

The plan is to enroll approximately 379 patients that have been diagnosed with COVID19 pneumonia and meet the entry criteria. Patients will be randomized at a 2:1 ratio to receive blinded treatment of either TCZ or placebo, respectively. Patients will be screened and randomized within 96 hours of hospital admission. Study treatment must be given within approximately 4 hours after randomization. TCZ and placebo will be given in combination with SOC.

If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of 2 screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 7 days after previously signing the consent form. The investigator will record the reasons for screen failure in the screening log.

Patients will be followed for a total of 60 days after first dose of study medication.

If patients are discharged from the hospital prior to Day 28 or discontinue the study, the Study Completion/Discontinuation assessments are to be conducted prior to discharge or at discontinuation from the study. In addition, if patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. Follow-up visits may be conducted by onsite clinic visits, telephone calls, or home visits. After Day 28, all patients should have a follow-up visit on approximately Day 60 which may be conducted as an onsite clinic visit, telephone call, or home visit for discharged patients.

During the study, standard supportive care will be given according to clinical practice.

3.1 RANDOMIZATION

After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS).

Patients will be randomly assigned to one of two treatment arms: TCZ in combination with SOC or placebo in combination with SOC. Randomization will occur in a 2:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. The randomization will be stratified by country (i.e., USA vs non-USA) and age (i.e., ≤60 and >60 years of age).

3.2 DATA MONITORING

An IMC will evaluate safety according to procedures and guidelines detailed in the IMC agreement. The IMC will consist of Sponsor representatives who are not members of the study management team and will not be blinded to study data.

The first IMC safety review will occur after approximately 30 patients (20 in TCZ and 10 in PBO) have completed the Day 14 visit. There will be further IMC meetings when approximately half of the targeted number of patients (i.e., n=189) have been enrolled; but all interim analyses are subject to change depending on enrollment and as appropriate.

The IMC will review unblinded summaries and listings of overall rates of death, serious adverse events (SAEs), and all adverse events (AEs) as well as other key safety data. All enrolled patients will be included in the interim safety summaries as there may be a lag time for obtaining treatment exposure data.

Deaths and serious infections will be reviewed in an expedited manner. The Study Medical director, Safety Scientist or IMC Chair may request additional meetings if concerns arise.

The unblinded safety summaries will be conducted by the IMC-Statistician and statistical programmer independent from the study management team. The list of the planned safety summary tables and listings are provided in the IMC agreement. Communications and recommendations from the IMC will be carried out as specified in the IMC agreement.

4. STATISTICAL METHODS

All primary and secondary efficacy endpoints will be analyzed in the modified intent-to-treat (mITT) population, with patients grouped according to the treatment assignment at randomization.

In all safety analyses, patients will be grouped according to the treatment that the patients actually received rather than the treatment assigned at randomization.

4.1 ANALYSIS POPULATIONS

Disposition summaries will be based on an All Patient population (all patients randomized and/or receiving study drug). Efficacy analyses will be based on the mITT population, if not otherwise specified. Analysis of safety data will be based on the safety population.

4.1.1 mITT Population

The mITT population is defined as all patients who are randomized in the study and received any amount of study medication, with patients grouped according to the treatment assignment at randomization.

4.1.2 Safety Population

Safety population will consist of all patients who receive any amount of study medication. In all safety analyses, patients will be grouped according to the treatment that the patients first actually received rather than the treatment assigned at randomization.

4.2 ANALYSIS OF STUDY CONDUCT

The number of patients enrolled, discontinued, or who complete the study up to Day 28 will be summarized. Reasons for premature study discontinuation will be listed and summarized. Listing of randomized patients and listing of investigators will be produced.

The number of patients discharged from hospital will be summarized by visit.

Eligibility criteria and other major protocol deviations will be listed and summarized by treatment group.

A listing by treatment group and patient of missed assessments for the primary endpoint will be produced through Day 28, including study day of missed assessment, study day of discharge and/or death, if any.

The patients excluded from the safety and mITT populations will be summarized, including the reason for exclusion by treatment group. A summary of enrollment by country and investigator name will be produced.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (including, but not limited to, age, sex, self-reported race/ethnicity, smoking history) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented by treatment group and will be presented for the mITT and may, in addition, be presented for the safety population.

4.3.1 Demographics

- Sex
- Age
- Weight
- BMI
- Race
- Ethnicity
- Employment status
- Education status
- Primary language
- Living situation (Alone, With Others)
- Smoking history (Never, Current, Former)
- Country (USA, non-USA)

4.3.2 Disease Characteristics

- Ordinal scale for clinical status at Day 1
- hs-CRP or CRP
- D-dimer
- Ferritin
- Symptoms at time of COVID 19 diagnosis
- Number of days from first COVID-19 symptom at baseline (to be derived from COVID 19 Diagnosis)
- COVID19 diagnosis based on PCR of specimen type
- Number of days from COVID-19 diagnosis at baseline (to be derived from COVID 19 Diagnosis)
- PCR result (Negative, positive)

4.3.3 Targeted and General Medical History

Targeted medical history, including Diabetes, hypertension, hyperlipidemia, asthma, COPD, obesity, myocardial infarction, atrial fibrillation, and stroke, will be summarized by treatment group.

General medical history data will be summarized descriptively by treatment group. Summaries of the targeted and general medical history will be provided for the safety population. A glossary showing the mapping of investigator verbatim terms to diseases will be produced for the medical history data.

4.3.4 Surgeries and Procedures

A listing of any previous or ongoing surgeries and procedures will be produced for the safety population.

4.3.5 Previous and Concomitant Medications

Previous and concomitant treatments will be summarized descriptively by treatment group for the safety population. Previous treatments that have been stopped prior to study Day 1 will be summarized separately. There will be a summary of all concomitant treatments, including those that were initiated prior to study Day 1.

4.4 EFFICACY ANALYSIS

All efficacy analyses will be performed on the mITT population with patients grouped according to treatment assigned at randomization.

Subgroup analyses to evaluate the consistency of results across prespecified subgroups may also be conducted as specified in Section 4.4.4.

Based on the protocol, study treatment must be given within approximately 4 hours after randomization. Therefore, the first treatment dose date will be used as Day 1 in the efficacy analysis.

4.4.1 Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of TCZ plus SOC compared with placebo plus SOC using the following endpoint:

- Cumulative proportion of patients with death or requiring mechanical ventilation by Day 28

The mechanical ventilation is defined as mechanical invasive ventilation or ECMO (extracorporeal membrane oxygen) per CRF.

The cumulative proportion of patients with event, i.e., death or requiring mechanical ventilation, will be estimated using the Kaplan-Meier methodology. The time to event is defined as the time (in days) from Day 1 till the date of first documented death or requiring mechanical ventilation due to any cause, whichever occurs first. The event and censoring rules for this endpoint are described in Table 1 below. Death after completion date or Day 28 will not be considered as an event.

Table 1 Time to Death or Requiring Mechanical Ventilation and Censoring Status

Event	Censor	Date
If study completion, patient with death or requiring mechanical ventilation recordings	No	Earlier of date of death and first date requiring mechanical ventilation
Else if study completion, patient without death and mechanical ventilation recordings	Yes	Completion date
Else if early discontinuation, patient with death or mechanical ventilation recordings	No	Earlier of the first date requiring mechanical ventilation and date of death
Else if early discontinuation, patient without death and mechanical ventilation recordings	Yes	Last in-hospital assessment* date prior to discontinuation
Else if early discharge, patient with mechanical ventilation recordings	No	First date requiring mechanical ventilation
Else if early discharge, patient without mechanical ventilation recordings		
patient without death during follow-up (on or prior to Day 28)	Yes	Last follow-up visit date (on or prior to Day 28)**
patient with death during follow-up (on or prior to Day 28)	No	Date of death (on or prior to Day 28)

* Assessment includes daily oxygen saturation assessment in hospital; ** Follow-up mortality and adverse event visits after discharge

The null and alternative hypotheses for the cumulative proportion of patients requiring mechanical ventilation analysis can be phrased in terms of the cumulative functions $F_A(t)$ and $F_B(t)$ in Arm A (TCZ plus SOC) and Arm B (placebo plus SOC), respectively:

H_0: $F_A(t) = F_B(t)$ versus H_1: $F_A(t) \neq F_B(t)$.

As the survival functions for $F_A(t)$ and $F_B(t)$ can be expressed as $S_A(t) = 1 - F_A(t)$ and $S_B(t) = 1 - F_B(t)$, respectively. The null and alternative hypotheses are equivalent to

H_0: $S_A(t) = S_B(t)$ versus H_1: $S_A(t) \neq S_B(t)$.

The above hypotheses will be tested between the two treatment groups based on the log-rank test stratified by the randomization stratum (country [USA, non-USA] and age [≤60, >60 years]) at the 2-sided 0.05 significance level. The estimated cumulative proportion of patients with death or requiring mechanical ventilation by day 28 will be provided by treatment group along with the associated 95% confidence interval (CI) calculated using Greenwood's formula. The p-value from the log-rank test, the difference in the cumulative proportions and the corresponding 95% CI will also be provided.

The Kaplan-Meier curves, the median time to event, and the associated 95% CIs on the median will be presented for each treatment arm. The Brookmeyer-Crowley

methodology will be used to construct the 95% CI for the median time to event for each treatment arm (Brookmeyer and Crowley 1982).

The Hazard Ratio, the ratio between the hazard of requiring mechanical ventilation or death in Arm A (TCZ plus SOC) and the hazard in Arm B (placebo plus SOC), will be estimated using a stratified Cox regression model with the same stratification variables used in the stratified log-rank test, including the 95% CI on the hazard ratio.

The cumulative proportion of requiring mechanical ventilation or death at various timepoints (i.e., at days 7, 14, and 21) will also be estimated using the Kaplan-Meier methodology for each treatment arm, along with 95% CIs calculated using Greenwood's formula.

4.4.2 Secondary Efficacy Endpoints

All secondary endpoints will be tested without overall type 1 error control to provide potentially clinically meaningful information.

- Time to improvement in ordinal clinical status

  For patients enrolled with ordinal category greater than 2, the endpoint is defined as time from Day 1 to the time when at least a 2-category improvement in the 7-category ordinal scale is observed. For patients enrolled with category 2, the endpoint is defined as time from Day 1 to the time when category 1 in the 7-category ordinal scale is observed. Assessment of patient status using an ordinal scale will be recorded at baseline and once daily while hospitalized. The ordinal scale categories are as follows:

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

The event and censoring rules for this endpoint are described in Table 2 below. This endpoint will be analyzed using the same methodologies as the primary efficacy endpoint.

