PROTOCOL

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF TOCILIZUMAB IN PATIENTS WITH SEVERE COVID-19 PNEUMONIA**
PROTOCOL NUMBER:	WA42380
VERSION NUMBER:	1
EUDRACT NUMBER:	2020-001154-22
IND NUMBER:	148225
NCT NUMBER:	To be determined
TEST PRODUCT:	Tocilizumab (RO4877533)
MEDICAL MONITOR:	Min Bao, M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
18-Mar-2020 19:35:26	Company Signatory	Eisner, Mark (markde)

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PROTOCOL ACCEPTANCE FORM

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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 the CRO.

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF TOCILIZUMAB IN PATIENTS WITH SEVERE COVID-19 PNEUMONIA**
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PHASE:	Phase III
INDICATION:	Severe COVID-19 pneumonia
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of tocilizumab (TCZ) compared with a matching placebo in combination with standard of care (SOC) in hospitalized patients with severe COVID-19 pneumonia. Specific objectives and corresponding endpoints for the study are outlined below.

This study will evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of TCZ compared with a matching placebo in combination with SOC in hospitalized patients with severe COVID-19 pneumonia. Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

Primary Efficacy Objective

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

- Clinical status assessed using a 7-category ordinal scale at Day 28

Secondary Efficacy Objective

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

- Time to clinical improvement (TTCI) defined as a National Early Warning Score 2 (NEWS2) of ≤ 2 maintained for 24 hours
- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status
- Incidence of mechanical ventilation
- Ventilator-free days to Day 28
- Organ failure-free days to Day 28
- Incidence of intensive care unit (ICU) stay

- Duration of ICU stay
- Time to clinical failure, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first)
- 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$2L supplemental oxygen)
- Duration of supplemental oxygen

Exploratory Efficacy Objective

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

- Incidence of vasopressor use
- Duration of vasopressor use
- Incidence of extracorporeal membrane oxygenation (ECMO)
- Duration of ECMO

Safety Objective

The safety objective for this study is to evaluate the safety of TCZ compared with placebo in combination with SOC for the treatment of 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 (NCI CTCAE) v5.0
- COVID-19 (SARS-CoV-2) viral load over time, as collected by nasopharyngeal swab and bronchoalveolar lavage (BAL) samples (if applicable)
- Time to reverse-transcriptase polymerase chain reaction (RT-PCR) virus negativity
- The proportion of patients with any post-treatment infection
- Change from baseline in targeted clinical laboratory test results

Pharmacodynamic Objective

The pharmacodynamic objective for this study is to characterize the pharmacodynamic effects of TCZ in patients with COVID-19 pneumonia via longitudinal measures of the following analytes relative to baseline

- Serum concentrations of IL-6, sIL-6R, ferritin, and CRP at specified timepoints

Pharmacokinetic Objective

The PK objective for this study is to characterize the TCZ PK profile in patients with COVID-19 pneumonia on the basis of the following endpoint:

- Serum concentration of TCZ at specified timepoints

Biomarker Objective

The exploratory biomarker objectives for this study is to identify and/or evaluate biomarkers that could be predictive of response to TCZ (i.e., predictive biomarkers), may serve as early surrogates of efficacy, may be associated with progression to a more severe disease state (i.e., prognostic biomarkers), may be associated with susceptibility to developing adverse events or could lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), could further evidence of TCZ pharmacological activity (i.e., pharmacodynamic biomarkers), and overall increase our knowledge and understanding of disease pathogenesis and drug safety, on the basis of the following endpoint:

- Assessments of individual biomarkers in relation to efficacy, safety, exposure and in both blood- and tissue-derived samples

STUDY DESIGN

Description of the Study

Overview of Study Design

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of TCZ in combination with SOC compared with matching placebo in combination with SOC in hospitalized adult patients with severe COVID-19 pneumonia. The Sponsor intends to enroll approximately 330 patients that have been diagnosed with COVID-19 pneumonia and meet the entry criteria in centers globally.

Patients must be at least 18 years of age with confirmed COVID-19 infection per WHO criteria, including a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have $SpO_2 \leq 93\%$ or $PaO_2/FiO_2 < 300$ mmHg) despite being on SOC, which may include anti-viral treatment, low dose steroids, and supportive care.

Patients in whom, in the opinion of the treating physician, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments, will be excluded from the study. Patients with active tuberculosis (TB) or suspected active bacterial, fungal, viral, or other infection (besides COVID-19) will be excluded from the study.

Patients will be randomized as soon as possible after screening at a 2:1 ratio to receive blinded treatment of either TCZ or a matching placebo, respectively. Study treatment must be given in combination with SOC. The randomization will be stratified by geographic region (North America, Europe, and other) and mechanical ventilation (yes, no).

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

For both arms, if the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–12 hours after the initial infusion.

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

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

After Day 28

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

For patients who are discharged between Day 28 and study completion, visits may be conducted via telephone.

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

Number of Patients

This study aims to enroll approximately 330 hospitalized patients with severe COVID-19 pneumonia.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form by any patient capable of giving consent, or, when the patient is not capable of giving consent, by his or her legal/authorized representative
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment

- Hospitalized with COVID-19 pneumonia confirmed per WHO criteria (including a positive PCR of any specimen; e.g., respiratory, blood, urine, stool, other bodily fluid) and evidenced by chest X-ray or CT scan
- $SpO_2 \leq 93\%$ or PaO2/$FiO_2 < 300$ mmHg
- 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 28 days after the final dose of TCZ

  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 28 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 COVID-19)
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
- Have received oral anti-rejection or immunomodulatory drugs (including TCZ) with the past 6 months
- Participating in other drug clinical trials (participation in COVID-19 anti-viral trials may be permitted if approved by Medical Monitor)
- ALT or AST > 10 x ULN detected within 24 hours at screening or at baseline (according to local laboratory reference ranges)
- ANC < 1000/μL at screening and baseline (according to local laboratory reference ranges)
- Platelet count < 50,000/μL at screening and baseline (according to local laboratory reference ranges)
- Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination

- Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (investigational COVID-19 antivirals may be permitted 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 (LPLV) occurs or the date at which the last data point required for last follow-up is received from the last patient, whichever occurs later. The end of the study is expected to occur approximately 2 months after the last patient is enrolled.

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

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 10 months.

