PROTOCOL

TITLE:	**A PHASE II, OPEN-LABEL, RANDOMIZED, MULTICENTER STUDY TO INVESTIGATE THE PHARMACODYNAMICS, PHARMACOKINETICS, SAFETY, AND EFFICACY OF 8 mg/kg OR 4 mg/kg INTRAVENOUS TOCILIZUMAB IN PATIENTS WITH MODERATE TO SEVERE COVID-19 PNEUMONIA**
PROTOCOL NUMBER:	CA42481
VERSION NUMBER:	2
IND NUMBER:	148225
NCT NUMBER:	*NCT04363736*
TEST PRODUCT:	Tocilizumab (RO4877533)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below.

FINAL PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
15-May-2020 13:33:01	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
1	15 April 2020

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol CA42481 has been amended in response to feedback from the U.S. Food and Drug Administration. Changes to the protocol, along with a rationale for each change, are summarized below:

- The primary pharmacodynamic (PD) endpoint—PD response to tocilizumab (TCZ) treatment, as measured by C-reactive protein (CRP) level at Day 7—has been deleted. In addition, the secondary clinical efficacy endpoints have been changed to exploratory endpoints (Section 2.4).
- Day 7 has been included as a timepoint to the exploratory endpoint of clinical status, assessed using a 7-category ordinal scale in addition to Days 14 and 28 (Section 2.4).
- The pharmacokinetic (PK) endpoint of the association between TCZ pharmacokinetics and CRP, interleukin-6, soluble IL-6 receptor, and ferritin has been moved from Section 2.2 and included as an exploratory biomarker endpoint in Section 2.5.
- Figure 1, the study schema, has been revised to reflect clinical outcomes at Day 28, and reference to the primary efficacy endpoint was removed (Section 3.1.1).
- The rationale section for TCZ has been revised and text justifying CRP levels as a biomarker surrogate for the primary efficacy endpoint deleted (Section 3.2.2).
- The determination of sample size (Section 6.1) has been updated. The figure depicting the total sample (n) to declare the 4-mg/kg dose non-inferior to the 8-mg/kg dose at Day 7 posttreatment has been deleted.
- As a result of the efficacy endpoints being changed to exploratory endpoints, PD analyses (Section 6.4) specifying that model adjustments and sensitivity analyses of different populations have deleted.
- The requirements for the scheduling of periodic safety reviews have been clarified (Section 6.9.1). The planned optional interim analysis has been removed (Section 6.9.2).

In addition, the following changes have been made:

- The Protocol Synopsis was revised based on amended changes made to the protocol.
- The background section (Section 1.4) on the real-world experience with TCZ treatment in the treatment of COVID-19 pneumonia has been revised and updated.
- The inclusion criterion requiring patient hospitalization with COVID-19 pneumonia confirmed by a positive polymerase chain reaction of any specimen (e.g., respiratory, blood, urine, stool, or other bodily fluids) and evidence of pneumonia on chest X-ray or computed tomography scan has been clarified, such that the onset of patient symptoms must be at least 3 days prior to enrollment (Section 4.1.1).

- Additional instructions permitting the signing and dating of the Informed Consent Form by the patient or the patient's legally authorized representative, or where allowed, health care consent on behalf of the patient have been included (Section 4.5.1). Furthermore, where allowed, verbal consent may be given by the patient or the patient's legally authorized representative and this must be documented by the investigator or authorized designee.
- Reference to serum exploratory biomarkers samples has been corrected to include plasma samples (Section 4.5.6 and Appendices 1, 2, and 3).
- The contact information for the primary Medical Monitor has been updated (Section 5.4.1).
- References have been revised (Section 10).
- The schedule of activities to be performed on Days 1 and 2 (Appendix 1) has been corrected to remove assessments inadvertently repeated on Day 1 postinfusion (e.g., review of eligibility criteria, randomization, medical history). In addition, the Day 2 assessments have been revised to now include review of adverse events and concomitant medications, hematology, and chemistry panel, and ordinal scoring.
- The schedule of activities to be performed on Days 2 and 3 (Appendix 2) has been revised to clarify study completion assessments column is for early study or treatment discontinuation. A serum PK sample has been added on Day 3.
- The schedule of activities after Day 28 (Appendix 3) has been revised to include sample collection for viral load, peripheral blood mononuclear cells, and blood for RNA analysis at Day 60 (the study completion visit).

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 PHASE II, OPEN-LABEL, RANDOMIZED, MULTICENTER STUDY TO INVESTIGATE THE PHARMACODYNAMICS, PHARMACOKINETICS, SAFETY, AND EFFICACY OF 8 mg/kg OR 4 mg/kg INTRAVENOUS TOCILIZUMAB IN PATIENTS WITH MODERATE TO SEVERE 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 of the signed form as instructed by your local monitor.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, OPEN-LABEL, RANDOMIZED, MULTICENTER STUDY TO INVESTIGATE THE PHARMACODYNAMICS, PHARMACOKINETICS, SAFETY, AND EFFICACY OF 8 mg/kg OR 4 mg/kg INTRAVENOUS TOCILIZUMAB IN PATIENTS WITH MODERATE TO SEVERE COVID-19 PNEUMONIA**
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IND NUMBER:	148225
NCT NUMBER:	*NCT04363736*
TEST PRODUCT:	Tocilizumab (RO4877533)
PHASE:	Phase II
INDICATION:	Moderate to severe COVID-19 pneumonia
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This Phase II study will investigate the pharmacodynamics, pharmacokinetics, safety, and efficacy of tocilizumab (TCZ) at two different doses in combination with standard-of-care (SOC) treatment in hospitalized patients with moderate to severe COVID-19 pneumonia. Specific objectives and corresponding endpoints for the study are outlined below.

Pharmacodynamic Objective

The *pharmacodynamic (PD) objective* for this study is to *assess* the *differences between two* doses of TCZ in combination with SOC for the treatment of moderate to severe COVID-19 pneumonia on the basis of the following endpoints:

- Serum concentrations of interleukin-6 (IL-6), soluble interleukin-6 receptor (sIL-6R), ferritin, and C-reactive protein (CRP) following administration of 8 mg/kg and 4 mg/kg IV TCZ at specified timepoints

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to *characterize* the pharmacokinetics of two different doses of TCZ in combination with SOC for the treatment of moderate to severe COVID-19 pneumonia on the basis of the following endpoints:

- Serum concentrations of TCZ following administration of 8 mg/kg and 4 mg/kg IV TCZ at specified timepoints

Safety Objective

The safety objective for this study is to compare the safety of two different doses of TCZ in combination with SOC for the treatment of moderate to severe 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, Version 5.0 (NCI CTCAE v5.0)

- *Severe acute respiratory syndrome corona virus 2* (SARS-CoV-2) (COVID-19) viral load over time, as collected by nasopharyngeal swab and bronchoalveolar lavage (BAL) samples (if applicable)
- Time to real-time polymerase chain reaction (RT-PCR) virus negativity
- The proportion of patients with any posttreatment infection
- Change from baseline in targeted clinical laboratory test results

Exploratory Objective

The exploratory objective for this study is to *assess* the efficacy of two different doses of TCZ in combination with SOC for the treatment of moderate to severe COVID-19 pneumonia on the basis of the following *endpoints*:

- Clinical status, as assessed using a 7-category ordinal scale at Days *7*, 14, and 28
- Time to clinical improvement, defined as a National Early Warning Score 2 (NEWS2) *score* of $\leq$2 maintained for 24 hours
- Time to improvement in at least two categories relative to baseline on a 7-category ordinal scale of clinical status
- Duration of supplemental oxygen use
- Incidence of intensive care unit (ICU) stays
- Incidence of mechanical ventilation
- Duration of ICU stay
- Time to clinical failure, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first)

  For patients entering the study already in an ICU, clinical failure is defined as a one-category worsening on the ordinal scale, withdrawal, or death.
- Mortality rate at Days 7, 14, 21, 28, and 60
- Time to hospital discharge or "ready for discharge" (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or $\leq$2 L supplemental oxygen)
- Frequency of the addition of a second dose of TCZ (8 mg/kg or 4 mg/kg) at the discretion of the treating physician
- Ventilator-free days from baseline to Day 28
- Organ failure–free days from baseline to Day 28

Exploratory Biomarker Objective

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that could provide further evidence of TCZ pharmacologic activity (i.e., mechanism of action), on the basis of the following *endpoints*:

- Assessments of *exploratory* biomarkers in relation to efficacy, exposure, and in both blood and tissue-derived samples
- *Association between TCZ pharmacokinetics and the following PD biomarkers: CRP, IL-6, sIL-6R, and ferritin*

Study Design

Description of Study

This is a Phase II, open-label, randomized, multicenter study to assess the pharmacodynamics, pharmacokinetics, safety and efficacy of two different doses of TCZ in combination with SOC in hospitalized adult patients with moderate to severe COVID-19 pneumonia. The Sponsor intends to enroll approximately 100 patients who have been diagnosed with COVID-19 pneumonia who meet the eligibility criteria at U.S. sites.

Patients must be at least 18 years old with confirmed SARS-CoV-2 (COVID-19) pneumonia per the World Health Organization criteria, including a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, *or* other bodily fluids). At the time of enrollment, patients must be hospitalized and have respiratory symptoms and radiologic findings of pneumonia. Patients with severe COVID-19 pneumonia must have $SpO_2 \leq 93\%$ or $PaO_2/FiO_2 < 300$ mmHg despite receiving SOC treatment, which may include anti-viral treatment, low-dose steroids, and supportive care. Patients with moderate COVID-19 pneumonia are hospitalized patients not meeting the criteria of severe COVID-19 pneumonia and with CRP $> 2 \times$ the upper limit of normal (ULN). For both *patients with* moderate and severe COVID-19, the onset of patient symptoms must be at least 3 days prior to enrollment.