Table 2 Time to Improvement in Ordinal Clinical Status and Censoring Status

Event	Censor	Date
When patient enrolled with scale>=3		
If patient died on or prior to Day 28	Yes	Day 29
Else If patient with 2-category improvement in ordinal clinical status	No	First improvement day
Else if study completion, patient without improvement	Yes	Completion date
Else if early discontinuation, patient without improvement	Yes	Last ordinal scale assessment date on or prior to discontinuation
When patient enrolled with scale=2		
If patient died on or prior to Day 28	Yes	Day 29
Else if patient with improvement to category 1 in ordinal clinical status	No	First improvement day
Else if study completion, patient without improvement	Yes	Completion date
Else if early discontinuation, patient without improvement	Yes	Last ordinal scale assessment date on or prior to discontinuation

- Time to clinical failure (days)

Defined as the time to first occurrence on study of death, mechanical ventilation, ICU admission, or withdrawal from study, whichever occurs first. Mechanical ventilation is defined as same as in the primary endpoint. The event and censoring rules for this endpoint are described in Table 3 below. This endpoint will be analyzed using the same methodologies as the primary efficacy endpoint.

Table 3 Time to Clinical Failure and Censoring Status

Event	Censor	Date
If study completion, patient with death, ICU admission, requiring mechanical ventilation recordings, or withdrawal from study	No	Earliest of the death date, first ICU admission date, first date requiring mechanical ventilation, and study withdrawal date
Else if study completion, patient without death, ICU admission, and mechanical ventilation recordings	Yes	Completion date
If early discharge, patient with death, ICU admission, requiring mechanical ventilation recordings, or withdrawal from study	No	Earliest date for first ICU admission date, first requiring mechanical ventilation date, and study withdrawal date
Else if early discharge, patient without ICU admission, requiring mechanical ventilation recordings and withdrawal from study	Yes	Latest date for discharge day and follow-up visit on or prior to Day 28**

* Assessment includes daily oxygen saturation assessment in hospital; ** Follow-up mortality and adverse events visits after discharge

- Mortality rate at Day 28

The difference in proportion of patients who have died by Day 28 will be compared using the Cochran-Mantel-Haenszel test statistic adjusted by the stratification factors. The proportion in each group will also be presented along with a 95% CI for the proportion in each group using the Clopper-Pearson method. The difference in proportions and its 95% CI for the treatment group comparison will be presented. Any mortality occurs between Day 1 and Day 28 (or prior to the early dropout date) will be included in the analysis.

- Time to hospital discharge or “ready for discharge” (days)

Defined as time from Day 1 to hospital discharge or “ready for discharge”. “Ready for discharge” defined as normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen based on the 7-category ordinal scale in CRF. Table 4 describes event/censoring rules for the time to hospital discharge. This endpoint will be analyzed using the same methodologies as primary efficacy endpoint.

Table 4 Time to Hospital Discharge and Censoring Status

Event	Censor	Date
If patient with discharge or “ready for discharge” recordings	No	Earliest discharge day
Else if study completion, patient without discharge or “ready for discharge”	Yes	Completion date
Else if early discontinuation	Yes	Last in-hospital assessment* date prior to discontinuation
Else if patient died on or prior to Day 28	Yes	Day 29

* Assessment includes daily vitals and ordinal scale assessments in-hospital.

- 7-category ordinal scale at Day 28

The patients’ status measured with 7-category ordinal scale at Day 28 will be analyzed for the difference in distributions between the TCZ plus SOC and Placebo plus SOC groups. Patients without record at Day 28 will be imputed by the last available assessment. The Van Elteren test will be used, including the stratification factors (country [USA, non-USA] and age [≤60, >60 years]). The median clinical outcome based on the ordinal scale for each treatment group and the corresponding 95% CI for the median will be presented along with the Van Elteren p-value, as well as the difference in medians and a 95% CI for the difference.

In addition, the 7-category ordinal scale at Day 28 will be compared the TCZ plus SOC and Placebo plus SOC groups using a proportional odds model accounting for stratification factors as sensitivity analysis. The odds ratio, p-value, and 95% confidence interval will be presented.

4.4.3 Exploratory Efficacy Endpoints

- Time to first requiring CPAP or BIPAP

Defined as the time from Day 1 to the first documented date of death, requiring CPAP or BIPAP, or requiring mechanical ventilation. Table 5 describes event/censoring rules for the time to requiring CPAP or BIPAP. This endpoint will be analyzed using the same methodologies as the primary efficacy endpoint.

Table 5 Time to Requiring CPAP or BIPAP and Censoring Status

Event	Censor	Date
If study completion, patient with death, requiring CPAP/BIPAP, or requiring mechanical ventilation recordings	No	Earlier of date of death and first date requiring CPAP/BIPAP and first date requiring mechanical ventilation
Else if study completion, patient without death, CPAP/BIPAP recordings, and mechanical ventilation recordings	Yes	Completion date
Else if early discontinuation, patient with death, CPAP/BIPAP recordings, or mechanical ventilation recordings	No	Earlier of date of death and first date requiring CPAP/BIPAP and first date requiring mechanical ventilation
Else if early discontinuation, patient without death, CPAP/BIPAP recordings, and mechanical ventilation recordings	Yes	Last in-hospital assessment* date prior to discontinuation
Else if early discharge, patient with CPAP/BIPAP recordings, or mechanical ventilation recordings	No	Earlier of date of first date requiring CPAP/BIPAP and first date requiring mechanical ventilation
Else if early discharge, patient without CPAP/BIPAP recordings and mechanical ventilation recordings		
patient without death during follow-up (on or prior to Day 28)	Yes	Last follow-up visit date (on or prior to Day 28)**
patient with death during follow-up (on or prior to Day 28)	No	Date of death (on or prior to Day 28)

* Assessment includes daily oxygen saturation assessment in hospital; ** Follow-up mortality and adverse event visits after discharge

- Change from baseline in inflammatory markers levels (hs-CRP/CRP, D-dimer, and ferritin) over time

The level of inflammatory markers will be summarized descriptively using means, standard deviations, medians, and ranges at baseline and post baseline, together with the change from baseline values. Baseline and post-baseline values are defined in Table 6.

Table 6 Time Windows for Assigning Baseline and Post Baseline to Study Visits for Lab parameters

Scheduled study visit	Time window
Baseline	≤ Day 1*
Post baseline	> Day 1 to ≤ Day 35**

*If there are multiple baseline records, use the ones most close to Day 1; **If there are multiple post baseline records, use the ones most close to Day 28

4.4.4 Subgroup Analyses

The primary endpoint “cumulative proportion of patients with death or requiring mechanical ventilation by Day 28”, the secondary endpoints “7-category ordinal scale at Day 28” and the “mortality rate at Day 28” will be examined by the same methodologies as mITT population in the following subgroups:

- Sex [Male, Female]
- Age [≤60, >60 years]
- Race [White, Black or African American, American Indian or Alaska Native, Other]
- Ethnicity [Hispanic or Latino vs Not Hispanic or Latino]
- Smoking history [Never, Current, Former]
- BMI [<30, >=30]
- Country [USA, non-USA]
- Steroid use at Day 1 and/or during study [Yes, No]
- Anti-viral treatment use at Day 1 and/or during study [Yes, No]

Summaries of the endpoints listed above will be produced, separately, for each level of the subgroup variables and displayed on Forest plots.

4.5 SAFETY ANALYSES

Safety assessments will be performed on the safety population. In all safety analyses, patients will be grouped according to the treatment that the patients first received rather than the treatment assigned at randomization.

Descriptive summaries of laboratory values and change from baseline throughout the study will be tabulated by treatment arm. For selected parameters, changes from the proportion of patients experiencing clinically significant changes relative to baseline will be summarized by treatment arm.

Values, along with change from baseline, will be summarized using descriptive statistics for each vital sign parameter.

4.5.1 Exposure of Study Medication

Exposure to study drug will be summarized including number of patients with one or two doses and number of patients with dose modification by treatment group.

A listing of patients by treatment group will be prepared detailing dosing of study drug, volume administered and any dose modification.

4.5.2 Adverse Events

Medical Dictionary for Regulatory Activities (MedDRA) will be used as the thesaurus for AEs and disease codes, and the WHO Drug Global B3 Format dictionary will be used for treatments. A glossary of these codes will be produced.

Only treatment-emergent AEs will be summarized. Treatment-emergent events are defined as those AEs with observed or imputed onset date on or after the start date of study treatment. Only where the most extreme intensity is greater than the initial intensity (or if most extreme intensity is not missing and initial intensity is missing) will events with an onset date prior to the start of trial treatment be considered treatment-emergent. An AE with a completely missing start date will be assumed to be treatment-emergent unless the AE has a complete non-imputed end date that is prior to study Day 1.

Adverse events will be coded and tabulated by system organ class (SOC), and/or preferred term (PT) and treatment arm. In tabulations, PTs and their associated SOC will be presented in order of descending frequency summed across the treatment arms.

Adverse events will also be tabulated by severity, as graded according to NCI CTCAE v5.0 scale, and relationship to study medication as indicated by the investigator.

The following will also be summarized:

- serious adverse events
- adverse events leading to withdrawal of study drug
- adverse events leading to discontinuation from the study
- adverse events leading to death
- hypersensitivity adverse events (adverse events occurring immediately after or within 24 hours of the end of an infusion that are not deemed “unrelated” to study treatment)

Adverse events of special interest will be defined using SOC, published Standard MedDRA Queries (SMQs) or AE Grouped Terms (AEGTs) defined by Roche Drug Safety. The groupings of AEs will include but may not be limited to the following:

- Post-treatment acute kidney injury (defined by 50% increase of creatinine from baseline)

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.
- Suspected transmission of an infectious agent by the study drug, 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.

- Serious and/or medically significant infections
- Myocardial infarction or acute coronary syndrome
- GI perforations
- Malignancies
- Anaphylaxis or hypersensitivity reactions
- Stroke
- Serious and/or medically significant bleeding events
- Serious and/or medically significant hepatic events
- Demyelinating disorders

A glossary showing the mapping of investigator verbatim terms to preferred terms will be produced for all AEs included in the analysis. For each AE of special interest table based on SMQs/AEGTs, a corresponding listing of the preferred terms that comprise the SMQ will be produced.

Listings of AEs and SAEs will be produced. Adverse events of special interest will also be listed.

The exposure duration on study (exposure duration is the date of the last safety assessment or death if present, minus the date of the first dose of TCZ plus one divided by 365.25) will be summarized.

4.5.3 Laboratory Data

Summary tables will detail the actual values and changes from baseline of the laboratory parameters to post baseline by treatment arm. Arterial blood gases will be summarized separately.

Patients with values outside the reference will be listed. A listing of all pregnancies will be presented.

Inflammatory markers hs-CRP, CRP, D-dimer, and ferritin will be analyzed by the methods in Section 4.4.3.

4.5.4 Oxygen Saturation and Vital Signs

Summary statistics on absolute values and their change from baseline for all observed vital signs (diastolic blood pressures, systolic blood pressures, respiratory rate, pulse rate, body temperature and peripheral oxygen saturation) will be presented over time by treatment group. Baseline is defined as the last assessment prior to treatment. Additionally, a graphical representation of means over time of oxygen saturation and temperature (daily to Day 28) will be presented.