Investigational Medicinal Products

Test Product (Investigational Drug)

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

Comparator

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

Statistical Methods

Primary Analysis

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

- Clinical status assessed using a 7-category ordinal scale at Day 28

Assessment of patient status using an ordinal scale will be recorded at baseline and daily in the morning (between 8 am and 12 pm) while hospitalized. The ordinal scale categories are as follows:

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

The clinical status according to the 7-category ordinal scale will be compared between the TCZ group and the placebo group at day 28, using a proportional odds model accounting for stratification factors at randomization in the model (region [North America, Europe, Other] and mechanical ventilation [yes, no]) and baseline status. The odds ratio, p-value, and 95% confidence interval will be presented.

Further details of the primary endpoint analysis will be included in the SAP.

The assumption of proportional odds will be evaluated and if it does not hold, a stratified Cochran-Mantel-Haenszel (CMH) test may be used to compare the treatment groups.

For patients who withdraw before day 28, their last post baseline ordinal category prior to withdrawal will be used in the analysis. Any other missing data handling rules for the primary endpoint will be specified in the SAP.

Determination of Sample Size

The estimated sample size was determined based on a time to event analysis for the secondary endpoint of improvement in clinical status as defined below. This sample size is also expected to be sufficient for the primary endpoint of comparison of clinical status based on the same 7-category ordinal scale at day 28 using a proportional odds model.

The total mITT sample size of 330 with a 2:1 randomization of TCZ to placebo patients provides approximately 80% power using a Logrank Chi-Square test to detect a 2-day difference between treatment groups in Time to Improvement in Ordinal Clinical Status as assessed using a 7-category ordinal scale (i.e. at least a 2 category improvement relative to baseline) under the following assumptions: median time to improvement in the TCZ group is 5 days, with 28 days follow-up, and using a one-sided 2.5% alpha. The minimal detectable difference is expected to be approximately 1.3 days (32 hours) under the same TCZ assumption.

Interim Analyses

Up to four interim looks for efficacy (including the final analysis) will be carried out on the data with mortality rate at 28 days (secondary endpoint) evaluated for interim efficacy analyses. The interim looks will occur after roughly 75, 150, 225, and 330 patients are enrolled, but all interims are subject to change depending on enrollment.

The first efficacy interim analysis will be conducted when approximately 75 patients (50 TCZ and 25 placebo) have reached the 28-day follow-up time point and will be based on the mortality rate at 28 days (secondary endpoint). If the results of one of the interim analyses meets the pre-specified criteria for efficacy, further enrollment in the placebo arm will be discontinued and all enrolled patients will receive open-label TCZ. At this point efficacy will be declared.

If there is a potential for further recruitment into the placebo arm to be stopped for positive efficacy because of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α-spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994). Interim analyses for efficacy will use the fisher's exact test for difference in proportions and will utilize an O'Brien-Fleming alpha-spending function. The efficacy boundaries for the z-scores at the four looks are 4.33, 2.96, 2.36, and 2.01.

Additional criteria for recommending that the study be stopped for positive efficacy may be added to the interim SAP. The critical value at the final analysis will be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

The study management team will remain blinded unless the results meet the efficacy criteria. The Interim efficacy analyses will be produced by a statistical programmer independent of the study management team and will reviewed by a Data Monitoring Committee (DMC).

Full statistical details of the planned interim analyses, along with the rationale and timing will be documented in an interim statistical analysis plan, which will be made available to the relevant health authorities before the data snapshot for the first interim.

A Data Monitoring Committee will also evaluate safety according to policies and procedures detailed in a DMC Charter. Regular safety reviews will begin after approximately 15 patients (10 TCZ, 5 placebo) have been enrolled and reached 28-day follow-up. Early stopping criteria based on compelling efficacy or an imbalance in adverse events will be detailed in the DMC charter. The safety interim analyses will also be conducted by a statistical programmer independent from the study management team and will be reviewed by the DMC. Interactions between the DMC and Sponsor will be carried out as specified in the DMC Charter.

The Data Monitoring Committee may initially consist of Sponsor representatives not involved in any operational aspects of the study before transitioning to a fully independent data monitoring committee (iDMC) when feasible.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ARDS	acute respiratory distress syndrome
AUC	area under the curve
BAL	bronchoalveolar lavage
CAR	chimeric antigen receptor
C_{max}	maximum serum concentration observed
CMH	Cochran-Mantel-Haenszel
CoV	coronaviruses
CRO	contract research organization
CRP	C-reactive protein
CRS	cytokine-release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	electronic Case Report Form
ECMO	extracorporeal membrane oxygenation
EDC	electronic data capture
FDA	Food and Drug Administration
GCA	giant cell arteritis
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
LPLV	last patient, last visit
MERS-CoV	Middle East respiratory syndrome
MOD	multiple organ dysfunction
MOF	multi organ failure
NCI	National Cancer Institute
NEWS2	National Early Warning Score 2
PaO_2	partial pressure of oxygen
PCR	polymerase chain reaction
pJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetic

Abbreviation	Definition
PRO	patient-reported outcome
PY	patient years
QTcF	QT interval corrected through use of Fridericia's formula
QW	once a week
Q2W	every 2 weeks
RA	rheumatoid arthritis
RBR	Research Biosample Repository
RT-PCR	real time polymerase chain reaction
SAP	Statistical Analysis Plan
SARS-CoV	severe acute respiratory syndrome
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 with a crown-like appearance under an electron microscope due to the presence of spike glycoproteins on the envelope. They are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV).

COVID-19, which is the acronym of "coronavirus disease 2019," is caused by a new coronavirus strain that has not been previously identified in humans and was newly named on 11 February 2020 by the World Health Organization (WHO). An epidemic of cases with unexplained lower respiratory tract infections was first detected in Wuhan, the largest metropolitan area in China's Hubei province, and was reported to the WHO Country Office in China on December 31, 2019. A pandemic was subsequently declared by the WHO on 11 March 2020.

According to the WHO, as of 17 March 2020 over 179,000 cases of COVID-19 were reported in over 100 countries worldwide, with over 7400 deaths. Up to ~20% of infected patients experienced complications related to a severe form of interstitial pneumonia, which may progress towards acute respiratory distress syndrome (ARDS) and/or multi organ failure (MOF) and death.