Patients who are on a mechanical ventilator $>$ 24 hours or extracorporeal membrane oxygenation (ECMO), in shock, or a combination thereof with other organ failure requiring treatment in an ICU will be excluded from the study. Patients for 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 TB or suspected active bacterial, fungal, viral, or other infection (other than COVID-19 pneumonia) will be excluded from the study.

Patients will be randomized as soon as possible after screening in a 1:1 ratio to receive treatment with either 8 mg/kg or 4 mg/kg IV TCZ. Study treatment must be given in combination with SOC treatment.

Patients assigned to the 8-mg/kg TCZ arm will receive one IV infusion of 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the 4-mg/kg TCZ arm will receive one IV infusion of 4 mg/kg TCZ. In addition, patients in both arms will receive SOC treatment.

For patients in both arms, if a patient *has a sustained fever or clinically significant worsening of signs or symptoms (e.g., an increased supplemental oxygen requirement*), one additional infusion of TCZ at the same dose as the initial infusion can be given within 8 to 24 hours after the initial *TCZ* 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 two 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 study assessments to be conducted include the following: complete and limited physical examinations, measurement of vital signs and oxygen saturation, assessment of consciousness, presence and absence of respiratory support, adverse events, concomitant therapies, clinical laboratory tests, and nasopharyngeal swabs.

Patients will be followed for a total of 60 days after the first dose of study drug.

If patients are discharged from the hospital prior to Day 28, follow-up visits should occur twice weekly through Day 28. Patients are encouraged to return for onsite visits at least weekly if possible; other follow-up visits may be conducted by telephone or home visits. Patients should return to the site for the Day 28 visit. After Day 28, all patients should have follow-up visits on Days 35, 45, and 60; the Day 35 and 45 visits may be conducted by telephone or by home visits for *patients who are* discharged, while the Day 60 visit should be conducted onsite.

During the study, standard supportive care will be given according to clinical practice.

Number of Patients

Approximately 100 patients will be enrolled in this study.

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 legally authorized representative
- Age $\geq$ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol

- Hospitalization with COVID-19 pneumonia confirmed by a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, *or* other bodily fluids) and evidence of pneumonia on chest X-ray or computed tomography scan

  The onset of patient symptoms must be at least 3 days prior to enrollment.
- For severe patients, $SpO_2 \leq 93\%$ or $PaO_2/FiO_2 < 300$ mmHg

  If a patient is on supplemental oxygen with $SpO_2 > 93\%$, but desaturation to $\leq 93\%$ on lower supplemental oxygen or ambient air is documented during screening, the inclusion criterion is met.
- For moderate patients (those who do not qualify as severe based oxygen requirements), CRP $> 2 \times$ ULN is required
- 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 TCZ. 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). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  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 TCZ 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.

<u>Exclusion Criteria</u>

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

- Known severe allergic reactions to TCZ or other monoclonal antibodies
- Active TB infection
- Suspected active bacterial, fungal, viral, or other infection (besides SARS-CoV-2)
- Patients who *meet any of the following at the time of randomization*: on a mechanical ventilator > 24 hours, *on* ECMO, in shock, or with other organ failure requiring treatment in an ICU
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments

- Receipt of oral anti-rejection or immunomodulatory drugs (including TCZ) within the past 3 months
- Participation in other drug clinical trials (participation in COVID-19 anti-viral trials may be permitted if confirmed by the Medical Monitor)
- ALT or AST $> 10 \times$ ULN detected within 24 hours at screening or at baseline (according to local laboratory reference ranges)
- ANC $< 1000/\mu L$ at screening and baseline (according to local laboratory reference ranges)
- Platelet count $< 50{,}000/\mu L$ at screening and baseline (according to local laboratory reference ranges)
- Pregnancy or breastfeeding, or positive pregnancy test at a predose examination
- Treatment with an investigational drug within 5 drug-elimination half-lives or 30 days (whichever is longer) of randomization (investigational SARS-CoV-2 [COVID-19]) anti-viral agents may be permitted after consultation with the 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

End of Study

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last datapoint required for the 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 4 months.

Investigational Medicinal Products

The investigational medicinal product for this study is TCZ.

Test Products (Investigational Drugs)

Patients assigned to the 4-mg/kg arm will receive the 4-mg/kg TCZ dose by IV infusion. The dose of TCZ infusion will be calculated on the basis of body weight measured prior to infusion. One additional infusion of TCZ can be given within 8 to 24 hours after the initial infusion.

Comparator

Patients assigned to the 8-mg/kg arm will receive the 8-mg/kg TCZ dose by IV infusion. The dose of TCZ infusion will be calculated on the basis of body weight measured prior to infusion. One additional infusion of TCZ can be given within 8 to 24 hours after the initial infusion.

Statistical Methods

PD Analysis

The PD outcome measures for this study are serum IL-6, sIL-6R, ferritin, and CRP levels at baseline and at specified timepoints after initiation of study drug. Data for all PD biomarkers will be presented using descriptive summary statistics, including the mean, median, range, standard deviation (SD), and coefficient of variation.

PK Analyses

The PK analysis population will consist of patients with sufficient data to enable estimation of key parameters (e.g., area under the concentration–curve [AUC], maximum serum concentration observed [C_{max}]), with patients grouped according to treatment received.

Non-linear mixed effects modeling will be used to analyze the serum TCZ concentration over time data collected in this study using existing population-PK models. Individual and mean serum TCZ concentration versus time data will be tabulated and plotted by dose level. The serum pharmacokinetics of TCZ will be summarized by estimating the total exposure (AUC), C_{max}, total clearance, and volume of

distribution. Estimates for these parameters will be tabulated and summarized (mean, SD, co-efficient of variation, median, minimum, and maximum). Interpatient variability will be evaluated.

Additional PK analyses will be conducted as appropriate. The PK parameters derived from these analyses may be used for exploratory graphical analyses of the PD parameters.

Determination of Sample Size

The purpose of this *open-label* study *is the comparison of TCZ pharmacokinetics* and *PK-*PD *relationship* between two doses of TCZ (8 and 4 mg/kg) in hospitalized patients with moderate to severe COVID-19 pneumonia. *The comparison will be assessed using modeling and evaluating the safety and efficacy measures between* Day *1 and Day 28 postrandomization. Data from the follow-up period from Days 28 to 60 may also be assessed. Approximately* 100 patients will be enrolled and randomized in a 1:1 ratio to the 8-mg/kg and 4-mg/kg IV TCZ arms in this study. *Disease severity type will also be stratified into moderate and severe COVID pneumonia, giving an overall equal four-way split between the two doses and type of disease severity and resulting in four groups of approximately 25* patients *each. Patients may receive* a *repeat* dose *within 8 to 24 hours after the first TCZ dose if clinicians judge it is necessary (resulting in a TCZ* dose *range from 4 to 16 mg/kg, with a maximum* dose *of 800 mg*). The *variability of PK parameters of TCZ in a heterogeneous COVID-19 population* in *an acute setting is unknown*; however, *20 to 30 patients is deemed adequate considering the between-subject variability in health volunteers and patients with RA provided by population-PK modeling. Data quality issues, patient dropouts, and early hospital discharge may all lead to missing data, especially in a pandemic setting; thus, enrolling 50 patients according to dose and disease severity type (25 per arm) may offset missing data and allow an adequate volume of PK and PD data to inform the population-*PK model *and allow a comparison of the 4- and 8-mg/kg doses.*

Interim Analysis

No interim analysis is planned for this study.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ARDS	acute respiratory distress syndrome
AUC	area under the concentration–time curve
BAL	bronchoalveolar lavage
CAR	chimeric antigen receptor
C_{max}	maximum serum concentration observed
CoV	coronavirus
CRP	C-reactive protein
CRS	cytokine-release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
eCRF	electronic Case Report Form
ECMO	extracorporeal membrane oxygenation
EDC	electronic data capture
FDA	(U.S.) Food and Drug Administration
FiO_2	fraction of inspired oxygen
GCA	giant cell arteritis
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
ICU	intensive care unit
IL-6	interleukin-6
IL-6R	interleukin-6 receptor
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
MedDRA	*Medical Dictionary for Regulatory Activities*
mIL-6R	*membrane-expressed IL-6R*
mITT	modified intent to treat (population)
NCI	National Cancer Institute
NEWS2	National Early Warning Score 2
NGS	next-generation sequencing
PaO_2	partial pressure of oxygen
PCR	polymerase chain reaction
PD	pharmacodynamic
PK	pharmacokinetic

Abbreviation	Definition
PY	patient-year
RA	rheumatoid arthritis
RT-PCR	real-time polymerase chain reaction
SARS-CoV(-2)	severe acute respiratory syndrome corona virus (strain) 2
SD	*standard deviation*
sIL6-R	soluble interleukin-6 receptor
sJIA	systemic juvenile idiopathic arthritis
SOC	standard of care
SpO_2	blood oxygen saturation
TAK	Takayasu arteritis
TB	tuberculosis
TCZ	tocilizumab
TTCI	time to clinical improvement
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 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 31 December 2019. The WHO subsequently declared a pandemic on 11 March 2020.

According to the WHO, as of 2 April 2020 more than 896,000 cases of COVID-19 infection were reported in more than 200 countries and territories worldwide, with more than 45,500 deaths (WHO 2020a). Up to approximately 20% of infected patients experience complications related to a severe form of interstitial pneumonia, which may progress to acute respiratory distress syndrome (ARDS) and/or multiple-organ failure and death (WHO 2020b).

To date, there is no vaccine and no specific anti-viral 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).

1.2 BACKGROUND ON TOCILIZUMAB

Tocilizumab (TCZ) is a recombinant humanized anti–human monoclonal antibody of the IgG1 subclass directed against soluble interleukin-6 receptor (sIL-6R) and membrane-bound IL-6R. TCZ binds specifically to both sIL-6R and membrane-bound IL-6R and has been shown to inhibit both soluble and membrane-bound IL-6R–mediated signaling. Interleukin-6 (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 physiologic 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 IV and 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.