For patients requiring supplemental oxygen, summary statistics on absolute values of the oxygen flow rate (L/min) and/or fraction of inspired oxygen (FiO2) will be produced by visit/ time point and treatment group.

The level of consciousness will be summarized over time.

The number and proportion of patients requiring oxygen supplementation or other form of ventilation will be summarized over time, including type of support given. Noninvasive mechanical ventilation will be summarized overall as well as by its component types (continuous positive airway pressure [CPAP], bi-level positive airway pressure [BiPAP], other). Invasive mechanical ventilation will also be summarized overall and by component types (Endotracheal tube, tracheostomy tube).

A listing of patients with chest X-ray, CT scans and ECGs (as a separate listing) with clinically significant abnormalities will be produced.

4.6 INTERIM ANALYSES

No interim efficacy analyses have been planned. Safety reviews by the IMC will be performed according to the IMC agreement (See Section 3.2).

5. REFERENCES

Xu X, Han M, Li, T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Submitted manuscript. [Resource on the internet]. 2020 [updated 5 March 2020; cited 17 March 2020]. Available from: http://www.chinaxiv.org/abs/202003.00026

Appendix 1 Protocol Synopsis

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF TOCILIZUMAB IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA**
PROTOCOL NUMBER:	ML42528
VERSION NUMBER:	2
EUDRACT NUMBER:	2020-001154-22
IND NUMBER:	148225
NCT NUMBER:	NCT04372186
TEST PRODUCT:	Tocilizumab (RO4877533)
PHASE:	Phase III
INDICATION:	COVID-19 pneumonia
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the efficacy and safety of tocilizumab (TCZ) compared with a placebo in combination with SOC in hospitalized patients with COVID-19 pneumonia. To enhance the understanding of the clinical profile of tocilizumab for patients who belong to high-risk and minority populations, an emphasis will be placed on including minority-enrolling sites. Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with standard of care (SOC) for the treatment of COVID-19 pneumonia on the basis of the following endpoint:

- Cumulative proportion of patients *with death or* requiring mechanical ventilation by Day 28

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status
- Time to clinical failure, defined as the time to death, mechanical ventilation, intensive care unit (ICU) admission, or withdrawal (whichever occurs first)
- Mortality rate by Day 28
- Time to hospital discharge or “ready for discharge” (e.g., awaiting social disposition) as evidenced by, for example, normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Change from baseline in inflammatory markers levels (high sensitivity C-reactive protein [hs-CRP]*/C-reactive protein [CRP]*, D-dimer, and ferritin) over time
- Cumulative proportion of patients requiring CPAP or BIPAP by Day 28

Safety Objective

The safety objective for this study is to evaluate the safety of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0
- Incidence of any post-treatment bacterial and/or fungal infection
- Incidence of any post-treatment acute kidney injury (defined by 50% increase of creatinine from baseline)

STUDY DESIGN

Description of the Study

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of TCZ in combination with SOC compared with placebo in combination with SOC in hospitalized adult patients with COVID-19. The Sponsor intends to enroll approximately 379 patients that have been diagnosed with COVID-19 pneumonia and meet the entry criteria.

Patients must be at least 18 years of age with confirmed SARS-CoV-2 (COVID-19) infection per World Health Organization (WHO) criteria, including a positive polymerase chain reaction (PCR) of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have SpO_2 <94% on ambient air and be on SOC, which may include anti-viral treatment, low dose systemic corticosteroids, and supportive care.

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. Patients with active tuberculosis (TB) or suspected active bacterial, fungal, viral, or other infection (besides COVID-19 and well-controlled HIV) will be excluded from the study.

Patients will be screened and randomized within *96* hours of hospital admission. Patients will be randomized at a 2:1 ratio to receive blinded treatment of either TCZ or placebo, respectively. Study treatment must be given within approximately 4 hours after randomization. TCZ and placebo will be given in combination with SOC.

Patients assigned to the TCZ arm will receive one infusion of TCZ 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the placebo arm will receive one infusion of placebo, both in addition to SOC.

If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion. *Note: Pre-dose assessments must be repeated and reviewed before an additional infusion of blinded treatment of TCZ or placebo is administered*

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity *within 96 hours of hospital admission* (for a total of 2 screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 7 days after previously signing the consent form. The investigator will record the reasons for screen failure in the screening log.

The study assessments to be conducted include the following: physical examination, vital signs, oxygen saturation, assessment of consciousness, presence and absence of respiratory support, adverse events, concomitant therapies, and clinical laboratory tests.

Patients will be followed up for a total of 60 days after first dose of study medication.

If patients are discharged from the hospital prior to Day 28 or discontinue the study, the Study Completion/Discontinuation assessments are to be conducted prior to discharge or at discontinuation from the study. In addition, if patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. Follow-up visits may be conducted by onsite clinic visits, telephone calls, or home visits. After Day 28, all patients should have a follow-up visit on approximately Day 60 which may be conducted as an onsite clinic visit, telephone call, or home visit for discharged patients.

During the study, standard supportive care will be given according to clinical practice. After study completion, patients should be referred to their regular healthcare provider based on their doctor's decision and as part of standard of care.

Number of Patients

This study aims to enroll approximately 379 hospitalized patients with COVID-19 pneumonia.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- *Documented i*nformed *c*onsent by any patient capable of giving consent, or, when the patient is not capable of giving consent, by his or her legal/authorized representative
- Age ≥18 years at time of *providing* Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Hospitalized
- COVID-19 pneumonia confirmed per a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid) and radiographic imaging (CT scan or chest X-ray)
- Able to complete screening within *96* hours of hospital admission
- Blood oxygen saturation (SpO_2) <94% while on ambient air

  If a patient is on supplemental oxygen with SpO_2 ≥94%, but desaturation to <94% on lower supplemental oxygen or ambient air is documented during screening, the inclusion criterion is met.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 90 days after the final dose of study drug. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

  Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 60 days after the final dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria

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

- Known severe allergic reactions to TCZ or other monoclonal antibodies
- Require CPAP, BIPAP, or mechanical ventilation
- Active TB infection or last TB infection within 1 month of randomization
- Suspected active bacterial, fungal, viral, or other infection (besides COVID-19 and well-controlled HIV)
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
- Immunocompromised (besides well-controlled HIV) or on immunosuppressive therapy (except for steroids for COVID), advanced cancer
- Have received oral anti-rejection or immunomodulatory drugs (including TCZ) within the past 3 months
- Participating in another IL-6 antagonist clinical trial or other drug clinical trials (participation in COVID-19 anti-viral trials may be permitted if approved by Medical Monitor)
- ALT or AST >5 x upper limit of normal (ULN) detected within 24 hours at screening (according to local laboratory reference ranges)
- ANC <1000/μL at screening (according to local laboratory reference ranges)
- Platelet count <50,000/μL at screening (according to local laboratory reference ranges)
- Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
- Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (investigational COVID-19 antivirals may be permitted if approved by Medical Monitor)
- Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Any history of diverticulitis or gastrointestinal perforation

The use of remdesivir, hydroxychloroquine, chloroquine, and convalescent plasma, is not an exclusion to participation in this trial, and is left to the discretion of the primary medical team.

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for last follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 2 months after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 8 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

Patients assigned to the active arm will receive one or two doses of tocilizumab (TCZ) via intravenous (IV) infusion at a dose of 8 mg/kg IV to a maximum of 800 mg per dose.

Comparator

Patients assigned to the comparator arm will receive one or two doses of placebo via IV infusion.

Statistical Methods

Primary Analysis

The primary efficacy objective for this study is to evaluate the efficacy of TCZ plus standard of care, compared with placebo plus standard of care using the following endpoint:

- Cumulative proportion of patients *with death or* requiring mechanical ventilation by Day 28

Time to *death or* the first utilization of mechanical ventilation after randomization will be *compared between the TCZ group and the placebo group using the stratified log-rank test with age group (age ≤60, age >60 years) as the stratification factor. T*he cumulative proportion of patients *with death or* requiring mechanical ventilation at Day 28 *will be estimated using the Kaplan-Meier method.*

Details of the primary endpoint analysis will be included in the Statistical Analysis Plan (SAP).

Determination of Sample Size

The estimated sample size was determined based on the time from randomization to the first utilization of mechanical ventilation by Day 28.

The total modified intent-to-treat (mITT) sample size of 379 patients with a 2:1 randomization of TCZ (n=253) to placebo (n=126) provides approximately 80% power using a Logrank test to detect a 15% difference between treatment groups in time to *death or* mechanical ventilation by Day 28 under the following assumptions: cumulative survival (i.e., *alive and* not requiring mechanical ventilation) rates of 75% in the TCZ group and 60% in placebo group, with 28-day follow-up, using a two-sided 5% alpha, and 10% dropout rate in each arm. Sample size re-estimation may be considered during the study based on updated assumptions of the treatment effect.

Planned Interim Analyses

An Internal Monitoring Committee (IMC) will evaluate safety according to procedures and guidelines detailed in the IMC agreement. The IMC will consist of Sponsor representatives who will not be blinded to study data. Details of the safety reviews will be provided in the SAP.

Appendix 2 Schedule of Activities: Days 1 and 2

	Screening [a, b]	Baseline		
Study Day	–4 to 0	1		2
Time Post Initial Treatment (Assessment Window)		0 min Pre-dose (approx. –4 hrs)	15 min After end of infusion (approx. +1 hr)	24 hrs (±12 hrs)
Informed consent	x			
Inclusion/exclusion criteria	x	x		
Demographic data	x			
Randomization		x		
Medical history	x			
Complete physical examination [c, d]	x			
Weight	x			
COVID-19 diagnosis [e]	x			
Chest X-ray/CT scan [d, f]	x			
ECG	x			
Pregnancy test [d, g]	x			
PaO_2/FiO_2 [d, h]	x (optional)	← Optional →		
SpO_2 [d, i]	x	x	x	x
Vital signs [d, i]	x	x	x	x
Ordinal scoring (including ventilation requirement) [j]		x		x
Adverse events [k]		x		x
Concomitant medications [l]		x		x
Hematology [d, m]	x			x
Chemistry [d, n]	x			x

	Screening [a, b]	Baseline		
Study Day	–4 to 0	1		2
Time Post Initial Treatment (Assessment Window)		0 *min* Pre-dose (approx. –4 hrs)	15 min After end of infusion (approx. +1 hr)	24 hrs (±12 hrs)
hs-CRP/*CRP*, D-dimer *(if available via local laboratory)*, and ferritin [d]	x			
Study drug administration [o]		x		

ALP=alkaline phosphatase; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; eCRF=electronic case report form; hr(s)=hour(s); hs-CRP=high sensitivity C-reactive protein; min=minutes; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0; PaO_2/FiO_2=arterial oxygen partial pressure/fraction of inspired oxygen; SpO_2=peripheral capillary oxygen saturation; TCZ=tocilizumab.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Results from standard-of-care tests or examinations performed prior to obtaining informed consent and within *96* hours before randomization may be used; such tests do not need to be repeated for screening.