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

1.2 BACKGROUND ON TOCILIZUMAB

Tocilizumab (TCZ) is a recombinant humanized, anti-human monoclonal antibody of the IgG1 subclass directed against soluble and membrane-bound IL-6R. TCZ binds specifically to both soluble IL-6R (sIL-6R) and membrane-bound IL-6R and has been shown to inhibit both soluble and membrane-bound IL-6R–mediated signaling. IL-6 is a pleiotropic pro inflammatory multifunctional cytokine produced by a variety of cell types and has been shown to be involved in diverse physiological processes such as T-cell activation; induction of acute phase proteins; stimulation of hematopoietic precursor cell growth and differentiation; proliferation of hepatic, dermal, and neural cells; bone metabolism; lipid metabolism; hepatoprotection; and fibrosis. Elevated tissue and serum levels of IL-6 have been implicated in the disease pathology of several inflammatory and autoimmune disorders including rheumatoid arthritis (RA), Castleman disease, systemic juvenile idiopathic arthritis (sJIA), polyarticular juvenile idiopathic arthritis (pJIA), giant cell arteritis (GCA), Takayasu arteritis (TAK), systemic sclerosis (SSc), and cytokine-release syndrome (CRS). Inhibition of the biological activity of IL-6 or IL-6R has been

effective in the treatment of these disorders, including chimeric antigen receptor (CAR) T-cell induced CRS, for which treatment with TCZ has been approved in many countries.

TCZ has 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 tocilizumab from the DIBD (28 April 1997) and until 10 April 2019 (DLP for PBRER) is 24,826 patients (40154.98 patient years [PY]). Since the IBD (11 April 2005), the estimated cumulative market exposure to tocilizumab until 10 April 2019 is 1,301,050 patients (1,053,779 PY). The combined cumulative post-marketing exposure of patients to IV tocilizumab is estimated to be 896,672 patients (726,347 PY). The combined cumulative postmarketing exposure of patients to SC tocilizumab is 404,378 (327,432 PY).

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

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

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

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

The approval of TCZ was based on a retrospective analysis of data for patients treated with TCZ who developed CRS after treatment with tisagenlecleucel (Kymriah®) or axicabtagene ciloleucel (Yescarta®) in prospective clinical trials, (Le et al. 2018). Thirty-one out of the 45 patients (69%) from the CTL019 series achieved a response (defined as being afebrile and off vasopressors for at least 24 hours within 14 days of the first dose of TCZ (maximum up to two doses) and without use of additional treatment other

than corticosteroids) within 14 days of the first dose of TCZ, and the median time from the first dose to response was 4 days. Eight of the 15 patients (53%) from the axicabtagene ciloleucel series achieved a response, and the median time to response was 4.5 days. The response rates were largely consistent among subgroups such as age group, sex, race, ethnicity, grade of CRS at first dose of TCZ, and duration of CRS prior to treatment with TCZ. There were no reports of adverse reactions attributable to TCZ.

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

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

1.4 REAL WORLD EXPERIENCE WITH TOCILIZUMAB IN COVID-19 PNEUMONIA

Physicians in China initiated the off-label usage of TCZ in the treatment of coronavirus (COVID-19) pneumonia (see “Results” section below). Based on the findings of an observational study of 21 COVID-19 patients treated with TCZ (manuscript submitted, Xu et al. 2020), an investigator-initiated randomized, open-label study ($n = 188$) was also initiated on 13 February 2020.

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

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

The dose regimen used in China is a single fixed dose of 400 mg TCZ IV as body weight measurement is not feasible (which equates to between 4–8 mg/kg based on the body weight range of the Chinese adult population), with the maximum single dose no more than 800 mg. If clinical signs/symptoms do not improve, an additional dose can be

administered after 12 hours. The guidance advises that no more than two doses should be given. TCZ treatment is not permitted for people with active infections including TB, bacterial, or fungal.

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

Results from 21 Patients Treated with Tocilizumab in China

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

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

Eighteen patients (85.7%) received TCZ once, and three patients (14.3%) had a second dose due to fever within 12 hours. According to the authors, after TCZ treatment, fever returned to normal and all other symptoms improved remarkably. Fifteen of the 20 patients (75.0%) had lowered their oxygen intake and one patient needed no oxygen therapy. CT scans showed significant remission of opacities in both lungs in 19/20 patients (90.5%) after treatment with TCZ. The percentage of lymphocytes in peripheral blood, which was decreased in 85.0% of patients (17/20) before treatment (mean, 15.52±8.89%), returned to normal in 52.6% of patients (10/19) on the fifth day after treatment. Abnormally elevated CRP decreased significantly in 84.2% patients (16/19). No adverse drug reactions and no subsequent pulmonary infections were reported.

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

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

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

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

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, pharmacodynamics, and pharmacokinetics of TCZ compared with a matching placebo in combination with SOC in hospitalized patients with severe COVID-19 pneumonia. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

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

- Clinical status assessed using a 7-category ordinal scale at Day 28

2.1.2 Secondary Efficacy Objectives

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

- Time to clinical improvement (TTCI) defined as a National Early Warning Score 2 (NEWS2) of ≤ 2 maintained for 24 hours
- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status
- Incidence of mechanical ventilation
- Ventilator-free days to Day 28
- Organ failure-free days to Day 28
- Incidence of intensive care unit (ICU) stay
- Duration of ICU stay
- Time to clinical failure, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first)
- 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$2L supplemental oxygen)
- Duration of supplemental oxygen

2.1.3 Exploratory Efficacy Objective

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

- Incidence of vasopressor use
- Duration of vasopressor use
- Incidence of extracorporeal membrane oxygenation (ECMO)
- Duration of ECMO

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of TCZ compared with placebo in combination with SOC for the treatment of 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 (NCI CTCAE) v5.0
- COVID-19 (SARS-CoV-2) viral load over time, as collected by nasopharyngeal swab and bronchoalveolar lavage (BAL) samples (if applicable)
- Time to reverse-transcriptase polymerase chain reaction (RT-PCR) virus negativity
- The proportion of patients with any post-treatment infection
- Change from baseline in targeted clinical laboratory test results

2.3 PHARMACODYNAMIC OBJECTIVE

The pharmacodynamic objective for this study is to characterize the pharmacodynamic effects of TCZ in patients with COVID-19 pneumonia via longitudinal measures of the following analytes relative to baseline:

- Serum concentrations of IL-6, sIL-6R, ferritin, and CRP at specified timepoints

2.4 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the TCZ PK profile in patients with COVID-19 pneumonia on the basis of the following endpoint:

- Serum concentration of TCZ at specified timepoints

2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objectives for this study are to identify and/or evaluate biomarkers that could be predictive of response to TCZ (i.e., predictive biomarkers), may serve as early surrogates of efficacy, may be associated with progression to a more severe disease state (i.e., prognostic biomarkers), may be associated with susceptibility to developing adverse events or could lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), could further evidence of TCZ pharmacological activity (i.e., pharmacodynamic biomarkers), and overall increase our knowledge and understanding of disease pathogenesis and drug safety, on the basis of the following endpoint:

- Assessments of individual biomarkers in relation to efficacy, safety, exposure (listed in Section 4.5.6) and in both blood- and tissue-derived samples

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of TCZ in combination with SOC compared with matching placebo in combination with SOC in hospitalized adult patients with severe COVID-19 pneumonia. The Sponsor intends to enroll approximately 330 patients that have been diagnosed with COVID-19 pneumonia and meet the entry criteria in centers globally.