The estimated cumulative clinical trial exposure to TCZ from the Development International Birth Date (IBD) (28 April 1997) and until 10 April 2019 (the data lock point for the Periodic Benefit–Risk Evaluation Report) was 24,826 patients (40154.98 patient-years [PYs]). Since the IBD (11 April 2005), the estimated cumulative market exposure to TCZ until 10 April 2019 was 1,301,050 patients (1,053,779 PYs). The combined cumulative postmarketing exposure of patients to IV TCZ is estimated to be 896,672 patients (726,347 PYs). The combined cumulative postmarketing exposure of patients to SC TCZ is 404,378 (327,432 PYs).

Refer to the Tocilizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.3 TOCILIZUMAB TREATMENT OF CYTOKINE-RELEASE SYNDROME WITH CAR T–CELL THERAPY

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

On 30 August 2017, the U.S. Food and Drug Administration (FDA) approved TCZ (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 an additional three doses may be given there is if no improvement of signs and 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 from patients treated with TCZ who developed CRS after treatment with tisagenlecleucel (Kymriah®) or axicabtagene ciloleucel (Yescarta®) in prospective clinical trials (Le et al. 2018). Of the 45 patients, 31 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 for a maximum of 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 with results from subgroup analyses of 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 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 administered at least 8 hours apart to patients with CRS.

TCZ is also approved for CAR T cell–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 from an initial 21-patient retrospective study in which patients with severe or critically ill patients with COVID-19 pneumonia were treated with TCZ (Xu et al. 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 on 3 March 2020. The Chinese Center for Disease Control and Prevention defined disease severity according to the following criteria:

- Severe disease: dyspnea, respiratory frequency $\geq$ 30/min, blood oxygen saturation (SpO_2) $\leq$ 93%, partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio (the ratio of blood pressure of oxygen [PaO_2] to the percentage of oxygen supplied [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 or multiple-organ failure; 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 administered to patients by IV infusion (which equates to between 4 and 8 mg/kg based on the body weight range of the Chinese adult population), with the maximum single dose of no more

than 800 mg. If clinical signs and 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 tuberculosis (TB), bacterial, or fungal infections.

Results from 21 Patients Treated with Tocilizumab in China

In February 2020, 21 patients with severe or critical COVID-19 pneumonia were treated with IV TCZ (400 mg) plus standard of care (SOC). The mean (±SD) age of patients was 56.8±16.5 years, ranging from 25 to 88 years. Seventeen patients (81.0%) were assessed as having severe cases and 4 patients (19.0%) were critical. Most patients (85%) presented with lymphopenia. C-reactive protein (CRP) levels were increased in all 20 patients (mean±SD, 75.06±66.80 mg/L). The median procalcitonin value was 0.33–0.78 ng/mL, and 2 of 20 patients (10.0%) presented with an abnormal value. The mean±*standard deviation* (SD) IL-6 level before TCZ treatment was 132.38±278.54 pg/mL (normal <7 pg/mL).

SOC consisted of lopinavir, methylprednisolone, other symptom relievers, and oxygen therapy, as recommended by the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (sixth revised edition). All 21 patients had received routine SOC treatment for 1 week before deteriorating with sustained fever, hypoxemia, and worsening on chest computed tomography (CT) scan.

Eighteen patients (85.7%) received TCZ once, and 3 patients (14.3%) had a second dose because of 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 1 patient needed no oxygen therapy. CT scans showed significant remission of opacities in both lungs in 19 of 20 patients (90.5%) after treatment with TCZ. The percentage of lymphocytes in peripheral blood, which was decreased in 85.0% of patients (17 of 20 patients) prior to treatment (mean±SD, 15.52±8.89%), returned to normal in 52.6% of patients (10 of 19 patients) on the fifth day after treatment. Abnormally elevated CRP levels decreased significantly in 84.2% of patients (16 of 19 patients). No adverse drug reactions and no subsequent pulmonary infections were reported.

Nineteen patients (90.5%) were discharged at the time of the report, including 2 critically *severe* patients. There were no deaths among the 21 treated patients.

The study's authors concluded that TCZ is an effective treatment for patients with severe COVID-19 pneumonia (Xu et al. 2020). *More recently, multiple prospective and retrospective studies have been conducted to describe the real-world experience with TCZ treatment of COVID-19 pneumonia (Alattar et al. 2020; Klopfenstein et al. 2020; Luo et al. 2020; Sciasci et al. 2020; Toniati et al. 2020).*

1.5 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

There are currently no drugs licensed for the treatment of patients with COVID-19 pneumonia. Given the results of studies outlined above, TCZ, along with SOC treatment, may 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. COVACTA (clinicaltrial.gov number NCT04320615) is an ongoing Phase III, randomized-controlled study evaluating the efficacy and safety of TCZ compared with placebo in patients with severe COVID-19 pneumonia. In the COVACTA study, the 8-mg/kg IV TCZ dose with an additional one infusion if clinical signs and symptoms worsen or do not improve was chosen based on the approved dose for CRS induced by CAR T–cell therapy in patients weighing ≥ 30 kg. The 21-patient study that supported the approval of TCZ in China used a fixed 400-mg dose of IV TCZ in combination with SOC treatment. Therefore, the optimal dose of TCZ in the treatment of COVID-19 is not known. This open-label, randomized study in combination with SOC will evaluate in hospitalized patients with COVID-19 pneumonia whether a lower dose of TCZ could show similar pharmacological effects of IL-6 pathway inhibition as the 8-mg/kg IV dose approved in CRS and is being evaluated in the COVACTA study.

2. OBJECTIVES AND ENDPOINTS

This Phase II study will investigate the pharmacodynamics, pharmacokinetics, safety, and efficacy of TCZ at two different doses in combination with SOC treatment in hospitalized patients with moderate to severe COVID-19 pneumonia. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 PHARMACODYNAMIC OBJECTIVE

The *pharmacodynamic (PD) objective* for this study is to *assess* the *differences between two* doses of TCZ in combination with SOC for the treatment of moderate to severe COVID-19 pneumonia on the basis of the following endpoints:

- Serum concentrations of IL-6, sIL-6R, ferritin, and CRP *following administration of 8 mg/kg and 4 mg/kg IV TCZ at specified timepoints (see Appendix 1, Appendix 2, and Appendix 3)*

2.2 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to *characterize* the pharmacokinetics of two different doses of TCZ in combination with SOC for the treatment of moderate to severe COVID-19 pneumonia on the basis of the following endpoints:

- *Serum concentrations of TCZ following administration of 8 mg/kg and 4 mg/kg IV TCZ at specified timepoints (see Appendix 1, Appendix 2, and Appendix 3)*

2.3 SAFETY OBJECTIVE

The safety objective for this study is to compare the safety of two different doses of TCZ in combination with SOC for the treatment of moderate to severe 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, Version 5.0 (NCI CTCAE v5.0)
- SARS-CoV-2 (COVID-19) viral load over time, as collected by nasopharyngeal swab and bronchoalveolar lavage (BAL) samples (if applicable)
- Time to real-time *polymerase chain reaction* (RT-PCR) virus negativity
- The proportion of patients with any posttreatment infection
- Change from baseline in targeted clinical laboratory test results

2.4 EXPLORATORY OBJECTIVE

The exploratory objective for this study is to *assess* the efficacy of two different doses of TCZ in combination with SOC for the treatment of moderate to severe COVID-19 pneumonia on the basis of the following endpoints:

- Clinical status, as assessed using a 7-category ordinal scale at Days 7, 14, and 28
- Time to clinical improvement (TTCI), defined as a National Early Warning Score 2 (NEWS2) *score* of ≤ 2 maintained for 24 hours
- Time to improvement in at least two categories relative to baseline on a 7-category ordinal scale of clinical status
- Duration of supplemental oxygen use
- Incidence of intensive care unit (ICU) stays
- Incidence of mechanical ventilation
- Duration of ICU stay
- Time to clinical failure, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first)

  For patients entering the study already in an ICU, clinical failure is defined as a one-category worsening on the ordinal scale, withdrawal, or death.
- Mortality rate at Days 7, 14, 21, 28, and 60
- Time to hospital discharge or “ready for discharge” (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2 L supplemental oxygen)
- Frequency of the addition of a second dose of TCZ (8 mg/kg or 4 mg/kg) at the discretion of the treating physician
- Ventilator-free days from baseline to Day 28
- Organ failure–free days from baseline to Day 28

2.5 EXPLORATORY BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to identify and/or evaluate biomarkers that could provide further evidence of TCZ pharmacologic activity (i.e., mechanism of action), on the basis of the following endpoints:

- Assessments of *exploratory* biomarkers in relation to efficacy, exposure (listed in Section 4.5.6), and in both blood and tissue-derived samples
- Association between TCZ pharmacokinetics and the following *PD* biomarkers: CRP, IL-6, sIL-6R, and ferritin

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase II, open-label, randomized, multicenter study to assess the pharmacodynamics, pharmacokinetics, safety, and efficacy of two different doses of TCZ in combination with SOC in hospitalized adult patients with moderate to severe COVID-19 pneumonia. The Sponsor intends to enroll approximately 100 patients who have been diagnosed with COVID-19 pneumonia who meet the eligibility criteria at U.S. sites.

Patients must be at least 18 years old with confirmed SARS-CoV-2 (COVID-19) pneumonia per the WHO criteria, including a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, *or* other bodily fluids). At the time of enrollment, patients must be hospitalized and have respiratory symptoms and radiologic findings of pneumonia. Patients with severe COVID-19 pneumonia must have $SpO_2 \leq 93\%$ or $PaO_2/FiO_2 < 300$ mmHg despite receiving SOC treatment, which may include anti-viral treatment, low-dose steroids, and supportive care. Patients with moderate COVID-19 pneumonia are hospitalized patients not meeting the criteria of severe COVID-19 pneumonia and with CRP $> 2\times$ the upper limit of normal (ULN). For both patients with moderate and severe COVID-19, the onset of patient symptoms must be at least 3 days prior to enrollment.