[b] Informed consent must be documented before any study-specific screening procedure is performed.

[c] A complete physical examination, performed at screening and per the investigator's discretion during the study, includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities identified during the study should be reported as adverse events.

[d] Physical examination, blood tests, and other assessments conducted after arrival at the hospital, but before the informed consent is signed, can be used as screening assessments.

[e] COVID-19 test (SARS-CoV2 PCR) to confirm diagnosis should be performed at or before screening (if testing is conducted before screening, documentation must be available).

[f] Screening chest X-ray or CT scans should be performed within *96* hours prior to randomization. If additional chest X-rays/CT scans are taken per local practice during the study, this information should be provided in the eCRF.

[g] For women of childbearing potential, including those who have had a tubal ligation, positive urine test results will be confirmed with a serum pregnancy test. Study drug infusion must not be administered unless the serum pregnancy test result is negative.

[h] If arterial blood gases are measured.

[i] All vital sign measurements (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressures, and body temperature) and oxygen saturation should be recorded together once daily while the patient remains hospitalized. If measured more than once daily, the worst values

(highest temperature, respiratory rate, and heart rate; lowest blood pressure, oxygen saturation, and consciousness level) during that period should be recorded on the eCRF.

[j] Assessment of clinical status using the ordinal scale, which includes change in ventilation usage (non-invasive or mechanical), should be recorded at baseline on Day 1 then again daily every morning (between approximately 8 am and 12 pm) for patients who remain hospitalized.

[k] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 60 days after the final dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment.

[l] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit.

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).

[n] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total bilirubin, ALP, ALT, and AST.

[o] The initial study drug infusion should be given within approximately 4 hours of randomization. If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion. *Note: Pre-dose assessments must be repeated and reviewed before an additional infusion of blinded treatment of TCZ or placebo is administered.*

Appendix 3 Schedule of Activities: Day 3–Study Completion

	Days 3–28 [a]																									Study Completion/ Discontinuation [i]
Study Day	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 [i]	
Vital signs [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PaO_2/FiO_2 [c]	← Optional →																										(optional)
SpO_2 [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ordinal scoring [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [e]	← →																										x
Concomitant medications [f]	← →																										x
Hematology [g]																										x	x
Chemistry [h]																										x	x
hs-CRP/*CRP*, D-dimer *(if available via local laboratory)*, and ferritin																										x	x

ALP=alkaline phosphatase; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; eCRF=electronic case report form; hs-CRP=high sensitivity C-reactive protein; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0; $PaO_2/FiO2$=arterial oxygen partial pressure/fraction of inspired oxygen; SpO_2=peripheral capillary oxygen saturation.

[a] If patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. Follow-up visits may be conducted by onsite clinic visits, telephone calls, or home visits.

[b] All vital sign measurements (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressures, and body temperature) and oxygen saturation should be recorded together once daily while the patient remains hospitalized. If measured more than once daily, the worst values (highest temperature, respiratory rate, and heart rate; lowest blood pressure, oxygen saturation, and consciousness level) during that period should be recorded on the eCRF.

[c] If arterial blood gases are measured.

[d] Assessment of clinical status using the ordinal scale should be recorded at baseline on Day 1 then again daily for patients who remain hospitalized.

[e] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 60 days after the final dose of study drug.

After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment.

[f] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit.

[g] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).

[h] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total bilirubin, ALP, ALT, and AST.

[i] If patients are discharged from the hospital prior to Day 28 or discontinue the study, the Study Completion/Discontinuation assessments are to be conducted prior to discharge or at discontinuation from the study. In addition, if patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. The Day 60 follow up may be conducted by an onsite clinic visit, telephone call, or home visit for discharged patients. Day 60 follow up is required to collect adverse events only.

STATISTICAL ANALYSIS PLAN

TITLE: **A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TOCILIZUMAB IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA**

PROTOCOL NUMBER: ML42528

STUDY DRUG: Tocilizumab (RO4877533)

VERSION NUMBER: 2.0

IND NUMBER: 148225

EUDRACT NUMBER: 2020-001154-22

SPONSOR: Genentech, Inc.

PLAN PREPARED BY: [redacted]

DATE FINAL: Version 1: June 25, 2020
Version 2: See electronic date stamp below

STATISTICAL ANALYSIS PLAN APPROVAL

Company Signatory:

Approval Date:
August 31, 2020

[redacted]

DocuSigned by:
[redacted]

CONFIDENTIAL

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Statistical Analysis Plan Update Rationale

The statistical analysis plan ML42528 Version 2 includes the following updates from Version 1:

- Key secondary endpoints were updated
- The Type I error control section was added to specify a hierarchy for testing of the primary endpoint followed by testing of the predefined key secondary endpoints
- Cumulative Incidence Function plots were specified for time to 'improvement' secondary endpoints
- The censoring rules for the time to event endpoints were updated
- Derivation of the time to clinical failure endpoint was clarified
- Pre-specification of the stratified efficacy analyses to include only the age randomization strata
- Definition of baseline was added
- Additional subgroup analyses for race/ethnicity combined category and elevated CRP were added
- Appendices 1, 2, and 3 were updated to be consistent with the current protocol version 3

Additional minor changes have been made to improve clarity and consistency.

TABLE OF CONTENTS

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
BIPAP	bilevel positive airway pressure
CoV	coronaviruses
CPAP	continuous positive airway pressure
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic Case Report Form
ECMO	extracorporeal membrane oxygenation
FiO_2	fraction of inspired oxygen
hs-CRP	high sensitivity C-reactive protein
ICU	intensive care unit
IL-6	interleukin 6
IMC	Internal Monitoring Committee
IxRS	interactive voice or web-based response system
LPLV	last patient, last visit
mITT	modified intent-to-treat
NCI	National Cancer Institute
PaO_2	partial pressure of oxygen
SARS-CoV	severe acute respiratory syndrome
SOC	standard of care
SpO_2	blood oxygen saturation
TB	tuberculosis
TCZ	tocilizumab
ULN	upper limit of normal
WHO	World Health Organization

1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for the clinical efficacy and clinical safety for Study ML42528.

There are currently no drugs approved for the treatment of patients with SAS-CoV-2 (COVID-19). Given the results of studies (Xu et al. 2020), tocilizumab (TCZ), along with standard of care (SOC) treatment, could provide efficacy, offering the potential to treat COVID-19 in hospitalized populations more effectively than current SOC alone. Extensive safety data have previously been generated on the use of TCZ in other indications. Therefore, a placebo-controlled study in combination with SOC to assess safety and efficacy of TCZ in hospitalized patients with COVID-19 pneumonia is justified to address the high unmet need.

2. STUDY DESIGN

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of TCZ in combination with SOC compared with placebo in combination with SOC in hospitalized adult patients with COVID-19. The Sponsor intends to enroll approximately 379 patients that have been diagnosed with COVID-19 pneumonia and meet the entry criteria.

Patients must be at least 18 years of age with confirmed SARS-CoV-2 (COVID-19) infection per WHO criteria, including a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have SpO2<94% on ambient air and be on SOC, which may include anti-viral treatment, low dose systemic corticosteroids, and supportive care.

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. Patients with active tuberculosis (TB) or suspected active bacterial, fungal, viral, or other infection (besides COVID-19 and well-controlled HIV) will be excluded from the study.

Eligible patients per study eligibility criteria will be randomly allocated in a 2:1 ratio to receive double-blind treatment with TCZ or placebo within 96 hours of hospital admission. Randomization will be stratified by country and age (≤60 and >60 years). The first dose of study drug will be administered within approximately 4 hours after randomization along with local SOC.

Patients assigned to the TCZ arm will receive one infusion of TCZ 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the placebo arm will receive one infusion of placebo.

If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status),

one additional double-blind infusion of TCZ or placebo can be given, 8–24 hours after the initial infusion. Note: Pre-dose assessments must be repeated and reviewed before an additional infusion of blinded treatment of TCZ or placebo is administered.

Patients who do not meet the study eligibility criteria (screen failure) may qualify for one re-screening opportunity within 96 hours of hospital admission (for a total of 2 screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 7 days after previously signing the consent form. The investigator will record the reasons for screen failure in the screening log.

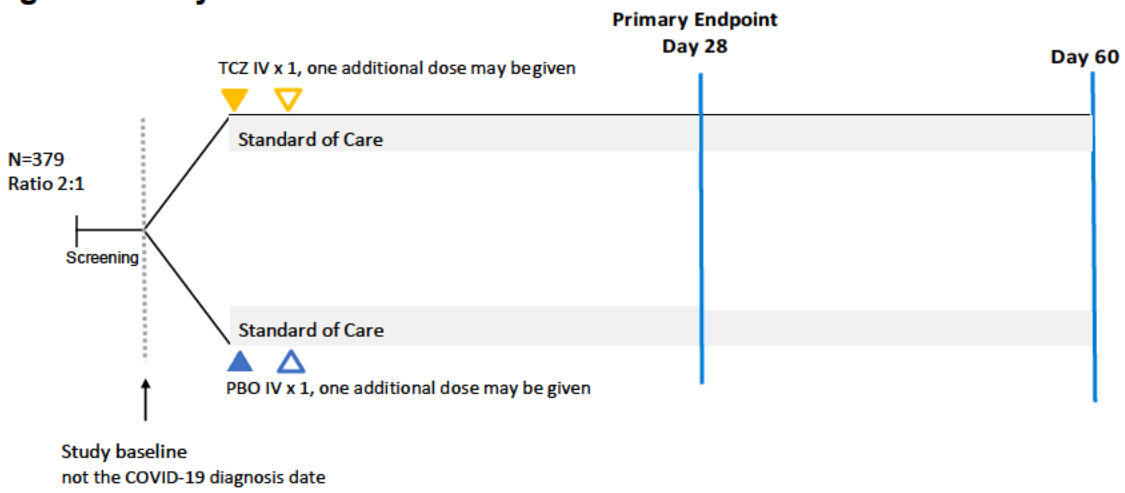
Safety and efficacy will be assessed according to the SOA (see Appendix 2 and Appendix 3).

If patients are discharged from the hospital prior to Day 28 or discontinued from the study, the Study Completion/Discontinuation assessments are to be conducted prior to discharge or at discontinuation from the study. In addition, if patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess adverse events including mortality. Follow-up visits may be conducted by onsite clinic visits, telephone calls, or home visits. After Day 28, all patients should have a follow-up visit on approximately Day 60 which may be conducted as an onsite clinic visit, telephone call, or home visit for discharged patients.

During the study, standard supportive care will be given according to clinical practice. After study completion, patients should be referred to their regular healthcare provider based on their doctor's decision and as part of standard of care.

Figure 1 presents an overview of the study design.