Patients must be at least 18 years of age with confirmed COVID-19 infection per WHO criteria, including a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have $SpO_2 \leq 93\%$ or $PaO_2/FiO_2 < 300$ mmHg) despite being on SOC, which may include anti-viral treatment, low dose steroids, and supportive care.

Patients in whom, in the opinion of the treating physician, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments, will be excluded from the study. Patients with active tuberculosis (TB) or suspected active bacterial, fungal, viral, or other infection (besides COVID-19) will be excluded from the study.

Patients will be randomized as soon as possible after screening at a 2:1 ratio to receive blinded treatment of either TCZ or a matching placebo, respectively. Study treatment must be given in combination with SOC. The randomization will be stratified by geographic region (North America, Europe, and other) and mechanical ventilation (yes, no).

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

For both arms, if the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–12 hours after the initial infusion.

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

The study assessments to be conducted include the following: physical examination, vital signs, oxygen saturation, assessment of consciousness, presence and absence of respiratory support, adverse events, concomitant therapies, clinical laboratory tests, and nasopharyngeal swabs. Please see Appendix 1, Appendix 2, and Appendix 3 for details concerning the timing of these assessments.

3.1.1.1 After Day 28

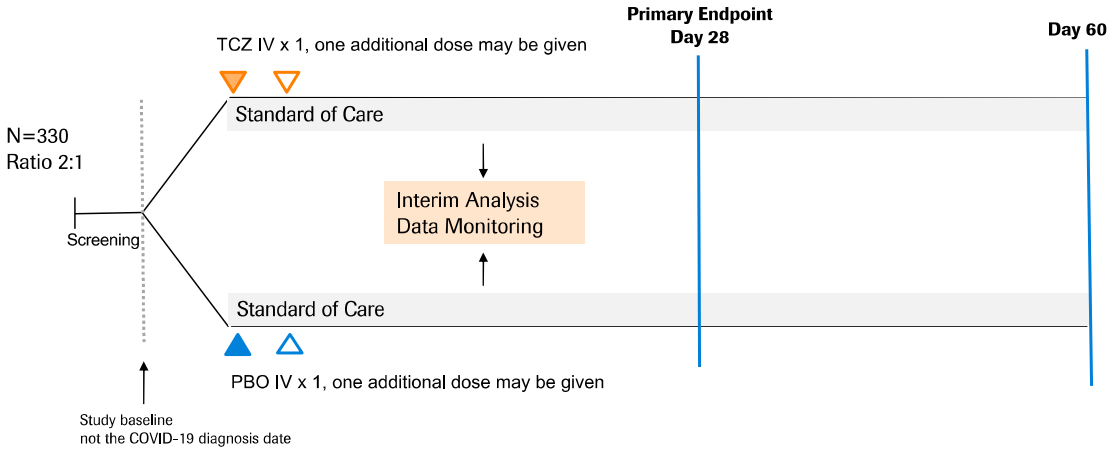
Patients will be followed up for a total of 60 days after first dose of study medication.

For patients who are discharged, between Day 28 and study completion visits may be conducted via telephone.

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

Figure 1 presents an overview of the study design. Schedules of activities are provided in Appendix 1, Appendix 2, and Appendix 3.

Figure 1 Study Schema



IV = intravenous; PBO = placebo; TCZ = tocilizumab.

3.2 END OF STUDY AND LENGTH OF STUDY

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

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

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 10 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Tocilizumab Dose and Schedule

At baseline, patients assigned to the TCZ arm will receive one infusion of TCZ 8 mg/kg IV, with a maximum dose of 800 mg. If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of TCZ 8 mg/kg IV can be given, 8–12 hours after the initial infusion.

The TCZ dose regimen chosen in this study for adult patients is consistent with the approved TCZ dose for patients experiencing CRS induced by CAR-T cell therapy who weigh ≥ 30 kg. Further, based on the off-label experience from China (one additional dose if fever is not improved within 12 hours) and the fact that up to 3 additional infusions of TCZ (with at least 8 hours in between infusions) are allowed for CAR-T induced CRS, the proposed additional one infusion if clinical signs/symptoms worsen or do not improve is justified.

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

3.3.2 Rationale for Patient Population

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

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

3.3.3 Rationale for Control Group

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

3.3.4 Rationale for Biomarker Assessments

COVID-19 infection is a heterogeneous disease, and the severe patients have shown various levels of IL-6 pathway activation (Xu et al. 2020). Therefore, all patients may not be equally likely to benefit from treatment with TCZ. Pharmacodynamic biomarkers will be assessed to demonstrate evidence of biologic 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 identify those patients who are most likely to respond to TCZ, to characterize TCZ mechanism of action, to provide further evidence of TCZ efficacy, and to understand progression of COVID-19.

4. MATERIALS AND METHODS

4.1 PATIENTS

This study aims to enroll approximately 330 hospitalized patients with severe COVID-19 pneumonia.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form by any patient capable of giving consent, or, when the patient is not capable of giving consent, by his or her legal/authorized representative
- Age $\geq$ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Hospitalized with COVID-19 pneumonia confirmed per WHO criteria (including a positive PCR of any specimen; e.g., respiratory, blood, urine, stool, other bodily fluid) and evidenced by chest X-ray or CT scan
- $SpO_2 \leq 93\%$ or PaO2/FiO_2 < 300 mmHg
- 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 28 days after the final dose of TCZ.

  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 28 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 COVID-19)
- In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
- Have received oral anti-rejection or immunomodulatory drugs (including TCZ) with the past 6 months
- Participating in other drug clinical trials (participation in COVID-19 anti-viral trials may be permitted if approved by Medical Monitor)
- ALT or AST > 10 x ULN detected within 24 hours at screening or at baseline (according to local laboratory reference ranges)
- ANC < 1000/μL at screening and baseline (according to local laboratory reference ranges)
- Platelet count < 50,000/μL at screening and baseline (according to local laboratory reference ranges)
- Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
- Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (investigational COVID-19 antivirals may be permitted if approved by Medial 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 AND BLINDING

4.2.1 Treatment Assignment

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

Patients will be randomly assigned to one of two treatment arms: TCZ in combination with SOC or placebo in combination with SOC. Randomization will occur in a 2:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. The randomization will be stratified by geographic region (North America, Europe, and other) and mechanical ventilation (yes, no).