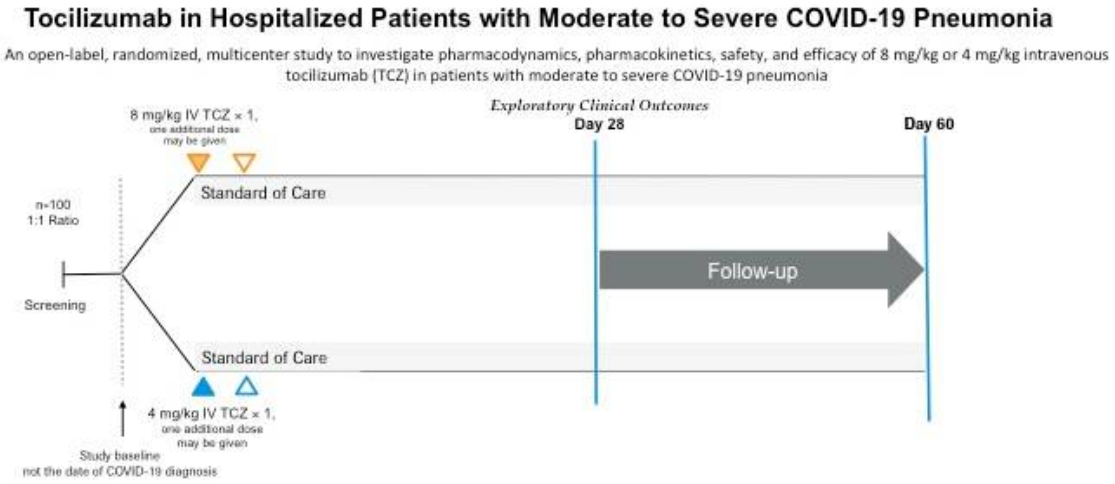
Patients who are on a mechanical ventilator $>$ 24 hours or *extracorporeal membrane oxygenation* (ECMO), in shock, or a combination thereof with other organ failure requiring treatment in an ICU will be excluded from the study. Patients for whom, in the opinion of the treating physician, progression 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 TB or suspected active bacterial, fungal, viral, or other infection (other than COVID-19 pneumonia) will be excluded from the study.

Patients will be randomized as soon as possible after screening in a 1:1 ratio to receive treatment with either 8 mg/kg or 4 mg/kg IV TCZ. Study treatment must be given in combination with SOC treatment.

Patients assigned to the 8-mg/kg TCZ arm will receive one IV infusion of 8 mg/kg, with a maximum dose of 800 mg, and patients assigned to the 4-mg/kg TCZ arm will receive one IV infusion of 4 mg/kg TCZ. In addition, patients in both arms will receive SOC treatment.

The study design is presented in Figure 1. The schedules of activities are presented in Appendix 1 (assessments to be performed on Days 1 and 2), Appendix 2 (assessments scheduled on Days 3–28), and Appendix 3 (assessments after Day 28).

Figure 1 Study Schema



For patients in both arms, if a *patient has a sustained fever or clinically significant worsening of signs or symptoms (e.g., an increased supplemental oxygen requirement*), one additional infusion of TCZ at the same dose as the initial infusion can be given within 8 to 24 hours after the initial *TCZ* 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 two 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 study assessments to be conducted include the following: complete and limited physical examinations, measurement of vital signs and oxygen saturation, assessment of consciousness, presence and absence of respiratory support, adverse events, concomitant therapies, clinical laboratory tests, and nasopharyngeal swabs (refer to Section 4.5 for the complete list of study assessments).

Patients will be followed for a total of 60 days after the first dose of study drug.

If patients are discharged from the hospital prior to Day 28, follow-up visits should occur twice weekly through Day 28. Patients are encouraged to return for onsite visits at least

weekly if possible; other follow-up visits may be conducted by telephone or home visits. Patients should return to the site for the Day 28 visit. After Day 28, all patients should have follow-up visits on Days 35, 45, and 60; the Day 35 and 45 visits may be conducted by telephone or by home visits for *patients who are* discharged, while the Day 60 visit should be conducted onsite.

During the study, standard supportive care will be given according to clinical practice.

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 occurs or the date at which the last data point required for the 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 4 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

The pneumonia caused by COVID-19 can be classified into four types: mild, common or moderate, severe, and critically severe (National Health Commission, trial Version 5). 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, owing to more severe disease (moderate, severe, or critically severe). Once hospitalized, 5%–26% patients are transferred to an ICU, 2.3% are mechanically ventilated, and 1.4%–15% of patients die (Huang et al. 2020; Guan et al. 2020; Wang et al. 2020).

Given the significant unmet need in patients hospitalized with COVID-19 infection and based on the emerging evidence for TCZ use in patients with COVID-19 pneumonia, COVACTA study, a Phase III, randomized, double-blind, placebo-controlled study is being conducted to evaluate the efficacy and safety of TCZ versus placebo in patients with severe COVID-19 pneumonia. Given that the optimal dose of TCZ in the treatment of COVID-19 pneumonia is not known, this Phase II, open-label, randomized study will investigate whether a lower dose of TCZ in combination with SOC could show similar pharmacologic effects of IL-6 pathway inhibition as the 8-mg/kg IV dose in combination with SOC treatment evaluated in the COVACTA study. Given that a lower dose is being assessed, critically severe patients will be excluded from this study; however, because hospitalized patients include those with moderate disease, patients with moderate and severe COVID-19 pneumonia will be included.

Patients with severe COVID-19 pneumonia will be defined as patients hospitalized with COVID-19 pneumonia that is confirmed according to the WHO criteria (including a positive PCR of any specimen [e.g., respiratory, blood, urine, stool, *or* other bodily fluids]) that is evidenced on chest X-ray or CT scan. Patients with severe COVID-19 may be mechanically ventilated for <24 hours or have $SpO_2 \leq 93\%$ or $PaO_2/FiO_2 < 300$ mmHg or are receiving supplemental oxygen with $SpO_2 > 93\%$, but desaturation to $\leq 93\%$ on lower supplemental oxygen or ambient air is documented. Patients not meeting the criteria of severe COVID-19 pneumonia will be considered as having moderate COVID-19 pneumonia. Patients with moderate COVID-19 pneumonia are required to have CRP $>2\times$ ULN.

3.3.2 Rationale for Tocilizumab Dose Regimen

On 30 August 2017, the U.S. FDA approved TCZ (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 TCZ dose is 8 mg/kg for body weight ≥ 30 kg and 12 mg/kg for body weight <30 kg. Up to an additional three doses of TCZ may be given if there is no improvement in the signs and symptoms of CRS and the interval between subsequent doses should be at least 8 hours.

This CRS label supported the selection of the dosing regimen in the ongoing COVACTA (WA42380) study, in which 8 mg/kg IV TCZ is administered to patients infected with severe COVID-19, with the possibility to repeat the dose within 8 to 24 hours after the initial infusion if clinically required. Nevertheless, the optimal dose and dosing frequency of TCZ in the treatment of CAR T cell–induced CRS are not known, and the dosing instructions provided in the current TCZ label provide only general recommendations for safe dosing (Le et al. 2018).

There is increasing evidence coming from real-world experience that lower doses of TCZ could show a similar efficacy *in treating COVID-19 pneumonia* as the one recommended in the CRS label. Treating physicians in China used a single fixed dose of 400 mg IV TCZ, as body weight measurement was not feasible (which equates to between 4 and 8 mg/kg based on the body weight range of the Chinese adult population).

In February 2020, 21 patients with severe or critical COVID-19 pneumonia were treated with IV TCZ (400 mg) in combination with SOC treatment. Nineteen patients (90.5%) were discharged at the time of the report, including 2 critically *severe* patients. No deaths were reported among the 21 treated patients. The study's authors concluded that TCZ is an effective treatment for patients with severe COVID-19 pneumonia (Xu et al. 2020).

TCZ competitively inhibits the binding of IL-6 to its sIL-6Rs and membrane-expressed IL-6Rs (mIL-6Rs). Inhibiting the entire receptor complex prevents IL-6 signal transduction to inflammatory mediators, including CRP, and significantly improves the chronic inflammatory process of RA (Rueda et al. 2011).

After IV administration, the observed concentrations of TCZ *declined* slowly over time. Elimination of TCZ is assumed to be a combination of a linear elimination through the non-specific binding and a target-mediated elimination related to TCZ binding to both sIL-6R and mIL-6R and subsequent elimination of the drug–target complex.

A PK/PD model (Gibiansky and Frey 2012) has been developed to describe the relationship between the TCZ concentration–time profile and the extent of target engagement as displayed by the sIL-6R time course.