Figure 1 Study Schema



IV=intravenous; PBO=placebo; TCZ=tocilizumab.
Note: Patients will be screened and randomized within 96 hours of hospital admission. Study treatment must be given within approximately 4 hours after randomization.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1.

2.2 ENDPOINTS

2.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is:

- Cumulative proportion of patients with death or requiring mechanical ventilation by Day 28

2.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Time to hospital discharge or “ready for discharge” (e.g., awaiting social disposition) up to Day 28 as evidenced by, for example, normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen
- Time to improvement in ordinal clinical status up to Day 28 relative to baseline based on a 7-category ordinal scale of clinical status
- Time to clinical failure up to Day 28, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal
- Mortality rate by Day 28
- 7-category ordinal scale at Day 28

2.2.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

- Change from baseline at Day 28/discharge/early dropout in inflammatory markers levels (hs-CRP/CRP, D-dimer, and ferritin)
- Time to first requiring CPAP or BIPAP

2.2.4 Safety Endpoints

The safety endpoints are as follows:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0
- Incidence of any post-treatment bacterial and/or fungal infection
- Incidence of any post-treatment acute kidney injury (defined by 50% increase of creatinine from baseline)

2.3 DETERMINATION OF SAMPLE SIZE

A total of approximately 379 patients will be randomized in this study. Patients will be randomly allocated in a 2:1 ratio to receive TCZ and or placebo, in addition to local SOC.

The sample size of 379 patients provides approximately 80% power using a logrank test to detect a 15% difference between treatment arms in the cumulative proportions of patients with death or mechanical ventilation by Day 28 under the following assumptions: cumulative survival (i.e., alive and not requiring mechanical ventilation) rates of 75% in the TCZ group and 60% in placebo group by Day 28, using a two-sided 5% alpha, and 10% dropout rate in each arm. Sample size re-estimation may be considered during the study based on updated assumptions of the treatment effect.

2.4 ANALYSIS TIMING

No interim efficacy analyses have been planned. Safety data will be reviewed by an Internal Monitoring Committee (IMC) during the study. The IMC will consist of Sponsor representatives who will not be blinded to study data. The planned safety interim review will occur when the first 30 patients have completed the Day 14 study visit. See Section 3.2 for further details.

The primary analysis of Day 28 outcomes will occur when the last patient either has withdrawn or completed the Day 28 visit. A snapshot of this data will be taken and the primary and key secondary efficacy analyses will be performed.

There will be one additional analyses on the final data when all patients have either reached Day 60 or withdrawn from study, all data from the study are in the database, and the database is locked.

3. STUDY CONDUCT

3.1 RANDOMIZATION

After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an interactive voice or web-based response system (IxRS).

Patients will be randomly assigned to one of two treatment arms: TCZ in combination with SOC or placebo in combination with SOC. Randomization will occur in a 2:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified by country (US, Peru, Brazil, Mexico, Kenya, South Africa) and age ($\leq$60 and $>$60 years).

3.2 DATA MONITORING

An IMC will evaluate safety according to procedures and guidelines detailed in the IMC agreement. The IMC will consist of Sponsor representatives who are not members of the study management team and will not be blinded to study data.

The first IMC safety review will occur after approximately 30 patients (20 in TCZ and 10 in PBO) have completed the Day 14 visit. There will be further IMC meetings when

approximately half of the targeted number of patients (i.e., n=189) have been enrolled; but all interim analyses are subject to change depending on enrollment and as appropriate.

The IMC will review unblinded summaries and listings of overall rates of death, serious adverse events (SAEs), and all adverse events (AEs) as well as other key safety data. All enrolled patients will be included in the interim safety summaries as there may be a lag time for obtaining treatment exposure data.

Deaths and serious infections will be reviewed in an expedited manner. The Study Medical director, Safety Scientist or IMC Chair may request additional meetings if concerns arise.

The unblinded safety summaries will be conducted by the IMC-Statistician and statistical programmer independent from the study management team. The list of the planned safety summary tables and listings are provided in the IMC agreement. Communications and recommendations from the IMC will be carried out as specified in the IMC agreement.

4. STATISTICAL METHODS

All primary and secondary efficacy endpoints will be analyzed in the modified intent-to-treat (mITT) population, with patients grouped according to the treatment assignment at randomization.

In all safety analyses, patients will be grouped according to the treatment that the patients actually received rather than the treatment assigned at randomization.

4.1 ANALYSIS POPULATIONS

Disposition summaries will be based on an All Patient population (all patients randomized regardless of whether study drug was received). Efficacy analyses will be based on the mITT population, if not otherwise specified. Analysis of safety data will be based on the safety population.

4.1.1 mITT Population

The mITT population is defined as all randomized patients in the study who received any amount of study medication, with patients grouped according to the treatment assignment at randomization.

4.1.2 Safety Population

Safety population will consist of all patients who received any amount of study medication. In all safety analyses, patients will be grouped according to the treatment that the patients first actually received rather than the treatment assigned at randomization.

4.2 DATA HANDLING CONVENTIONS

4.2.1 Definition of Study Day

Based on the protocol, study treatment must be given within approximately 4 hours after randomization. Therefore, the first treatment dose date will be used as Day 1 in all analyses. The day immediately following the first treatment dose date is study Day 2 and so on.

The detailed analysis windows for inflammatory markers, vital signs, and laboratory data will be defined in the specifications of the planned tables, listings, and graphs.

4.2.2 Definition of Baseline

Baseline value is defined as value from Day 1. The last value from screening will be used for baseline assessment if there is no baseline value. Pretreatment assessments will be used preferentially on study Day 1 for baseline.

4.3 ANALYSIS OF STUDY CONDUCT

The number of patients enrolled, discontinued, or who completed the study up to Day 28 will be summarized. Reasons for premature study discontinuation will be listed and summarized. Listing of randomized patients and listing of investigators will be produced. A summary of enrollment by country and investigator name will be produced.

The number of patients discharged from hospital will be summarized over time.

Eligibility criteria deviations and other major protocol deviations will be listed and summarized by treatment arm.

Randomized patients excluded from the safety and mITT populations will be summarized, including the reason for exclusion by treatment arm.

4.4 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (including, but not limited to, age, sex, self-reported race/ethnicity, smoking history) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented by treatment arm based on the mITT population; additional summary may be based on the safety population, as needed.

4.4.1 Demographics and Social Status

- Sex
- Age
- Weight
- BMI
- Race

- Ethnicity
- Race/Ethnicity Combined [Hispanic or Latino, American Indian or Alaska Native, Black or African American, WHITE, Other/unknown]
- Employment status
- Education status
- Primary language
- Living situation (Alone, With Others)
- Smoking history (Never, Current/Former)
- Country group (US, ex-US)

4.4.2 Disease Characteristics

- Ordinal scale for clinical status
- CRP and hs-CRP
  - Elevated CRP (CRP >50 mg/L or hs-CRP >3 mg/L)
- D-dimer
- Ferritin
- Symptoms at time of COVID 19 diagnosis
- Number of days from first COVID-19 symptom at baseline (to be derived from COVID 19 Diagnosis)
- COVID19 diagnosis based on PCR of specimen type
- Number of days from COVID-19 diagnosis at baseline (to be derived from COVID 19 Diagnosis)
- PCR result (Negative, positive)
- ICU admission status at baseline (yes, no)
- Steroid use (part of previous and concomitant medications), including prior (treatment started within 7 days of Day 1) and concurrent treatment (yes, no)
- Antiviral use (part of previous and concomitant medications), including prior (treatment started within 7 days of Day 1) and concurrent treatment (yes, no)

4.4.3 Targeted and General Medical History

Targeted medical history, including Diabetes, hypertension, hyperlipidemia, asthma, COPD, obesity, myocardial infarction, atrial fibrillation, and stroke, will be summarized by treatment arm.

General medical history data will be summarized descriptively by treatment arm. Summaries of the targeted and general medical history will be provided for the safety population. A glossary showing the mapping of investigator verbatim terms to coded disease terms will be produced for the general medical history data.

4.4.4 Surgeries and Procedures

A listing of any previous or ongoing surgeries and procedures will be produced for the safety population.

4.4.5 Previous and Concomitant Medications

Previous and concomitant treatments will be summarized descriptively by treatment arm for the safety population. Previous treatments that have been stopped prior to study Day 1 will be summarized separately. There will be a summary of all concomitant treatments, including those that were initiated prior to study Day 1.

4.5 EFFICACY ANALYSIS

All efficacy analyses will be performed on the mITT population with patients grouped according to treatment assigned at randomization.

While two-sided unadjusted p-values will be reported, the overall study-level type 1 error will be controlled at a two-sided α=0.05 level according to the type 1 error control plan detailed in Section 4.5.2.

All efficacy analyses will be stratified by age ($\leq$60 and $>$60 years). Country group (US, Peru, Brazil, Mexico, Kenya, South Africa) will not be included as a stratification variable in the efficacy analyses to avoid the likelihood of getting unreliable estimates due to small sample size in a particular stratum (there are only 16 patients in the ex-US countries and age >60 years stratum, with possibly fewer than 10 patients in one of the treatment arms).

Consistent treatment effect in the country group and other prespecified subgroup will be evaluated through subgroup analysis specified in Section 4.5.5.

4.5.1 Primary Efficacy Endpoint

The primary efficacy objective for this study is to evaluate the efficacy of TCZ plus SOC compared with placebo plus SOC using the following endpoint:

- Cumulative proportion of patients with death or requiring mechanical ventilation by Day 28

For this endpoint, mechanical ventilation is defined as mechanical invasive ventilation or ECMO (extracorporeal membrane oxygen). Any patient, who died prior to requiring invasive mechanical ventilation on or prior to Day 28, will be considered as having an event for this endpoint. Time to primary endpoint event is defined as time from Day 1 to the first occurrence of death or requiring mechanical ventilation by Day 28. The cumulative proportions of patients who experienced events by Day 28 will be estimated using the Kaplan-Meier methodology and compared between the TCZ group and the placebo group using the stratified log-rank test with age group as stratification factor.

The cumulative incidence function will be used to estimate and plot the cumulative primary efficacy event rates up to Day 28 for each treatment arm. The estimated cumulative primary efficacy event rates and their 95% confidence intervals (CIs) at Days 7, 14, 21 and 28 will be summarized by treatment arm. The median time to event will also be provided along with the corresponding 95% CIs by treatment arm.

The stratified Cox proportional hazard model, with age group as stratification factor, will be used to estimate the hazard ratio (HR) between the two treatment arms and its 95% CI.

The primary efficacy event and the censoring rules are described in Table 1 below. Death after Day 28 will not be considered as an event.