4.2.2 Blinding

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

While PK samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK results for these patients are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g. to evaluate a possible error in dosing).

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

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

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

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

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Tocilizumab and Placebo

TCZ/placebo 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/placebo). An appropriate number of vials (depending on the patient's bodyweight) of TCZ/placebo 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

The treatment regimens are summarized in Section 3.1.

4.3.2.1 Tocilizumab and Placebo

TCZ/placebo will be administered by IV infusion at doses of 8 mg/kg. The maximum dose of TCZ that will be administered is 800 mg. The dose of TCZ infusion will be calculated on the basis of body weight measured prior to infusion (see Appendix 1).

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

The TCZ/placebo vials will be stored at a temperature of 2°C–8°C. The infusion bag of TCZ may be stored at 2°C–8°C for 24 hours providing that the infusion is prepared aseptically and allowed to return to room temperature before administration. The TCZ will be administered at room temperature by controlled infusion into a vein over a 1-hour period. In exceptional cases this time may be extended to up to 6 hours. The infusion speed must be 10 mL/hr for 15 minutes and then increased to 130 mL/hr to complete the dosing in 1 hour. The entire 100 mL-content of the infusion bag must be administered. A total of 20 mL of normal saline will be administered following the infusion of study medication to flush the remaining study drug through the intravenous set.

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

4.3.3 Investigational Medicinal Product Handling and Accountability

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

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

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

TCZ/placebo will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

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

4.3.4 Continued Access to Tocilizumab

Since the TCZ treatment is not intended for continued therapy, the Sponsor does not have any plans to provide 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 is available at the following website:

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

4.4 CONCOMITANT THERAPY

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

4.4.1 Permitted Therapy

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

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

4.4.2 Cautionary Therapy

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

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

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

4.4.2.2 Herbal Therapies

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

4.4.3 Prohibited Therapy

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

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

4.5 STUDY ASSESSMENTS

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

1. Efficacy assessments: clinical status, clinical signs and symptoms, oxygen saturation
2. Safety assessments: vital signs, review of adverse events, concomitant medications
3. Laboratory samples: on days when study drug is administered, all samples (including for predose PK, safety and biomarkers) must be taken prior to study drug treatment, except for postdose samples for PK analyses, which will be obtained after study drug treatment.
4. IV infusion of TCZ/placebo (only at baseline and an additional dose if needed)
5. Safety assessments; vital signs post TCZ (if applicable)
6. Post-dose PK samples

Schedules of assessments are found in Appendix 1, Appendix 2, and Appendix 3.

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). 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 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, 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.

In addition, patient body weight will be measured at the timepoints specified in the schedule of activities (see Appendix 1, Appendix 2, and Appendix 3).

4.5.4 Vital Signs and Oxygen Saturation

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure, and body temperature. Peripheral oxygen saturation should also be measured at the same time as the vitals. For patients requiring supplemental oxygen, the oxygen flow rate (L/min) and/or fraction of inspired oxygen (FiO2) should be recorded.

In order to allow assessment of the NEWS2 score (see section 4.5.5), all of the vital sign parameters and oxygen saturation should be recorded together four times per day, with several hours between timepoints, for the duration of the hospitalization during the study. This is to ensure that the measurements reflect the patient's condition over the entire

study day, where possible. 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" can include other forms of ventilation to maintain oxygen saturation (see Appendix 4).

These should be recorded at the same time points as the vital sign measurements (see Section 4.5.4 and Appendix 1, Appendix 2, and Appendix 3).

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 in the appropriate eCRF.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

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

- Partial pressure of oxygen (PaO_2, if arterial blood gases are performed during screening or follow-up)
- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes), and lymphocyte subsets (T cells, B cells, and NK cells; if the test is available at the site)
- 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, 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.
- COVID-19 PCR (screening): nasopharyngeal swab, BAL, or other respiratory specimen, blood, urine, stool, other bodily fluid

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 samples for pharmacodynamic analysis (IL-6, sIL-6R and CRP) and exploratory biomarker research
- Nasopharyngeal swabs and BAL, if applicable for COVID-19 virology tests (viral load and exploratory analysis)
- Whole blood PAXgene® RNA for RNA sequencing or QPCR
- Cryopreserved PBMCs for high dimensional cytometry analysis (for sites capable of sample collection)

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

In countries where acceptable, 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.

Screening blood (serum, plasma, PBMCs) blood PAX®gene RNA, and tissue-derived samples (nasopharyngeal swabs and BAL, if applicable), including those collected from patients who do not enroll in the study, may be used for future research and/or development of disease-related tests or tools.

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, PBMCs), blood PAX®gene RNA, and tissue-derived samples (nasopharyngeal swabs and BAL, if applicable) collected for pharmacodynamic 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 or matching placebo. On Day 1, the assessment is mandatory. On Day 1, the local laboratory full blood chemistry panel required as part of screening can be used for this assessment or prior blood results if tests conducted within 24 hours prior to screening. Results must be reviewed by the investigator before dose administration. Dosing will occur only if the clinical assessment and local laboratory liver chemistry panel values are acceptable.

4.5.8 Chest X-Rays and CT Scan

If a chest X-ray has not been taken within the 24 hours prior to screening, it must be performed on Day 1. If a chest X-ray was performed within 24 hours prior to screening, no additional chest X-ray needs to be performed. A chest CT scan can be performed as alternative to the chest X-ray.

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

4.5.9 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1, Appendix 2, and Appendix 3) and may be obtained at unscheduled timepoints if needed per investigator's discretion.

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

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

4.5.10 Ordinal Scale Determination

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

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

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. However, actual clinical status category should be recorded on the eCRF. Patients on supplemental oxygen should be evaluated at least daily and considered for reduction or discontinuation of oxygen support. Actual changes in level of support will be at the discretion of the clinician(s) treating the patient based on the patient's overall condition and may be dictated by other clinical and non-clinical considerations.

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient

- Pregnancy
- Any event that meets stopping criteria defined in Section 5.1.1
- Severe allergic reaction to TCZ

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

4.6.2 Patient Discontinuation from the Study

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

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

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up

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

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

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

- Excessively slow recruitment

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

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

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events and laboratory abnormalities, including criteria for 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 1–2 doses of TCZ. For a complete list of all identified or potential risks of TCZ therapy, please refer to the current version of the TCZ Investigator's Brochure.

5.1.1.1 Hypersensitivity Reactions, Including Anaphylaxis

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

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

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

be treated according to the standard of care for management of the hypersensitivity reaction.