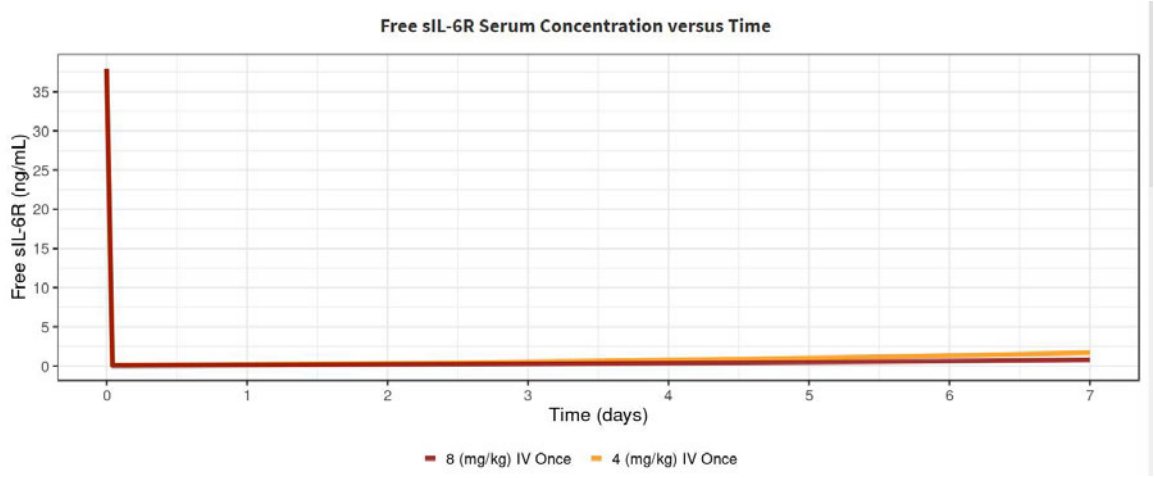
This model has been used to illustrate the expected decrease in estimated free sIL-6R levels achieved with different IV TCZ dosing regimens (Gibiansky and Frey 2012). It is worth highlighting that 8-mg/kg IV (tested in Phase III COVACTA trial) and 4-mg/kg IV dosing regimens elicit a similar onset and magnitude of the IL-6 pathway inhibition. The only difference lies with the duration of the inhibition as reflected by the sIL-6R blockade over a defined period of time. These results support the choice of testing 4 mg/kg IV TCZ in patients presenting with COVID-19 pneumonia based on the understanding of the PK–PD relationship of TCZ and on predictions from a well-established model *in RA*.

The level of target IL-6Rs in patients has the greatest effect on both the exposure of TCZ and the duration of the IL-6 pathway inhibition. Although these levels are well characterized in patients with RA, the level of IL-6Rs in patients with COVID-19 pneumonia is unknown at this stage.

To account for potentially higher levels of IL-6Rs in patients with severe COVID-19 pneumonia, two approaches were investigated, the first assuming IL-6R levels *were similar to levels in patients with RA*. For each of these two approaches, simulated free sIL-6R levels were predicted for patients with a low body weight (50 kg), an average body weight (75 kg), and a higher body weight (100 kg). Because all three profiles are identical, only the plots for patients weighing 75 kg are reported below.

In the case in which the levels of IL-6Rs are similar to *levels* observed in patients with RA, the 4-mg/kg and 8-mg/kg inhibition profiles overlap over 7 days across the body range tested, showing an almost complete receptor blockade of up to 7 days following a single IV infusion of TCZ (see Figure 2).

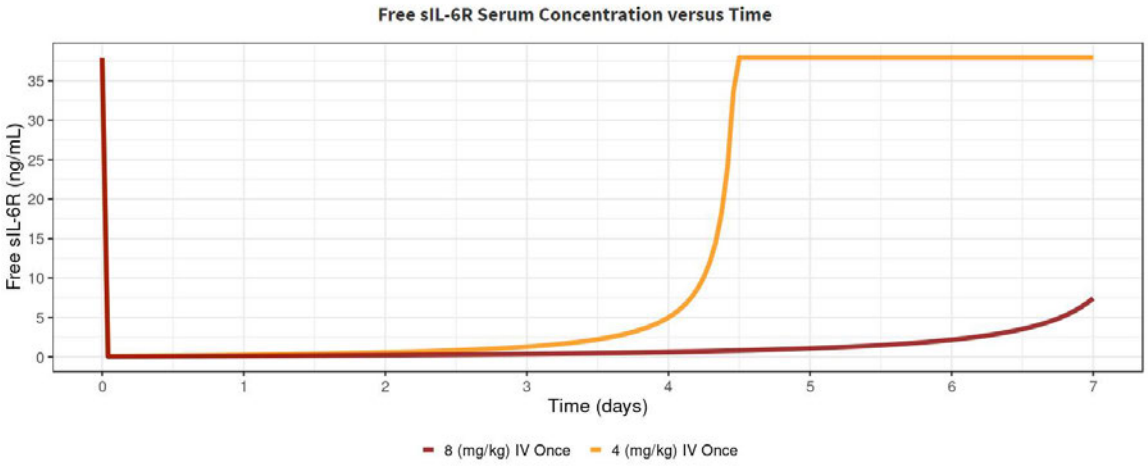
Figure 2 Predicted Median Free sIL-6R Serum Concentrations versus Time (over 7 Days) in Patients Weighing 75 kg with RA (Assumption: Similar IL-6R Levels as in Patients with RA)



IL-6R = interleukin-6 receptor; RA = rheumatoid arthritis; sIL-6R = soluble interleukin-6 receptor.

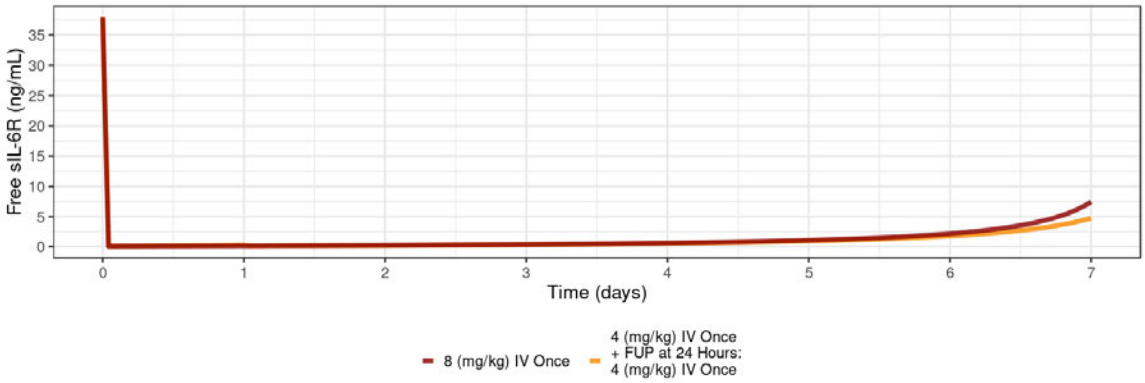
Under the assumption that the level of IL-6Rs in patients with COVID-19 pneumonia would be 10-fold higher than in patients with RA, the 4-mg/kg infusion results in the same inhibition level compared with 8-mg/kg up to 4 days after the infusion (see Figure 3); beyond that, a second infusion would be required to ensure maximal blockade for 7 days, mimicking the effect of one single IV infusion of 8 mg/kg (see Figure 4).

Figure 3 Predicted Median Free IL-6R Serum Concentration versus Time (over 7 Days) in Patients Weighing 75 kg (Assumption: 10-Fold Higher IL-6R Levels Than in Patients with RA)



IL-6R = interleukin-6 receptor; RA = rheumatoid arthritis; sIL-6R = soluble interleukin-6 receptor.

Figure 4 Predicted Median Free IL-6R Serum Concentrations versus Time (over 7 Days) in Patients Weighing 75 kg (Assumption: 10-Fold Higher IL-6R Levels Than in Patients with RA, Two Doses of 4 mg/kg Administered 24 Hours Apart)



F-UP = follow-up; IL-6R = interleukin-6 receptor; RA = rheumatoid arthritis; sIL-6R = soluble interleukin-6 receptor.

In RA, there are sound scientific arguments supporting that 4 mg/kg IV TCZ can elicit a similar onset and magnitude of IL-6 pathway inhibition as 8 mg/kg IV TCZ. Nevertheless, it is acknowledged that the model may not accurately predict the pharmacokinetics and pharmacodynamics of TCZ in patients with COVID-19 pneumonia, given that the *turnover rate and the* level of target IL-6Rs in patients with moderate to severe COVID-19 pneumonia is currently unknown. However, these limitations are mitigated by considering significantly greater levels of sIL-6Rs in patients with COVID-19 compared with what is known in patients with RA and the possibility of administering a second dose of TCZ.

3.3.3 Rationale for Biomarker Assessments

COVID-19 is a heterogeneous disease, and patients with severe COVID-19 infection have shown various levels of IL-6 pathway activation (Xu et al. 2020). Therefore, all patients may not be equally likely to respond to TCZ treatment.

PD biomarkers (i.e., IL-6, sIL-6R, CRP, and ferritin) will be assessed to demonstrate evidence of pharmacological activity of TCZ in patients, to support selection of a recommended dose and dosing regimen, and to inform potential revisions to the PK sample collection schedule.

The exploratory biomarkers will be assessed to further characterize *TCZ* mechanism of action *in relation to efficacy and exposure*.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study aims to enroll approximately 100 hospitalized patients with moderate to severe COVID-19 pneumonia.

4.1.1 Inclusion Criteria

- 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 legally authorized representative
- Age $\geq$ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol
- Hospitalization with COVID-19 pneumonia confirmed by a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, *or* other bodily fluids) and evidence of pneumonia on chest X-ray or CT scan

  The onset of patient symptoms must be at least 3 days prior to enrollment.

- For severe patients, $SpO_2 \leq 93\%$ or $PaO_2/FiO_2 < 300$ mmHg

  If a patient is on supplemental oxygen with $SpO_2 > 93\%$, but desaturation to $\leq 93\%$ on lower supplemental oxygen or ambient air is documented during screening, the inclusion criterion is met.