Table 1 Time to Death or Requiring Mechanical Ventilation and Censoring Status

Event	Censor	Date
Patient with death or requiring mechanical ventilation* recordings on or prior to Day 28	No	Earlier of date of death and/or first date requiring mechanical ventilation
Patient without death and not requiring mechanical ventilation recordings on or prior to Day 28;		
If patient with safety follow-up	Yes	Earlier of the date of Day 28 and the date of last available follow-up**
If patient without safety follow-up	Yes	Earlier of the date of Day 28 and the date of last available in-hospital assessment ***

* Mechanical ventilation is defined as mechanical invasive ventilation or ECMO per CRF; ** Follow-up includes (1) safety follow-up per CRF, (2) 7-ordinal scale assessment in hospital, (3) oxygen saturation assessment in hospital; *** In-hospital assessment includes (1) 7-ordinal scale assessment in hospital, (2) oxygen saturation assessment in hospital. For patients without any oxygen saturation or ordinal scale assessment in-hospital assessment, date is set to Day 1.

4.5.2 Controlling for Type I Error

The primary and key secondary efficacy endpoints will be evaluated in a hierarchical manner to control the overall study-wide Type 1 error rate at the 5% significance level. If the primary efficacy endpoint reaches statistical significance at the two-sided 5% significance level, the following list of key secondary efficacy endpoints will be tested at the two-sided 5% significance level in the predefined order below:

1. Time to hospital discharge or “ready for discharge” up to Day 28
2. Time to improvement in ordinal clinical status up to Day 28 relative to baseline based on a 7-category ordinal scale of clinical status

3. Time to clinical failure up to Day 28, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first)
4. Mortality rate by Day 28

Testing of the first secondary endpoint will be gated on the success (significance $p<0.05$) of the primary efficacy endpoint, and testing of subsequent secondary endpoints will be gated on the success (significance $p<0.05$) of the previous secondary endpoint. Testing will stop once an endpoint fails to reach statistical significance ($p\geq0.05$).

Other secondary endpoint and exploratory efficacy endpoints will be tested at the nominal two-sided 5% significance level for exploratory purposes without any adjustment for multiplicity.

4.5.3 Secondary Efficacy Endpoints

Time to event secondary endpoints will be compared between the TCZ group and the placebo group using similar analytic methodologies as the primary efficacy endpoint. The Kaplan-Meier approach will be used to estimate and plot survival rates up to Day 28 for each treatment arm. The median time to event with its 95% CI will be summarized by treatment whenever they are estimable.

For the endpoints of time to hospital discharge or "ready for discharge" and time to improvement in clinical status, deaths will be right censored (at Day 28). Consequently, for these endpoints, patients censored on Day 28 could have two different states, death or failure to meet the criterion of improvement outcome. Therefore, it is important to understand the efficacy outcome in the context of the number and timing of deaths by treatment arm. In addition, in order to evaluate the effect of competing risk of death in these endpoints, the cumulative incidence function plots for both death and the event of interest will be produced using the non-parametric Aalen–Johansen estimator.

4.5.3.1 Key Secondary Efficacy Endpoints

- Time to hospital discharge or "ready for discharge" up to Day 28

This key secondary endpoint is defined as time from Day 1 to hospital discharge or "ready for discharge" up to Day 28 based on the 7-category ordinal scale.

Assessment of clinical status using an ordinal scale will be recorded at baseline and once daily while hospitalized.

The ordinal scale categories are as follows:

1. Discharged (or "ready for discharge" as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or $\leq$2L supplemental oxygen)
2. Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen
3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen

4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen
5. ICU, requiring intubation and mechanical ventilation
6. ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy)
7. Death

The efficacy event and the censoring rules for this endpoint are described in Table 2.

Table 2 Time to Hospital Discharge and Censoring Status

Event	Censor	Date
If patient with discharge or "ready for discharge" recordings on or prior to Day 28	No	Earliest discharge day
Else if before discharge or "ready for discharge", patient died on or prior to Day 28	Yes	Day 28
Else if patient without discharge or "ready for discharge" recordings on or prior to Day 28	Yes	Earlier of the date of Day 28 and the date of last ordinal scale assessment*

* For patients without any ordinal scale assessment in-hospital assessment, date is set to Day 1.

- Time to improvement in clinical status up to Day 28 relative to baseline based on a 7-category ordinal scale of clinical status

This secondary endpoint is defined as time from Day 1 to the time when at least a 2-category improvement in the 7-category ordinal scale is observed on or prior to Day 28. For patients in category 2 at baseline, having a clinical status of category 1 (discharge or "ready for discharge") on or prior to Day 28 will be considered as meeting the threshold.

The event and the censoring rules for this endpoint are described in Table 3 below.

Table 3 Time to Improvement in Ordinal Clinical Status and Censoring Status

Event	Censor	Date
Patient enrolled with scale≥3		
If patient with 2-category improvement in ordinal clinical status on or prior to Day 28 (regardless of whether the patient die after the improvement)	No	First improvement day
Else if patient died prior to improvement in ordinal clinical status	Yes	Day 28
Else if patient without 2-category improvement in ordinal clinical status on or prior to Day 28	Yes	Earlier of the date of Day 28 and the date of last ordinal scale assessment*
Patient enrolled with scale=2		
If patient with 1-category improvement in ordinal clinical status on or prior to Day 28 (regardless of whether the patient die after the improvement)	No	First improvement day
Else if patient died prior to improvement in ordinal clinical status	Yes	Day 28
Else if patient without 1-category improvement in ordinal clinical status on or prior to Day 28	Yes	Earlier of the date of Day 28 and the date of last ordinal scale assessment*

* For patients without any ordinal scale assessment in-hospital assessment, date is set to Day 1.

- Time to clinical failure up to Day 28

This secondary efficacy endpoint is defined as time from Day 1 to first occurrence of death, mechanical ventilation (defined same as in primary endpoint), ICU admission, or withdrawal from study due to any reason on or prior to Day 28. For patients entering the study already in the ICU, time to clinical failure is defined as the first occurrence of, death, mechanical ventilation (defined same as in primary endpoint), two-category worsening in the 7-category ordinal scale from baseline, or withdrawal from study due to any reason on or prior to Day 28.

The event and censoring rules for this endpoint are described in Table 4 below.

Table 4 Time to Clinical Failure and Censoring Status

Event	Censor	Date
No ICU admission prior to first study treatment		
Patient with death, ICU admission, requiring mechanical ventilation* recordings, or withdrawal from study before discharge on or prior to Day 28	No	Earliest of the death date, first ICU admission date, first date requiring mechanical ventilation, and study withdrawal date
Patient without death, ICU admission, requiring mechanical ventilation recordings, and withdrawal from study before discharge on or prior to Day 28		
with safety follow-up	Yes	Earlier of the date of Day 28 and the date of last available follow-up**
without safety follow-up	Yes	Earlier of the date of Day 28 and the date of last available in-hospital assessment ***
For patients whose ICU admission is prior to first study medication administration		
Patient with death, two-category worsening on the ordinal scale, requiring mechanical ventilation* recordings or withdrawal from study before discharge on or prior to Day 28	No	Earliest of the death date, first date with two-category worsening on the ordinal scale, requiring mechanical ventilation* recordings, and study withdrawal date
Patient without death, two-category worsening on the ordinal scale, requiring mechanical ventilation* recordings, and withdrawal from study before discharge on or prior to Day 28		
with safety follow-up	Yes	Earlier of the date of Day 28 and the date of last available follow-up**
without safety follow-up	Yes	Earlier of the date of Day 28 and the date of last available in-hospital assessment ***

* Mechanical ventilation is defined as mechanical invasive ventilation or ECMO per CRF; ** Follow-up includes (1) safety follow-up per CRF, (2) 7-ordinal scale assessment in hospital, (3) oxygen saturation assessment in hospital; *** In-hospital assessment includes (1) 7-ordinal scale assessment in hospital, (2) oxygen saturation assessment in hospital. For patients without any oxygen saturation or ordinal scale assessment in-hospital assessment, date is set to Day 1.

- Mortality rate at Day 28

The difference in proportion of patients who have died by Day 28 will be compared between the treatment arms using the Cochran-Mantel-Haenszel test adjusted for stratification factor age. The adjusted proportion in each treatment arm will be presented along with its 95% CI. Adjusted difference in proportions and its associated 95% CI for the treatment group comparison will also be presented. Any mortality that occurs between Day 1 and Day 28 will be included in the analysis.

4.5.3.2 Other Secondary Efficacy Endpoint

- 7-category ordinal scale at Day 28

The patients' clinical status as assessed by the 7-category ordinal scale at Day 28 will be analyzed by comparing the difference in distributions of the ordinal scale between the TCZ and placebo groups. Patients with missing ordinal scale status at Day 28 will have the value imputed by the last post-baseline available assessment. The Van Elteren test will be used, including the stratification factor age for this comparison. The count and proportion of patients with scores at each category of the scale at Day 28 will be summarized along with the p-value from the Van Elteren test.

In addition, the 7-category ordinal scale at Day 28 will be compared between the TCZ and placebo groups using a proportional odds model stratified by age group as a sensitivity analysis. The odds ratio, p-value, and 95% CI on the odds ratio will be presented.

4.5.4 Exploratory Efficacy Endpoints

- Time to first requiring CPAP or BIPAP

Defined as the time from Day 1 to the first documented date of death, requiring CPAP or BIPAP, or requiring mechanical ventilation (as defined in primary endpoint). Table 5 describes the event/censoring rules for the time to requiring CPAP or BIPAP. This endpoint will be analyzed using the same methodologies as the primary efficacy endpoint.

Table 5 Time to Requiring CPAP or BIPAP and Censoring Status

Event	Censor	Date
Patient with death or requiring CPAP or BIPAP, or requiring mechanical ventilation* on or prior to Day 28	No	Earlier of date of death, and/or first date requiring CPAP or BIPAP, and/or mechanical ventilation
Patient without death, requiring CPAP or BIPAP, and requiring mechanical ventilation recordings on or prior to Day 28		
Patient with safety follow-up	Yes	Earlier of the date of Day 28 and the date of last available follow-up**
Patient without safety follow-up	Yes	Earlier of the date of Day 28 and the date of last available in-hospital assessment ***

* Mechanical ventilation is defined as mechanical invasive ventilation or ECMO; ** Follow-up includes (1) safety follow-up, (2) 7-ordinal scale assessment in hospital, (3) oxygen saturation assessment in hospital; *** In-hospital assessment includes (1) 7-ordinal scale assessment in hospital, (2) oxygen saturation assessment in hospital. For patients without any oxygen saturation or ordinal scale assessment in-hospital assessment, date is set to Day 1.

- Change from baseline in inflammatory markers levels (hs-CRP/CRP, D-dimer, and ferritin) over time

CRP and hs-CRP will be summarized separately. Elevated CRP (yes) will be defined as CRP >50 mg/L or hs-CRP >3 mg/L.

The level of inflammatory markers will be summarized descriptively using means, standard deviations, medians, and ranges at baseline and post baseline, together with the change from baseline values. This summary will be provided for patients with observed data, missing data will not be imputed.