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

5.1.1.2 Serious Infections and Opportunistic Infections

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

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

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

5.1.1.3 Gastrointestinal Perforations

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

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

5.1.1.4 Hematologic Abnormalities

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

5.1.1.5 Demyelinating Disorders

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

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

5.1.1.6 Elevated Liver Enzymes

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

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

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

5.1.1.7 CYP450 Enzyme Normalization

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

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

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures 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 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

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

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

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

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Serious and/or medically significant infections
- Myocardial infarction or acute coronary syndrome
- GI perforations
- Malignancies
- Anaphylaxis or hypersensitivity reactions
- Stroke
- Serious and/or medically significant bleeding events
- Serious and/or medically significant hepatic events
- Demyelinating disorders

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

investigators

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

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

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

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

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

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

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

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

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

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

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

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

Table 2 Causal Attribution Guidance

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

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

5.3.5.2 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

5.3.5.3 Persistent or Recurrent Adverse Events

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

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

5.3.5.4 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., 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

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

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

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

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

5.3.5.5 Abnormal Vital Sign Values

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

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., 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 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

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

5.3.5.7 Deaths

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

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

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

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

5.3.5.8 Preexisting Medical Conditions

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

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

5.3.5.9 Lack of Efficacy or Worsening of COVID-19 Pneumonia

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

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

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

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

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

  The patient has not experienced an adverse event

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

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

5.3.5.11 Cases of Accidental Overdose or Medication Error

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

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

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

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately

(i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For TCZ (or matching placebo), adverse events associated with special situations should be recorded as described below for each situation:

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

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

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

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.12 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.

5.4.1 Medical Monitors and Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

Medical Monitor:	Min Bao, M.D.
Mobile Telephone No.:	+1 (650) 296-3298

Alternate Medical Monitor Contact Information for All Sites

Medical Monitor:	Balpreet Matharu, M.D.
Mobile Telephone No.:	+44 7834814352

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.

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

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

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

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

6.1 DETERMINATION OF SAMPLE SIZE

The estimated sample size was determined based on a time to event analysis for the secondary endpoint of improvement in clinical status as defined below. This sample size is also expected to be sufficient for the primary endpoint of comparison of clinical status based on the same 7-category ordinal scale at day 28 using a proportional odds model.

The total mITT sample size of 330 with a 2:1 randomization of TCZ to placebo patients provides approximately 80% power using a Logrank Chi-Square test to detect a 2-day difference between treatment groups in Time to Improvement in Ordinal Clinical Status as assessed using a 7-category ordinal scale (i.e. at least a 2 category improvement relative to baseline) under the following assumptions: median time to improvement in

the TCZ group is 5 days, with 28 days follow-up, and using a one-sided 2.5% alpha. The minimal detectable difference is expected to be approximately 1.3 days (32 hours) under the same TCZ assumption.

Table 3 shows the Power under varying assumptions of the TCZ and placebo groups.

Table 3 Power under Varying Assumptions of Tocilizumab and Placebo Responses with Evaluable 330 Patients (220 TCZ, 110 Placebo)

TCZ Assumption (days)	Placebo Assumption (days)	Power (%)
5	7	80
6	8	65
7	9	53
8	10	42
8	11	71
7.75	11	80
5	6.33	50

This sample size also provides 80% power to detect a 10% absolute difference in mortality rate under the assumption of a 15% mortality rate in the placebo group.

A sample size re-estimation may be considered during the study to help verify the assumptions of the primary and/or secondary endpoints. Further details will be included in the statistical analysis plan if applicable.

6.2 SUMMARIES OF CONDUCT OF STUDY

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

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

6.3 TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (including, but not limited to, age, sex, race, geographic region, NEWS2, ordinal scale for clinical status, IL-6, mechanical ventilation, anti-viral treatment at baseline, steroids at baseline) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented by treatment group and will be presented for the mITT and may, in addition, be presented for the safety population.

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

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

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

6.4 EFFICACY ANALYSES

All efficacy analyses will use the mITT population.

Sensitivity analyses to evaluate the robustness of results to the primary analysis methods (e.g., handling of dropouts) may be conducted and will be described in the statistical analysis plan.

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

Full details of adjustments to significance levels for hypothesis tests resulting from efficacy interims; and for multiplicity and/or sequential order of analyses will be predefined in the statistical analysis plan.

6.4.1 Primary Efficacy Endpoint

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

- Clinical status assessed using a 7-category ordinal scale at Day 28

Assessment of patient status using an ordinal scale will be recorded at baseline and once daily in the morning (between 8 am and 12 pm) while hospitalized. The ordinal scale categories are as follows:

1. Discharged (or “ready for discharge” as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or $\leq$2L supplemental oxygen)
2. Non-ICU hospital ward (or “ready for hospital ward”) not requiring supplemental oxygen

3. Non-ICU hospital ward (or “ready for hospital ward”) requiring supplemental oxygen
4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen
5. ICU, requiring intubation and mechanical ventilation
6. ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g. vasopressors, renal replacement therapy)
7. Death

The clinical status according to the 7-category ordinal scale will be compared between the TCZ group and the placebo group at Day 28, using a proportional odds model accounting for stratification factors at randomization in the model (region [North America, Europe, Other] and mechanical ventilation [yes, no]), and baseline status. The odds ratio, p-value, and 95% confidence interval will be presented.

Further details of the primary endpoint analysis will be included in the SAP.

The assumption of proportional odds will be evaluated and if it does not hold, a stratified Cochran-Mantel-Haenszel (CMH) test may be used to compare the treatment groups.

For patients who withdraw before Day 28, their last post baseline ordinal category prior to withdrawal will be used in the analysis. Any other missing data handling rules for the primary endpoint will be specified in the SAP.

6.4.2 Secondary Efficacy Endpoints

Time to event secondary endpoints will be compared between the TCZ group and the placebo group using the stratified log-rank test with geographic region (North America, Europe, and Other), mechanical ventilation (yes, no), and anti-viral treatment (yes, no) included as the stratification factors. The Kaplan-Meier plot, median time to response, and their 95% CIs, and a p-value will be presented. If the assumption of proportional hazards does not hold, an appropriate alternative method will be used. Further details will be described in the SAP.

- Time to clinical improvement (TTCI)

  Defined as time from randomization to NEWS2 of ≤ 2 maintained for 24 hours
- Time to improvement in ordinal clinical status

  Defined as time from randomization to the time when at least a 2-category improvement in the 7-category ordinal scale is observed

- Time to clinical failure

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

- Time to hospital discharge or "ready for discharge"

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

Secondary efficacy incidence and rate endpoints will be analyzed using the Cochran-Mantel-Haenszel test statistic adjusted by the stratification factors at baseline geographic region (North America, Europe, and Other) and mechanical ventilation (yes, no), unless stated otherwise. The weighted difference in proportions for the treatment group comparison will be presented, together with a 95% CI using the extended Mantel-Haenszel method. Missing data will be imputed as a non-responder, unless specified otherwise in the statistical analysis plan.