- For moderate patients (those who do not qualify as severe based oxygen requirements), CRP $> 2 \times$ ULN is required
- 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 TCZ. 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 ($\geq$ 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). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  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 TCZ 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
- Active TB infection
- Suspected active bacterial, fungal, viral, or other infection (besides SARS-CoV-2)
- Patients who *meet any of the following at the time of randomization*: on a mechanical ventilator $>$ 24 hours, *on* ECMO, in shock, or with other organ failure requiring treatment in an ICU
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
- Receipt of oral anti-rejection or immunomodulatory drugs (including TCZ) within the past 3 months
- Participation in other drug clinical trials (participation in COVID-19 anti-viral trials may be permitted if confirmed by the Medical Monitor)
- ALT or AST $>10\times$ ULN detected within 24 hours at screening or at baseline (according to local laboratory reference ranges)
- ANC $<1000/\mu$L at screening and baseline (according to local laboratory reference ranges)
- Platelet count $<50{,}000/\mu$L at screening and baseline (according to local laboratory reference ranges)
- Pregnancy or breastfeeding, or positive pregnancy test at a predose examination
- Treatment with an investigational drug within 5 drug-elimination half-lives or 30 days (whichever is longer) of randomization (investigational SARS-CoV-2 [COVID-19]) anti-viral agents may be permitted after consultation with the 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

4.2 METHOD OF TREATMENT ASSIGNMENT

4.2.1 Treatment Assignment

This is a randomized, open-label study with an active comparator and no placebo. 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: 8 mg/kg IV TCZ dose (the comparator) or 4 mg/kg IV TCZ (experimental treatment); *in addition, patients in both arms will receive SOC treatment.* Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified by pneumonia type (moderate, severe). The number of patients who have moderate COVID-19 pneumonia will be capped at no more than 50% of the overall study population.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is IV TCZ.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Tocilizumab

TCZ will be supplied by the Sponsor as a sterile IV injection for reconstitution in 20-mL glass vials with a 10 mL fill in each (200 mg /10 mL of TCZ). An appropriate number of vials (depending on the patient's bodyweight) of TCZ will be assigned 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.

4.3.2 Study Treatment Dosage, Administration, and Compliance

TCZ will be administered to patients by IV infusion at doses of 8 mg/kg or 4 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. One additional infusion of TCZ can be given within 8 to 24 hours after the initial infusion.

TCZ 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.

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

If stored at 2°C–8°C (36°F–46°F), the infusion bag should be allowed to return to room temperature prior to administration. 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 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 drug to flush the remaining study drug through the IV set.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration eCRF. Cases of accidental overdose or medication error along with any associated adverse events should be reported as described in Section 5.3.5.10.

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) 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, and only authorized staff may supply or administer TCZ.

TCZ 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 IMP 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 Tocilizumab Investigator's Brochure for information on IMP handling, including preparation 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 Roche TCZ or any other study treatments to patients who have completed the study.

The Roche Global Policy on Continued Access to Investigational Medicinal Product, 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 electronic Case Report Form (eCRF).

4.4.1 Permitted Therapy

All patients will receive SOC treatment per local practice for the treatment of COVID-19 pneumonia. *SOC* may include anti-viral treatment, low-dose steroids, and supportive care.

Chloroquine or hydroxychloroquine (with or without azithromycin) is permitted as part of local practice. Chloroquine is recommended with a maximum dose of 400 mg twice a day.

Clinical management guidelines from *the* WHO recommend against the use of corticosteroids in patients with COVID-19 pneumonia. However, region-specific guidelines recommend considering corticosteroids in some patients with COVID-19 pneumonia. 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 H_2-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 states of 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, cyclosporine, 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 and 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 a 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 *activities*):

- Efficacy assessments: clinical status, clinical signs and symptoms, and oxygen saturation
- Safety assessments: recording of vital signs, review of adverse events, and concomitant medications
- Laboratory samples: On days when study drug is administered, all samples (including predose PK, safety, and biomarker samples) must be obtained within 6 hours prior to study drug treatment, except for postdose samples for PK analyses, which will be obtained after study drug treatment.
- IV infusion of TCZ (only at baseline and an additional dose if needed)
- Safety assessments and recording of vital signs post-TCZ administration (if applicable)

If patients are discharged from the hospital prior to Day 28, follow-up visits should occur twice a week through Day 28. Patients are encouraged to return for onsite visits at least once a week, if possible; other follow-up visits may be conducted by telephone. Patients should return to the site for the Day 28 visit. After Day 28, all patients should have follow-up visits on Days 35, 45, and 60; the Day 35 and 45 visits may be conducted by telephone, whereas the Day 60 visit should be conducted in person.

Patients who are discharged after Day 28 but prior to Day 60 should return for a study completion visit at Day 60 and be followed by telephone for visits at Days 35 and 45 if an onsite visit is not feasible.

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). *The Informed Consent Form must be signed and dated by the patient or the patient's legally authorized representative or where allowed, health care provider 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 or 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 informed consent was obtained prior to participation in the study. Additional details concerning obtaining signed informed consent are available to sites and are based on the U.S. FDA's updated guidance on conduct of clinical trials of medical products during COVID-19 public health*

emergency (FDA 2020). 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. 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 the 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, and self-reported race/ethnicity.

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, musculoskeletal, respiratory, gastrointestinal (GI), genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions 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.

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 (in liters per minute [L/min]) and/or FiO_2 should be recorded.

In order to allow assessment of the NEWS2 score (see Section 4.5.5 and Appendix 4), all of the vital sign parameters and oxygen saturation should be recorded together twice per day, with approximately 12 hours in between, for the duration of a patient's hospitalization during the study. This is to ensure that the measurements reflect the

patient's condition over the entire study day, whenever possible. If vital signs or oxygen saturation are measured more than once during a 12-hour period, 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. Following hospital discharge, these parameters should be recorded once at each return visit to the clinic. Vital signs and oxygen saturation will not be recorded if follow-up visits are conducted by telephone.

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 Assessments Specific to National Early Warning Score 2

In addition to the vital measurements, the patient's consciousness level and the presence or absence of respiratory support must be recorded. The NEWS2 parameter for respiratory support is the selection of either air or "oxygen" and can include other forms of ventilation to maintain oxygen saturation (see Appendix 4). The form of ventilation used should be recorded on the eCRF.

NEWS2 values do not need to be calculated by the site but will be calculated electronically by the Sponsor based on vital sign parameters and NEWS2-related assessments recorded by the investigator on the appropriate eCRF.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Local Laboratory Assessments

Samples for the following laboratory tests will be measured by the 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), and lymphocyte subsets (T cells, B cells, and natural killer cells; if the test is available at the site *or if the site can ship the blood sample on the day of collection to the central laboratory for testing)*
- 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 protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and/or AST, uric acid, LDH, D-dimer, CRP, 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 PCR (screening): nasopharyngeal swab, BAL or other respiratory specimen, blood, urine, stool, *or* other bodily *fluids*

Central Laboratory Assessments

Samples for the following laboratory tests will be sent to designated central laboratories or to the Sponsor or a designee for analysis:

- Serum samples for PK analysis
- Serum *and plasma* samples for PD analysis (IL-6, sIL-6R, and CRP) and exploratory biomarker research
- Serum samples for SARS-CoV-2 antibody titer
- Nasopharyngeal swabs and BAL (if applicable) for SARS-CoV-2 virology tests (viral load and exploratory analysis)
- Blood *in* PAXgene® *tubes* for RNA for sequencing or quantitative PCR
- *Blood for* cryopreserved peripheral blood mononuclear cells *isolation* (for sites capable of sample collection *or if the site can ship the blood sample on the day of collection to the central laboratory for isolation*)
- *Blood for testing T cells, B cells, and natural killer cells (if the site ships the blood sample on the day of collection to the central laboratory for testing)*

Exploratory biomarker research may include, but will not be limited to, analysis of inflammatory mediators and/or cytokines, ARDS-related variables, serum viral load, and virus resistance and mutation analysis.

In countries where acceptable, biomarker research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of next-generation sequencing (NGS) of a comprehensive panel of genes.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Serum samples collected for PK analysis may be needed for additional PK assay development and validation, and biomarker research; therefore, these samples will be destroyed no later than 15 years after the final Clinical Study Report has been completed.
- Blood (serum, *plasma,* and *peripheral blood mononuclear cells*), blood RNA, and tissue-derived samples (nasopharyngeal swabs and BAL, if applicable) collected for PD analysis and biomarker research will be destroyed no later than 15 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

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.

4.5.7 Liver Function Monitoring

Patients should be assessed for liver function prior to each dose of TCZ. 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 prior to study drug administration. Dosing will occur only if the clinical assessment and local laboratory liver chemistry panel values are acceptable.

4.5.8 Chest X-Ray 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 according to the schedules of activities (see Appendix 1, Appendix 2, and Appendix 3).

Chest X-ray or CT scan findings should be recorded on the appropriate eCRF per the schedule of activities. If additional chest X-rays or CT scans are performed per local practice, this information should be provided on 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 at the 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 a day every morning (between 8 a.m. and 12 p.m.) while a patient is 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$2 L 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

Patients who are ready to be discharged but are still hospitalized (e.g., because of 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 $\leq$90% should be considered for escalation to a higher clinical status category, while patients with oxygen saturation consistently $\geq$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 nonclinical considerations.

Normal body temperature is defined as oral, rectal, axillary, or tympanic temperature 36.1C°–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 a reason for patient discontinuation from the study. The primary reason for discontinuation 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 postmarketing 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 dosage modification and 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 one or two doses of TCZ. For a complete list of all identified or potential risks of TCZ therapy, please refer to the current version of the Tocilizumab 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 postmarketing 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 SOC 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 at increased risk of infection, such as a history of recurring infections or with underlying conditions (e.g., diabetes mellitus), that 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 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 labeled 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 those populations are not applicable to this study owing to single-dose therapy (with possible additional infusion) with 4 mg/kg and 6 mg/kg TCZ.

Patients who develop elevated liver function test abnormalities 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 medicines *that* are individually dose adjusted and are metabolized by means of 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 5.3.5.7 and 5.3.5.8 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 such as biopsies)

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 5.3.5.9)
- 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 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:

- 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
- 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 non-directive 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 re-challenge.
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).

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

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 GI 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., dosage modification, 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

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

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., ALP 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 5.3.5.3 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., dosage modification, 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 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.

5.3.5.7 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").

5.3.5.8 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 5.3.5.6). 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.

5.3.5.9 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

5.3.5.10 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, 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 TCZ, 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.

5.3.5.11 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

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 IRB/EC.