4.5.5 Subgroup Analyses

The primary endpoint (cumulative proportion of patients with death or requiring mechanical ventilation by Day 28) and the key secondary endpoint (time to hospital discharge or “ready for discharge”) will be assessed by the same methodologies as in the mITT population for the following subgroups:

- Sex [Male, Female]
- Age [⩽60, >60 years]
- Race/Ethnicity Combined [Hispanic or Latino, American Indian or Alaska Native, Black or African American, White, Other/unknown]
- Smoking history [Never, Current/Former]
- BMI [<30, >=30]

- Country group [US, ex-US]
- Steroid use, prior (within 7 days of Day 1) and concurrent [Yes, No]
- Anti-viral treatment use, prior (within 7 days of Day 1) and concurrent [Yes, No]
- Elevated CRP [Yes, No; see definition in Section 4.5.4]

Summaries of the endpoints listed above will be produced, separately, for each level of the subgroup variables and displayed on Forest plots. Small subgroups (e.g., with number of patients <30) may be combined to enable meaningful analysis as appropriate.

4.6 SAFETY ANALYSES

Safety assessments will be performed on the safety population. In all safety analyses, patients will be grouped according to the treatment that the patients first received rather than the treatment assigned at randomization.

Descriptive summaries of laboratory values and change from baseline throughout the study will be tabulated by treatment arm. For selected parameters, changes from the proportion of patients experiencing clinically significant changes relative to baseline will be summarized by treatment arm.

Values, along with change from baseline, will be summarized using descriptive statistics for each vital sign parameter.

4.6.1 Exposure of Study Medication

Exposure to study drug will be summarized including number of patients with one or two doses and number of patients with dose modification by treatment group.

A listing of patients by treatment group will be prepared detailing dosing of study drug, volume administered and any dose modification.

4.6.2 Adverse Events

Medical Dictionary for Regulatory Activities (MedDRA) will be used as the thesaurus for AEs and disease codes, and the WHO Drug Global B3 Format dictionary will be used for treatments. A glossary of these codes will be produced.

Only treatment-emergent AEs will be summarized. Treatment-emergent events are defined as those AEs with observed or imputed onset date on or after the start date of study treatment. Only where the most extreme intensity is greater than the initial intensity (or if most extreme intensity is not missing and initial intensity is missing) will events with an onset date prior to the start of trial treatment be considered treatment-emergent. An AE with a completely missing start date will be assumed to be treatment-emergent unless the AE has a complete non-imputed end date that is prior to study Day 1.

Adverse events will be coded and tabulated by system organ class (SOC), and/or preferred term (PT) and treatment arm. In tabulations, PTs and their associated SOC will be presented in order of descending frequency summed across the treatment arms.

Adverse events will also be tabulated by severity, as graded according to NCI CTCAE v5.0 scale, and relationship to study medication as indicated by the investigator.

The following will also be summarized:

- serious adverse events
- adverse events leading to withdrawal of study drug
- adverse events leading to discontinuation from the study
- adverse events leading to death
- hypersensitivity adverse events (adverse events occurring during or within 24 hours of the end of an infusion that are deemed “related” to study treatment)

Adverse events of special interest will be defined using SOC, published Standard MedDRA Queries (SMQs) or AE Grouped Terms (AEGTs) defined by Roche Drug Safety. The groupings of AEs will include but may not be limited to the following:

- Infections (Infections and Infestations SOC)
- Opportunistic infections (Roche Standard AEGT Basket)
- Malignancies (Malignant or Unspecified tumors SMQ Narrow)
- Hepatic events (Hepatic failure, Fibrosis, and Cirrhosis and Other Liver Damage-related Conditions SMQ Wide or Hepatitis, non-infectious SMQ Wide)
- Stroke (Ischemic Cerebrovascular Conditions SMQ Wide or Hemorrhagic Cerebrovascular SMQ Wide)
- Myocardial infarction [MI] (MI SMQ Wide)
- Anaphylactic reaction events (utilizing Roche Standard AEGT Basket according to Sampson’s criteria) [Sampson et al. 2006] occurring during or within 24 hours of the end of tocilizumab infusion; and a separate summary using the Anaphylactic Reaction SMQ Narrow for events occurring during or within 24 hours of the end of tocilizumab infusion)
- Gastrointestinal perforations (Gastrointestinal perforation SMQ Wide)
- Bleeding events (Hemorrhages SMQ Wide)
- Demyelinating events (Demyelination SMQ Narrow)

A glossary showing the mapping of investigator verbatim terms to preferred terms will be produced for all AEs included in the analysis. For each AE of special interest table based on SMQs/AEGTs, a corresponding listing of the preferred terms that comprise the SMQ will be produced.

Listings of AEs and SAEs will be produced. Adverse events of special interest will also be listed.

Listings and summary tables for post-treatment acute kidney injury (defined by 50% increase of creatinine from baseline) will be produced.

The exposure duration in days on study (exposure duration is the date of the last safety assessment or death if present, minus the date of the first dose of TCZ plus one divided by 365.25) will be summarized.

4.6.3 Laboratory Data

Summary tables will detail the actual values and changes from baseline of the laboratory parameters to post baseline by treatment arm. Arterial blood gases will be summarized separately.

Patients with values outside the reference normal ranges will be listed. A listing of all pregnancies will be presented.

Inflammatory markers hs-CRP, CRP, D-dimer, and ferritin will be analyzed by the methods in Section 4.5.4.

4.6.4 Oxygen Saturation and Vital Signs

Summary statistics on absolute values and their change from baseline for all observed vital signs (diastolic blood pressures, systolic blood pressures, respiratory rate, pulse rate, body temperature and peripheral oxygen saturation) will be presented over time by treatment group. Additionally, a graphical representation of means over time of oxygen saturation and temperature (daily to Day 28) will be presented by treatment group.

For patients requiring supplemental oxygen, summary statistics on absolute values of the oxygen flow rate (L/min) and/or fraction of inspired oxygen (FiO2) will be produced by visit/ time point and treatment group.

The level of consciousness will be summarized over time.

The number and proportion of patients requiring oxygen supplementation or other form of ventilation will be summarized over time, including type of support given. Noninvasive mechanical ventilation will be summarized overall as well as by its component types (continuous positive airway pressure [CPAP], bi-level positive airway pressure [BiPAP], other). Invasive mechanical ventilation will also be summarized overall and by component types (Endotracheal tube, tracheostomy tube).

A listing of patients with chest X-ray, CT scans and ECGs (as a separate listing) with clinically significant abnormalities will be produced.

4.7 INTERIM ANALYSES

No interim efficacy analyses have been planned. Safety reviews by the IMC will be performed according to the IMC agreement (See Section 3.2).

5. REFERENCES

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391–7.

Xu X, Han M, Li, T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Submitted manuscript. [Resource on the internet]. 2020 [updated 5 March 2020; cited 17 March 2020]. Available from: http://www.chinaxiv.org/abs/202003.00026.

Appendix 1 Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF TOCILIZUMAB IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA**
PROTOCOL NUMBER:	ML42528
VERSION NUMBER:	3
EUDRACT NUMBER:	2020-001154-22
IND NUMBER:	148225
NCT NUMBER:	NCT04372186
TEST PRODUCT:	Tocilizumab (RO4877533)
PHASE:	Phase III
INDICATION:	COVID-19 pneumonia
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

This study will evaluate the efficacy and safety of tocilizumab (TCZ) compared with a placebo in combination with SOC in hospitalized patients with COVID-19 pneumonia. To enhance the understanding of the clinical profile of tocilizumab for patients who belong to high-risk and minority populations, an emphasis will be placed on including minority-enrolling sites. Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with standard of care (SOC) for the treatment of COVID-19 pneumonia on the basis of the following endpoint:

- Cumulative proportion of patients with death or requiring mechanical ventilation by Day 28

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status
- Time to clinical failure, defined as the time to death, mechanical ventilation, intensive care unit (ICU) admission, or withdrawal (whichever occurs first)
- Mortality rate by Day 28
- Time to hospital discharge or “ready for discharge” (e.g., awaiting social disposition) as evidenced by, for example, normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Change from baseline in inflammatory markers levels (high sensitivity C-reactive protein [hs-CRP]/C-reactive protein [CRP], D-dimer, and ferritin) over time
- Cumulative proportion of patients requiring CPAP or BIPAP by Day 28

Safety Objective

The safety objective for this study is to evaluate the safety of TCZ compared with placebo in combination with SOC for the treatment of COVID-19 pneumonia on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0
- Incidence of any post-treatment bacterial and/or fungal infection
- Incidence of any post-treatment acute kidney injury (defined by 50% increase of creatinine from baseline)

STUDY DESIGN

Description of the Study

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of TCZ in combination with SOC compared with placebo in combination with SOC in hospitalized adult patients with COVID-19. The Sponsor intends to enroll approximately 379 patients that have been diagnosed with COVID-19 pneumonia and meet the entry criteria.

Patients must be at least 18 years of age with confirmed SARS-CoV-2 (COVID-19) infection per World Health Organization (WHO) criteria, including a positive polymerase chain reaction (PCR) of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have $SpO_2 < 94\%$ on ambient air and be on SOC, which may include anti-viral treatment, low dose systemic corticosteroids, and supportive care.

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. Patients with active tuberculosis (TB) or suspected active bacterial, fungal, viral, or other infection (besides COVID-19 and well-controlled HIV) will be excluded from the study.

Patients will be screened and randomized within 96 hours of hospital admission. Patients will be randomized at a 2:1 ratio to receive blinded treatment of either TCZ or placebo, respectively. Study treatment must be given within approximately 4 hours after randomization. TCZ and placebo will be given in combination with SOC.

Patients assigned to the TCZ arm will receive one infusion of TCZ 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the placebo arm will receive one infusion of placebo, both in addition to SOC.

If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion. Note: Pre-dose assessments must be repeated and reviewed before an additional infusion of blinded treatment of TCZ or placebo is administered.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity within 96 hours of hospital admission (for a total of 2 screenings per participant) at the investigator's discretion. Patients are not required to re-sign the consent form if they are re-screened within 7 days after previously signing the consent form. The investigator will record the reasons for screen failure in the screening log.

The study assessments to be conducted include the following: physical examination, vital signs, oxygen saturation, assessment of consciousness, presence and absence of respiratory support, adverse events, concomitant therapies, and clinical laboratory tests.

Patients will be followed up for a total of 60 days after first dose of study medication.

If patients are discharged from the hospital prior to Day 28 or discontinue the study, the Study Completion/Discontinuation assessments are to be conducted prior to discharge or at discontinuation from the study. In addition, if patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. Follow-up visits may be conducted by onsite clinic visits, telephone calls, or home visits. After Day 28, all patients should have a follow-up visit on approximately Day 60 which may be conducted as an onsite clinic visit, telephone call, or home visit for discharged patients.

During the study, standard supportive care will be given according to clinical practice. After study completion, patients should be referred to their regular healthcare provider based on their doctor's decision and as part of standard of care.