- Incidence of mechanical ventilation by Day 28
- Incidence of intensive care unit (ICU) stay by Day 28
- Mortality rate at Days 7, 14, 21, 28, and 60 will be summarized descriptively. The weighted difference in proportions for the treatment group comparison will be presented, together with a 95% CI using the extended Mantel-Haenszel method.

Comparison of clinical status according to the 7-category ordinal scale (detailed for the primary endpoint at day 28) may also be analyzed using a proportional odds model at additional time points, including day 7, 14, 21 and day 60.

The NEWS2 score and the ordinal clinical status will be summarized descriptively by visit.

Other secondary endpoints include:

- Ventilator-free days to Day 28
- Organ failure-free days to Day 28
- Duration of ICU stay
- Duration of supplemental O2

Duration endpoints will be summarized using the medians, with 95% CIs for the medians by treatment group, along with a difference in medians and a 95% CI for the difference.

6.4.3 Exploratory Efficacy Endpoints

Incidence of vasopressor use and incidence of extracorporeal membrane oxygenation (ECMO) will be summarized descriptively.

Duration of vasopressor use and ECMO will be summarized using the median along with 95 % CIs for the median by treatment group.

6.5 SAFETY ANALYSES

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

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

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

The proportion of patients with any post-treatment infection will be summarized at time points 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 and change from baseline throughout the study will be tabulated by treatment arm. For selected parameters, changes from the proportion of patients experiencing clinically significant changes relative to baseline will be summarized by treatment arm.

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

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

Time to reverse-transcriptase polymerase chain reaction (RT-PCR) COVID-19 virus negativity will be analyzed using similar methods to the other time to analyses.

6.6 PHARMACODYNAMIC ANALYSES

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

6.7 PHARMACOKINETIC ANALYSES

The PK analysis population will consist of patients with sufficient data to enable estimation of key parameters (e.g., area under the 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 pre-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 total exposure (AUC), C_{max}, total clearance, volume of distribution. Estimates for these parameters will be tabulated and summarized (mean, standard deviation, co-efficient of variation, median, minimum, and maximum). Inter-patient variability will be evaluated.

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

These analyses will be reported separately in a stand-alone report.

6.8 BIOMARKER ANALYSES

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 PLANNED INTERIM ANALYSES

Up to four interim looks for efficacy (including the final analysis) will be carried out on the data with mortality rate at 28 days (secondary endpoint) evaluated for interim efficacy analyses. The interim looks will occur after roughly 75, 150, 225, and 330 patients are enrolled, but all interims are subject to change depending on enrollment.

The first efficacy interim analysis will be conducted when approximately 75 patients (50 TCZ and 25 placebo) have reached the 28-day follow-up time point and will be based on the mortality rate at 28 days (secondary endpoint). If the results of one of the interim analyses meets the pre-specified criteria for efficacy, further enrollment in the placebo arm will be discontinued and all enrolled patients will receive open-label TCZ. At this

point efficacy will be declared. Recruitment into the TCZ arm will continue until 220 patients have been enrolled.

If there is a potential for further recruitment into the placebo arm to be stopped for positive efficacy because of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α-spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets- and Lan 1994). Interim analyses for efficacy will use the fisher's exact test for difference in proportions for mortality at 28 days and will utilize an O'Brien-Fleming alpha-spending function. The efficacy boundaries for the z-scores at the four looks are 4.33, 2.96, 2.36, and 2.01.

Additional criteria for recommending that the study be stopped for positive efficacy may be added to the interim SAP. The critical value at the final analysis will be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

The study management team will remain blinded unless the results meet the efficacy criteria (boundary is crossed). The Interim efficacy analyses will be produced by a statistical programmer and statistician independent of the study management team and will reviewed by a Data Monitoring Committee (DMC).

Full statistical details of the planned interim analyses, along with the rationale and timing will be documented in an interim statistical analysis plan, which will be made available to the relevant health authorities before the data snapshot for the first interim.

A Data Monitoring Committee will also evaluate safety according to policies and procedures detailed in a DMC Charter. Regular safety reviews will begin after approximately 15 patients (10 TCZ, 5 placebo) have been enrolled and reached 28-day follow-up. Early stopping criteria based on compelling efficacy or an imbalance in adverse events will be detailed in the DMC charter. The safety interim analyses will also be conducted by a statistical programmer and statistician independent from the study management team and will be reviewed by the DMC. Interactions between the DMC and Sponsor will be carried out as specified in the DMC Charter.

The Data Monitoring Committee will initially consist of Sponsor representatives not involved in any operational aspects of the study before transitioning to a fully independent data monitoring committee (iDMC) when feasible.

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

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

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

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. 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 before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

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

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative

must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 MANAGEMENT OF STUDY QUALITY

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

9.4 SITE INSPECTIONS

Site visits will be conducted 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 50 sites globally will participate to enroll approximately 330 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. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

A DMC will be employed to monitor and evaluate patient safety throughout the study. Tumor response and progression will be evaluated by an IRC.

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).

10. REFERENCES

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Appendix 1
Schedule of Activities: Days 1 and 2

	Screening [a]	Baseline					
Study Day	−2 to 0	1			2		
Hours Post Treatment		0	8	16	24	36	40
Informed consent	x [b]						
Inclusion/exclusion criteria	x	x					
Demographic data	x						
Randomization		x					
Medical history		x					
Complete physical examination [c]	x						
Weight		x					
COVID-19 diagnosis	x						
Chest X-ray/CT scan	x [d]						
ECG	x						
Pregnancy test [e]	x						
COVID-19 viral load [f]		x			x		
PaO_2/FiO_2 [g]	x	x	x	x	x		x
SpO_2 [h]	x	x	← x →				
Vital signs [h]	x	x	← x →				
Ordinal scoring [i]		x			x		
Hematology [j]	x	x			x		
Chemistry [k]	x	x					

Appendix 1: Schedule of Activities: Days 1 and 2

Central Labs							
CRP	x	x	x	x	x	x	x
Serum PK sampling [l]		x [m]	x	x	x	x	x
Serum IL-6	x	x [n]	x	x	x	x	x
Serum sIL-6R	x	x [n]	x	x	x	x	x
Serum sample for exploratory biomarkers		x			x		
Cryopreserved PBMCs [o]		x			x		
Whole blood in PAXgene® tubes for RNA analyses [p]		x					
Study drug administration [q]		x					
Adverse events [r]		x			x		
Concomitant medications [s]		x			x		

CRP = c-reactive protein; CT = computed tomography; ECG = electrocardiogram; eCRF = electronic case report form; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0; NEWS2 = National Early Warning Score; $PaO_2/FiO2$ = arterial oxygen partial pressure/fraction of inspired oxygen; PBMCs = peripheral blood mononuclear cells; PK = pharmacokinetic; PRO-CTCAE = NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; SpO_2 = peripheral capillary oxygen saturation.