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 IRB/EC.

5.4.1 Medical Monitors and Emergency Medical Contacts

Contact Information for All Sites

Medical Monitor: [redacted], M.D. (Primary)

Telephone No.: [redacted]

Alternate Contact Information for All Sites

Medical Monitor: [redacted], M.D. (Secondary)

Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center will be available 24 hours per day, 7 days per week, in case the above-listed contacts cannot be reached. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

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 Roche 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.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

A modified intent-to-treat (mITT) population will be used to perform all statistical analyses. All patients randomized and receiving at least one dose of TCZ will be included. All reasons for exclusion will be properly documented and the criteria for them

set before database lock. Intercurrent events like rescue therapy will be addressed with sensitivity analyses defined in the Statistical Analysis Plan and Data Analysis Plan.

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this *open-label* study *is the comparison of TCZ pharmacokinetics* and *PK*-PD *relationship* between two doses of TCZ (8 and 4 mg/kg) in hospitalized patients with moderate to severe COVID-19 pneumonia. *The comparison will be assessed using modeling and evaluating the safety and efficacy measures between* Day *1 and Day 28 postrandomization. Data from the follow-up period from Days 28 to 60 may also be assessed. Approximately* 100 patients will be enrolled and randomized in a 1:1 ratio to the 8-mg/kg and 4-mg/kg IV TCZ arms in this study. *Disease severity type will also be stratified into moderate and severe COVID pneumonia, giving an overall equal four-way split between the two doses and type of disease severity and resulting in four groups of approximately 25* patients *each. Patients may receive* a *repeat* dose *within 8 to 24 hours after the first TCZ dose if clinicians judge it is necessary (resulting in a TCZ* dose *range from 4 to 16 mg/kg, with a maximum* dose *of 800 mg*). The *variability of PK parameters of TCZ in a heterogeneous COVID-19 population* in *an acute setting is unknown*; however, *20 to 30 patients is deemed adequate considering the between-subject variability in health volunteers and patients with RA provided by population-PK modeling. Data quality issues, patient dropouts, and early hospital discharge may all lead to missing data, especially in a pandemic setting; thus, enrolling 50 patients according to dose and disease severity type (25 per arm) may offset missing data and allow an adequate volume of PK and PD data to inform the population-*PK model *and allow a comparison of the 4- and 8-mg/kg doses*.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (including, but not limited to, age, sex, race/ethnicity, severity, NEWS2 score, ordinal scale for clinical status, IL-6, IL-6R, mechanical ventilation, anti-viral treatment, and previous and concomitant medications (e.g., steroids and drug exposure) will be summarized using means, *SDs*, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment arm.

Medical history data, including surgery and procedures, and conditions other than COVID-19 pneumonia, will be summarized descriptively by treatment arm using the safety-evaluable population.

6.4 PHARMACODYNAMIC *ANALYSES*

The PD outcome measures for this study are *serum* IL-6, sIL-6R, ferritin, and CRP *levels at baseline and* at *specified timepoints after initiation of study drug. Data for all PD biomarkers will be presented using descriptive summary statistics, including the mean, median, range, SD, and coefficient of variation.*

6.5 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients with sufficient data to enable estimation of key parameters (e.g., area under the concentration–curve [AUC], maximum serum concentration observed [C_{max}]), with patients grouped according to treatment received.

Non-linear mixed effects modeling will be used to analyze the serum TCZ concentration over time data collected in this study using existing population-PK models. Individual and mean serum TCZ concentration versus time data will be tabulated and plotted by dose level. The serum pharmacokinetics of TCZ will be summarized by estimating the total exposure (AUC), C_{max}, total clearance, and volume of distribution. Estimates for these parameters will be tabulated and summarized (mean, *SD*, co-efficient of variation, median, minimum, and maximum). Interpatient variability will be evaluated.

Additional PK analyses will be conducted as appropriate. The PK parameters derived from these analyses may be used for exploratory graphical analyses of the PD parameters.

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 drug. In all safety analyses, patients will be grouped according to the treatment that patients actually receive 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 Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0 scale.

The proportion of patients with any posttreatment infection will be summarized by timepoint, including Day 60.

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 *outside the normal range, including both higher and lower values,* from baseline throughout the study will be tabulated by treatment arm.

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

COVID-19 (SARS-CoV-2) viral load over time, as collected by nasopharyngeal swab and BAL samples (if applicable) will be summarized descriptively by *timepoint* and treatment *arm*.

Time to RT-PCR COVID-19 virus negativity will be analyzed using similar methods to the other time to analyses.

6.7 EXPLORATORY ANALYSES

The exploratory objective for this study is to *assess* the efficacy of two different doses of TCZ in combination with SOC treatment for the treatment of moderate to severe COVID-19 on the basis of the endpoints *presented in Section 2.4*.

The analysis population for the exploratory analyses will consist of the mITT population (i.e., all randomized patients who receive at least one dose of TCZ).

Any subgroup analysis will be of exploratory nature.

6.8 EXPLORATORY BIOMARKER ANALYSIS

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and in aggregate with data from other studies.

6.9 INTERIM ANALYSES

6.9.1 Periodic Safety Reviews

Periodic safety reviews will be performed on unblinded data when at least 10 patients per arm have been *in the study for at least 7 days. The number of subsequent safety reviews, including PK data, will depend on the recruitment rate.*

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. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these 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

Because of 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 on the eCRFs by authorized site personnel are accurate and complete. Sites will be asked to implement a quality control step of a second person reviewing the data entry on the eCRFs 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, 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 on 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. 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, health care provided 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.

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 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 9.7).

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 9.5).

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 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. 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. 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 F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 25 sites in the United States will participate to enroll approximately 100 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

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

Time after Initial Treatment (Assessment Window)	Screening [a]	Day 1		Day 2
		Baseline		
	Days −2 to 0	0 Predose (−4 hr)	15 min Postinfusion (+1 hr)	24 hr (± 4 hr)
Informed consent	x			
Review of inclusion and exclusion criteria	x	x		
Demographics	x			
Randomization		x		
Medical history		x		
Complete physical examination [c]	x			
Weight		x		
COVID-19 diagnosis [d]	x			
Chest X-ray or CT scan	x			
ECG	x			
Pregnancy test [f]	x			
PaO_2/FiO_2 [g]	x	Optional		
SpO_2 [h]	x	x	x	x
Vital signs [h]	x	x	x	x
Ordinal scoring [i]		x		x
Adverse events [j]		x		x
Concomitant medications [k]		x		x

Appendix 1: Schedule of Activities: Days 1 and 2 (cont.)

Time after Initial Treatment (Assessment Window)	Screening [a]	Day 1		Day 2
		Baseline		
	Days −2 to 0	0 Predose (−4 hr)	15 minutes Postinfusion (+1 hr)	24 hours (± 4 hr)
Hematology [l]	x (24 hr) [m]	x		*x*
Chemistry panel [n]	x (24 hr) [m]	x		*x*
Study drug administration [o]		x		
Central laboratory assessments				
Serum PD sample (CRP, IL-6, and sIL-6R) [p]		x [p]	x [p]	x
Serum PK sample [q]		x [q]	x [q]	x
Serum *and plasma samples* for exploratory biomarkers		x		x
SARS-CoV-2 viral load [r]		x		x
Serum SARS-CoV-2 antibody titer		x		
Cryopreserved PBMCs [s]		x		x
Blood in PAXgene® tubes for RNA analyses [t]		x		

CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiogram; eCRF = electronic Case Report Form; IL-6 = interleukin-6; *NEWS2 = National Early Warning Score 2*; PaO_2/FiO_2 = arterial oxygen partial pressure/fraction of inspired oxygen; PBMC = peripheral blood mononuclear cell; PCR = polymerase chain reaction; PD = pharmacodynamic; PK = pharmacokinetic; SARS-CoV-2 = severe acute respiratory syndrome corona virus (strain) 2; sIL-6R = soluble interleukin-6 receptor; 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 48 hours before randomization may be used; such tests do not need to be repeated for screening. *An exception to this is clinical chemistry and hematology tests obtained prior to informed consent, which do not need to be repeated for screening if conducted within **24 hours** before randomization.*

[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, musculoskeletal, respiratory, gastrointestinal, genitourinary, 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] COVID-19 test (SARS-CoV2 PCR) to confirm diagnosis should be performed within 7 days of randomization.

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

[f] 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.

[g] If arterial blood gases are measured.

[h] All vital sign measurements (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressures, and body temperature), oxygen saturation and NEWS2-specific assessments (i.e., consciousness and presence or absence of oxygen support) should be recorded together twice daily with approximately 12 hours in between while the patient remains hospitalized. If measured more than once during a 12-hour period, 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.

[i] Assessment of clinical status using the ordinal scale should be recorded at baseline (Day 1, Visit 1) and then again daily every morning (between 8 a.m. and 12 p.m.) for patients who remain hospitalized.

[j] 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).

[k] 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.

[l] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes), and lymphocyte subsets (T cells, B cells, and natural killer cells; if the test is available at the site).

[m] *Hematology and chemistry panel assessments performed as part of standard of care, prior to consent but within 24 hours of randomization, do not need to be repeated.*

[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 protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and/or AST, uric acid, LDH, CRP, ferritin, and D-dimer.