Number of Patients

This study aims to enroll approximately 379 hospitalized patients with COVID-19 pneumonia.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Documented informed consent by any patient capable of giving consent, or, when the patient is not capable of giving consent, by his or her legal/authorized representative
- Age ≥18 years at time of providing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Hospitalized
- COVID-19 pneumonia confirmed per a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid) and radiographic imaging (CT scan or chest X-ray)
- Able to complete screening within 96 hours of hospital admission
- Blood oxygen saturation (SpO_2) <94% while on ambient air

  If a patient is on supplemental oxygen with SpO_2 ≥94%, but desaturation to <94% on lower supplemental oxygen or ambient air is documented during screening, the inclusion criterion is met.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of <1% per year during the treatment period and for 90 days after the final dose of study drug. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis).

  Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential or pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 60 days after the final dose of study drug to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of preventing drug exposure. If required per local guidelines or regulations, information about the reliability of abstinence will be described in the local Informed Consent Form.

Exclusion Criteria

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

- Known severe allergic reactions to TCZ or other monoclonal antibodies
- Require CPAP, BIPAP, or mechanical ventilation
- Active TB infection or last TB infection within 1 month of randomization
- Suspected active bacterial, fungal, viral, or other infection (besides COVID-19 and well-controlled HIV)
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
- Immunocompromised (besides well-controlled HIV) or on immunosuppressive therapy (except for steroids for COVID), advanced cancer
- Have received oral anti-rejection or immunomodulatory drugs (including TCZ) within the past 3 months
- Participating in another IL-6 antagonist clinical trial or other drug clinical trials (participation in COVID-19 anti-viral trials may be permitted if approved by Medical Monitor)
- ALT or AST $>$5 x upper limit of normal (ULN) detected within 24 hours at screening (according to local laboratory reference ranges)
- ANC $<$1000/μL at screening (according to local laboratory reference ranges)
- Platelet count $<$50,000/μL at screening (according to local laboratory reference ranges)
- Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
- Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (investigational COVID-19 antivirals may be permitted if approved by Medical Monitor)
- Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study
- Any history of diverticulitis or gastrointestinal perforation

The use of remdesivir, hydroxychloroquine, chloroquine, and convalescent plasma, is not an exclusion to participation in this trial, and is left to the discretion of the primary medical team.

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for last follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 2 months after the last patient is enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 8 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

Patients assigned to the active arm will receive one or two doses of tocilizumab (TCZ) via intravenous (IV) infusion at a dose of 8 mg/kg IV to a maximum of 800 mg per dose.

Comparator

Patients assigned to the comparator arm will receive one or two doses of placebo via IV infusion.

Statistical Methods

Primary Analysis

The primary efficacy objective for this study is to evaluate the efficacy of TCZ plus standard of care, compared with placebo plus standard of care using the following endpoint:

- Cumulative proportion of patients with death or requiring mechanical ventilation by Day 28

Time to death or the first utilization of mechanical ventilation after randomization will be compared between the TCZ group and the placebo group using the stratified log-rank test with age group (age ≤60, age >60 years) as the stratification factor. The cumulative proportion of patients with death or requiring mechanical ventilation at Day 28 will be estimated using the Kaplan-Meier method.

Details of the primary endpoint analysis will be included in the Statistical Analysis Plan (SAP).

Determination of Sample Size

The estimated sample size was determined based on the time from randomization to the first utilization of mechanical ventilation by Day 28.

The total modified intent-to-treat (mITT) sample size of 379 patients with a 2:1 randomization of TCZ (n=253) to placebo (n=126) provides approximately 80% power using a Logrank test to detect a 15% difference between treatment groups in time to death or mechanical ventilation by Day 28 under the following assumptions: cumulative survival (i.e., alive and not requiring mechanical ventilation) rates of 75% in the TCZ group and 60% in placebo group, with 28-day follow-up, using a two-sided 5% alpha, and 10% dropout rate in each arm. Sample size re-estimation may be considered during the study based on updated assumptions of the treatment effect.

Planned Interim Analyses

An Internal Monitoring Committee (IMC) will evaluate safety according to procedures and guidelines detailed in the IMC agreement. The IMC will consist of Sponsor representatives who will not be blinded to study data. Details of the safety reviews will be provided in the SAP.

Appendix 2 Schedule of Activities: Days 1 and 2

	Screening [a, b]	Baseline		
Study Day	−4 to 0	1		2
Time Post Initial Treatment (Assessment Window)		0 min Pre-dose (approx. −4 hrs)	15 min After end of infusion (approx. +1 hr)	24 hrs (±12 hrs)
Informed consent	x			
Inclusion/exclusion criteria	x	x		
Demographic data	x			
Randomization		x		
Medical history	x			
Complete physical examination [c, d]	x			
Weight	x			
COVID-19 diagnosis [e]	x			
Chest X-ray/CT scan [d, f]	x			
ECG	x			
Pregnancy test [d, g]	x			
PaO_2/FiO_2 [d, h]	x (optional)	← Optional →		
SpO_2 [d, i]	x	x	x	x
Vital signs [d, i]	x	x	x	x
Ordinal scoring (including ventilation requirement) [j]		x		x
Adverse events [k]		x		x
Concomitant medications [l]		x		x
Hematology [d, m]	x			x

	Screening [a, b]	Baseline		
Study Day	−4 to 0	1		2
Time Post Initial Treatment (Assessment Window)		0 min Pre-dose (approx. −4 hrs)	15 min After end of infusion (approx. +1 hr)	24 hrs (±12 hrs)
Chemistry [d, n]	x			x
hs-CRP/CRP, D-dimer (if available via local laboratory), and ferritin [d]	x			
Study drug administration [o]		x		

ALP=alkaline phosphatase; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; eCRF=electronic case report form; hr(s)=hour(s); hs-CRP=high sensitivity C-reactive protein; min=minutes; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0; PaO_2/FiO_2=arterial oxygen partial pressure/fraction of inspired oxygen; SpO_2=peripheral capillary oxygen saturation; TCZ=tocilizumab.

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] Results from standard-of-care tests or examinations performed prior to obtaining informed consent and within 96 hours before randomization may be used; such tests do not need to be repeated for screening.

[b] Informed consent must be documented before any study-specific screening procedure is performed.

[c] A complete physical examination, performed at screening and per the investigator's discretion during the study, includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, respiratory, gastrointestinal, and neurologic systems. Any abnormality identified at screening should be recorded on the General Medical History and Baseline Conditions eCRF. New or worsened clinically significant abnormalities identified during the study should be reported as adverse events.

[d] Physical examination, blood tests, and other assessments conducted after arrival at the hospital, but before the informed consent is signed, can be used as screening assessments.

[e] COVID-19 test (SARS-CoV2 PCR) to confirm diagnosis should be performed at or before screening (if testing is conducted before screening, documentation must be available).

[f] Screening chest X-ray or CT scans should be performed within 96 hours prior to randomization. If additional chest X-rays/CT scans are taken per local practice during the study, this information should be provided in the eCRF.

[g] For women of childbearing potential, including those who have had a tubal ligation, positive urine test results will be confirmed with a serum pregnancy test. Study drug infusion must not be administered unless the serum pregnancy test result is negative.

[h] If arterial blood gases are measured.

[i] All vital sign measurements (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressures, and body temperature) and oxygen saturation should be recorded together once daily while the patient remains hospitalized. If measured more than once daily, the worst values (highest temperature, respiratory rate, and heart rate; lowest blood pressure, oxygen saturation, and consciousness level) during that period should be recorded on the eCRF.

[j] Assessment of clinical status using the ordinal scale, which includes change in ventilation usage (non-invasive or mechanical), should be recorded at baseline on Day 1 then again daily every morning (between approximately 8 am and 12 pm) for patients who remain hospitalized.

[k] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 60 days after the final dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[l] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit.

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).

[n] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total bilirubin, ALP, ALT, and AST.

[o] The initial study drug infusion should be given within approximately 4 hours of randomization. If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion. Note: Pre-dose assessments must be repeated and reviewed before an additional infusion of blinded treatment of TCZ or placebo is administered.

Appendix 3 Schedule of Activities: Day 3–Study Completion

	Days 3–28 [a]																									Study Completion/ Discontinuation [i]
Study Day	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 [i]	
Vital signs [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PaO_2/FiO_2 [c]	← Optional →																										(optional)
SpO_2 [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ordinal scoring [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [e]	←																									→	x
Concomitant medications [f]	←																									→	x
Hematology [g]																										x	x
Chemistry [h]																										x	x
hs-CRP/CRP, D-dimer (if available via local laboratory), and ferritin																										x	x

ALP=alkaline phosphatase; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; eCRF=electronic case report form; hs-CRP=high sensitivity C-reactive protein; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0; $PaO_2/FiO2$=arterial oxygen partial pressure/fraction of inspired oxygen; SpO_2=peripheral capillary oxygen saturation.

[a] If patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. Follow-up visits may be conducted by onsite clinic visits, telephone calls, or home visits.

[b] All vital sign measurements (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressures, and body temperature) and oxygen saturation should be recorded together once daily while the patient remains hospitalized. If measured more than once daily, the worst values (highest temperature, respiratory rate, and heart rate; lowest blood pressure, oxygen saturation, and consciousness level) during that period should be recorded on the eCRF.

[c] If arterial blood gases are measured.

[d] Assessment of clinical status using the ordinal scale should be recorded at baseline on Day 1 then again daily for patients who remain hospitalized.

[e] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 60 days after the final dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6).

[f] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit.

[g] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes).

[h] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total bilirubin, ALP, ALT, and AST.

[i] If patients are discharged from the hospital prior to Day 28 or discontinue the study, the Study Completion/Discontinuation assessments are to be conducted prior to discharge or at discontinuation from the study. In addition, if patients are discharged from the hospital prior to Day 28, follow-up visits should occur weekly, or more often if clinically relevant, through Day 28 to assess mortality and adverse events. The Day 60 follow up may be conducted by an onsite clinic visit, telephone call, or home visit for discharged patients. Day 60 follow up is required to collect adverse events only.

Statistical Analysis Plan Update Rationale

The statistical analysis plan ML42528 Version 2 includes the following updates from Version 1:

- Key secondary endpoints were updated
- The Type I error control section was added to specify a hierarchy for testing of the primary endpoint followed by testing of the predefined key secondary endpoints
- Cumulative Incidence Function plots were specified for time to 'improvement' secondary endpoints
- The censoring rules for the time to event endpoints were updated
- Derivation of the time to clinical failure endpoint was clarified
- Pre-specification of the stratified efficacy analyses to include only the age randomization strata
- Definition of baseline was added
- Additional subgroup analyses for race/ethnicity combined category and elevated CRP were added
- Appendices 1, 2, and 3 were updated to be consistent with the current protocol version 3

Additional minor changes have been made to improve clarity and consistency.