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

[a] Results from standard-of-care tests or examinations performed prior to obtaining informed consent and within 24 hours before randomization may be used; such tests do not need to be repeated for screening.

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

[c] A complete physical examination, performed at screening and other specified visits, 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 baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

[d] Screening chest X-ray or CT scans should be performed within 24 hours prior to randomization.

[e] 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.

[f] Viral load will be assessed by nasopharyngeal swab. Patients who are intubated and undergo BAL 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.

[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 four times daily at timepoints separated by several hours while the patient remains hospitalized during the primary study period. After Day 28, for patients who remain in hospital, vital sign measurements and NEWS2-specific assessments should be conducted once per day. 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.

[i] Assessment of patient status using the ordinal scale should be recorded at baseline on Day 1/Visit 1 then again daily every morning (between 8 am and 12 pm) for patients who remain hospitalized.

[j] 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 NK cells; if the test is available at the site).

[k] 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, and ferritin.

[l] Patents receiving a second infusion of study drug should provide an extra PK sample prior to and 15 minutes after the end of the infusion, on the opposite arm as the infusion.

[m] On Day 1, PK samples should be drawn within 15 minutes after the end of the infusion, on the opposite arm as the infusion.

[n] On Day 1, IL-6 and sIL-6R samples should be drawn 0–4 hours before the start of infusion and then within 15 minutes after the end of the infusion, on the opposite arm as the infusion. Patents receiving a second infusion of study drug should provide extra samples for IL-6 and sIL-6R prior to and 15 minutes after the end of the infusion, on the opposite arm as the infusion.

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

[p] The first draw of blood should not be for PAXgene® tubes to avoid contact with RNA preservation reagent inside the tube.

[q] Study drug should be administered after collection of all samples for pharmacodynamic and exploratory biomarker analyses. If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–12 hours after the initial infusion.

[r] 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).

[s] 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.

Appendix 2
Schedule of Activities: Days 3–28

	Primary Phase																									Study Completion/ Discontinuation
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	
Complete physical examination [a]												x														x	x
Chest X-ray/CT scan					x							x							x							x	x
ECG					x							x							x							x	x
COVID-19 viral load [b]	x	x	x	x	x			x				x							x							x	x
Vital signs [c]	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 [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
SpO2 [c]	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 [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
Hematology [f]	x				x			x				x							x							x	x
Chemistry [g]	x				x			x				x							x							x	x
CRP	x				x							x							x							x	x
Serum PK sampling	x				x							x							x							x	x
Serum IL-6	x				x							x							x							x	x
Serum sIL-6R	x				x							x							x							x	x
Serum sample for exploratory biomarkers	x				x							x							x							x	x
Cryopreserved PBMCs [h]	x				x							x							x							x	x

Appendix 2: Schedule of Activities: Days 3-28

	Primary Phase																									Study Completion/ Discontinuation
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	
Whole blood in PAXgene® tubes for RNA analyses [i]	x				x							x							x							x	x
Adverse events [j]	x	x	x	x	x	x	x	x	x	x	x	x							x							x	x
Concomitant medications [k]	x	x	x	x	x	x	x	x	x	x	x	x							x							x	x

BAL = bronchoalveolar lavage; CRP = c-reactive protein; CT = computed tomography; ECG = electrocardiogram; eCRF = electronic case report form; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events v.5.0; $PaO_2/FiO2$ = arterial oxygen partial pressure/fraction of inspired oxygen; PBMCs = peripheral blood mononuclear cells; PK = pharmacokinetic; PRO-CTCAE = NCI Patient-Reported Outcomes Common Terminology Criteria for Adverse Events; SpO_2 = peripheral capillary oxygen saturation..

Note: All assessments should be performed within ±3 days of the scheduled visit.

[a] A complete physical examination, performed at screening and other specified visits, 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 baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

[b] Viral load will be assessed by nasopharyngeal swab. Patients who are intubated and undergo BAL 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.

[c] 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 four times daily at timepoints separated by several hours while the patient remains hospitalized during the primary study period. After Day 28, for patients who remain in hospital, vital sign measurements and NEWS2-specific assessments should be conducted once per day. 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] If arterial blood gases are measured.

[e] Assessment of patient status using the ordinal scale should be recorded at baseline on Day 1/Visit 1 then again daily every morning (between 8 am and 12 pm) for patients who remain hospitalized

[f] 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 NK cells; if the test is available at the site).

[g] 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, and ferritin.

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

[i] The first draw of blood should not be for PAXgene® tubes to avoid contact with RNA preservation reagent inside the tube.

[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.

Appendix 3
Schedule of Activities: After Day 28

			Study Completion
Study Day	35	45	60
Chest X-ray/CT scan			x
COVID-19 viral load [a]	x	x	x
Vital signs [b]	x	x	x
SpO_2 [b]	x	x	x
Ordinal scoring [c]	x	x	x
Hematology [d]	x	x	x
Chemistry [e]	x	x	x
CRP	x		x
PK	x		x
Serum IL-6	x		x
Serum sIL-6R	x		x
Serum sample for exploratory biomarkers	x		x
Adverse events [f]	x	x	x
Concomitant medications [g]	x	x	x

CRP = c-reactive protein; CT = computed tomography; NEWS2 = National Early Warning Score; PK = pharmacokinetic; SpO_2 = peripheral capillary oxygen saturation.

[a] Patient who remain in hospital will have viral load assessed by nasopharyngeal swabs, these will be done if there is evidence of on-going infection.

[b] After Day 28, for patients who remain in hospital, vital sign measurements and NEWS2-specific assessments should be conducted once per day. 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] Assessment of patient status using the ordinal scale should be recorded at baseline on Day 1/Visit 1 then again daily every morning (between 8 am and 12 pm) for patients who remain hospitalized

[d] 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 NK cells)

[e] 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, and ferritin.

[f] 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).

[g] 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.

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.

The oxygen saturation 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 [COPD]). 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 in the appropriate eCRF.

Example Case Calculation:

An 82-year-old lady 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 min)	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.