[o] Study drug should be administered after collection of all samples for *PK*, PD, and exploratory biomarkers. The initial study drug infusion should be given within 4 hours of randomization. *For patients in both arms of the study, if a patient has a sustained fever or clinically significant worsening of signs or symptoms (e.g., an increased supplemental oxygen requirement), one additional infusion of TCZ at the same dose as the initial infusion can be given within 8 to 24 hours after the initial TCZ infusion.*

[p] On Day 1, CRP, IL-6, and sIL-6R samples should be drawn 0–4 hours before the start of infusion and then within 15 minutes (to 1 hour) after the end of the infusion *from* the opposite arm as the infusion. Patents receiving a second infusion of study drug should provide extra samples for CRP, IL-6, and sIL-6R prior to and 15 minutes after the end of the infusion *from* the opposite arm as the infusion. *If the second infusion falls within the window for the Day 2 PD sample (20–24 hours) for the first infusion, it can be combined with the postinfusion sample for the second infusion.*

[q] On Day 1, PK samples should be drawn 0–4 hours before the start of infusion and then within 15 minutes (to 1 hour) after the end of the infusion *from* the opposite arm as the infusion. Patents receiving a second infusion of study drug should provide an extra PK sample prior to and 15 minutes (to 1 hour) after the end of the infusion *from* the opposite arm as the infusion. *If the second infusion falls within the window for the Day 2 PK sample (20–24 hours) for the first infusion, it can be combined with the postinfusion sample for the second infusion.*

[r] Viral load will be assessed by nasopharyngeal swab. Patients who are intubated and undergo bronchoalveolar lavage will have samples taken for virological assessment. It may only be possible to access one nostril if a patient has a nasogastric tube in place, in which case sites may collect a sample from one nostril only and when possible the same nostril should be used.

[s] For sites capable of sample collection for analysis of T cells by high-dimensional cytometry.

[t] The PAXgene® *blood* tube *should be the last tube drawn in the phlebotomy procedure* to avoid contact with *the* RNA preservation reagent inside the tube.

Appendix 2
Schedule of Activities: Days 3–28

	Days 3–28 [a]																										*Early Tx or Study*
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	Discon
Chest X-ray or CT scan					x							x							x							x	x
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	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
Concomitant medications [f]	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
Hematology [g]	x				x			x				x							x							x	x
Chemistry profile [h]	x				x			x				x							x							x	x
Central laboratory assessments																											
Serum PD sample (CRP, IL-6, and sIL-6R)	x				x							x							x							x	x
Serum PK sample	*x*				x							x							x							x	x
Serum *and plasma samples* for exploratory biomarkers	x				x							x							x							x	x
SARS-CoV-2 viral load [i]	x	x	x	x	x			x				x							x							x	x
Serum SARS-CoV-2 antibody titer																										x	x
Cryopreserved PBMCs [j]	x				x							x							x							x	x

Appendix 2: Schedule of Activities: Days 3–28 (cont.)

	Days 3–28 [a]																									*Early Tx or Study* Discon
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	
Blood in PAXgene® tubes for RNA analyses [k]	x				x																					x	x

CRP = C-reactive protein; CT = computed tomography; Discon = discontinuation; ECG = electrocardiogram; eCRF = electronic Case Report Form; IL-6 = interleukin-6; NEWS2 = National Early Warning Score; PaO_2/FiO_2 = arterial oxygen partial pressure/fraction of inspired oxygen; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamic; PK = pharmacokinetic; SARS-CoV-2 = severe acute respiratory syndrome corona virus (strain) 2; sIL-6R = soluble interleukin-6 receptor; SpO_2 = peripheral capillary oxygen saturation; *Tx = treatment;* TCZ = tocilizumab.

Note: For patients who have been discharged, all assessments should be performed within ±3 days of the scheduled onsite visit.

[a] If patients are discharged from hospital prior to Day 28, follow-up visits should occur twice weekly through Day 28. Patients are encouraged to return for onsite visits at least weekly if possible; other follow-up visits may be conducted by telephone or home visits. Patients should return to the site for the Day 28 visit.

[b] All vital sign measurements (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressures, and body temperature), oxygen saturation and NEWS2-specific assessments (i.e., consciousness and presence or absence of oxygen support) should be recorded together twice daily with approximately 12 hours in between while the patient remains hospitalized. If measured more than once during a 12-hour period, 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. Following hospital discharge these parameters should be recorded once at each return visit to the clinic. Vital signs and oxygen saturation will not be recorded if follow-up visits are conducted by telephone.

[c] If arterial blood gases are measured.

[d] Assessment of clinical status using the ordinal scale should be recorded at baseline (Day 1, Visit 1) and then again daily every morning (between 8 a.m. and 12 p.m.) 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), and lymphocyte subsets (T cells, B cells, and natural killer cells; if the test is available at the site).

[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 protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and/or AST, uric acid, LDH, ferritin, and D-dimer.

[i] Viral load will be assessed by nasopharyngeal swab. Patients who are intubated and undergo bronchoalveolar lavage will have samples taken for virological assessment. It may only be possible to access one nostril if a patient has a nasogastric tube in place, in which case sites may collect a sample from one nostril only and when possible the same nostril should be used.

[j] For sites capable of sample collection for analysis of T cells by high-dimensional cytometry.

[k] The PAXgene® *blood* tube *should be the last tube drawn in the phlebotomy procedure* to avoid contact with *the* RNA preservation reagent inside the tube..

Appendix 3
Schedule of Activities: After Day 28

			Study Completion
Study Day (Assessment Window)	35 [a] (±3 days)	45 [a] (±3 days)	60 (±3 days)
Chest X-ray or CT scan			x
SARS-CoV-2 viral load [b]	x	x	x
Vital signs [c]	x	x	x
SpO_2 [c]	x	x	x
Ordinal scoring [d]	x	x	x
Adverse events [e]	x	x	x
Concomitant medications [f]	x	x	x
Hematology [g]	x	x	x
Chemistry panel [h]	x	x	x
Central laboratory assessments			
Serum PD sample (CRP, IL-6, and sIL-6R)	x		x
Serum PK sample	x		x
Serum *and plasma samples* for exploratory biomarkers	x		x
SARS-CoV-2 viral load [i]			*x*
Cryopreserved PBMCs [j]			*x*
Blood in PAXgene® tubes for RNA analyses [k]			*x*
Serum SARS-Cov-2 antibody titer			x

CRP = C-reactive protein; CT = computed tomography; eCRF = electronic Case Report Form; IL-6 = interleukin-6; PD = pharmacodynamic; PK = pharmacokinetic; SARS-CoV-2 = severe acute respiratory syndrome corona virus (strain) 2; sIL-6R = soluble interleukin-6 receptor; SpO_2 = peripheral capillary oxygen saturation.

[a] If patients are unable to return for onsite visits at Day 35 and/or Day 45, these may be conducted by telephone or home visits. Patients should return to the site for the Day 60 study completion visit.

[b] Patients who remain in hospital will have viral load assessed by nasopharyngeal swabs; these will be done if there is evidence of ongoing infection.

[c] For patients who remain in the hospital, vital sign measurements and NEWS2-specific assessments should be conducted twice daily. Following hospital discharge, these parameters should be recorded once at each return visit to the clinic. Vital signs and oxygen saturation will not be recorded if follow-up visits are conducted by telephone.

[d] Assessment of clinical status using the ordinal scale should be recorded at baseline (Day 1, Visit 1)δ and then again daily every morning (between 8 a.m. and 12 p.m.) 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), and lymphocyte subsets (T cells, B cells, and natural killer cells). Hematology labs will not be performed if follow-up visits are conducted by telephone.

[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 protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and/or AST, uric acid, LDH, ferritin, and D-dimer. Chemistry laboratory assessments will not be performed if follow-up visits are conducted by telephone.

[i] *Viral load will be assessed by nasopharyngeal swab. Patients who are intubated and undergo bronchoalveolar lavage will have samples taken for virological assessment. It may only be possible to access one nostril if a patient has a nasogastric tube in place, in which case sites may collect a sample from one nostril only and when possible the same nostril should be used.*

[j] *For sites capable of sample collection for analysis of T cells by high-dimensional cytometry.*

[k] *The PAXgene® blood tube should be the last tube drawn in the phlebotomy procedure to avoid contact with the RNA preservation reagent inside the tube.*

Appendix 4
National Early Warning Score 2 (NEWS2)

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

SpO_2 = oxygen saturation.

Oxygen saturation *(SpO_2)* should be scored according to either the SpO_2 Scale 1 or 2 presented in the table above. The SpO_2 Scale 2 is for patients with a target oxygen saturation requirement of 88%–92% (e.g., in patients with hypercapnic respiratory failure related to advanced lung diseases, such as chronic obstructive pulmonary disease). This should only be used in patients confirmed to have hypercapnic respiratory failure by blood gas analysis on either a prior or their current hospital admission.

The decision to use the SpO_2 Scale 2 should be made by the treating physician and should be recorded in the eCRF. In all other circumstances, the SpO_2 Scale 1 should be used.

For physiological parameter “Air or Oxygen?”: Any patients requiring the use of oxygen or other forms of ventilation to maintain oxygen saturations and support respiration should be assigned a score of 2.

The consciousness level should be recorded according to the best clinical condition of the patient during the assessment. Patients who are assessed as “Alert” (A) should be assigned a score of 0. Patients assessed as “New Confusion” (C), “Responsive to Voice” (V), “Responsive to Pain” (P), or “Unconscious” should be assigned a score of 3.

Scores should be assigned for respiratory rate, systolic blood pressure, pulse, and temperature according to the table above.

NEWS2 values will be calculated electronically throughout the study by the Sponsor based upon entry of vital sign parameters by the investigator on the appropriate electronic Case Report Form.

Example Case Calculation:

An 82-year-old woman was admitted, tested positive to COVID-19, and admitted to high-dependency unit for non-invasive ventilation. Her taken observations and corresponding NEWS2 score are as follows:

Physiological Parameter	Observation	Component Score
Respiratory rate (per minute)	26	3
Oxygen saturation (SpO_2 %)	95%	1
Supplemental oxygen	Yes	2
Systolic blood pressure (mmHg)	95	2
Pulse rate (bpm)	109	1
Conscious level	New confusion	3
Temperature (^oC)	39	1
	Total NEWS2 score	**13**

REFERENCE

Royal College of Physicians. National early warning score (NEWS) 2. Standardizing the assessment of acute-illness severity in the NHS. London: RCP, 2017.