Protocol

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

Protocol for: Rosas IO, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. N Engl J Med. DOI: 10.1056/NEJMoa2028700

Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia

This supplement contains the following items:

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

PROTOCOL

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF TOCILIZUMAB IN PATIENTS WITH SEVERE COVID-19 PNEUMONIA**
PROTOCOL NUMBER:	WA42380
VERSION NUMBER:	1
EUDRACT NUMBER:	To be determined
IND NUMBER:	To be determined
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

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PHASE:	Phase III
INDICATION:	Severe COVID-19 pneumonia
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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

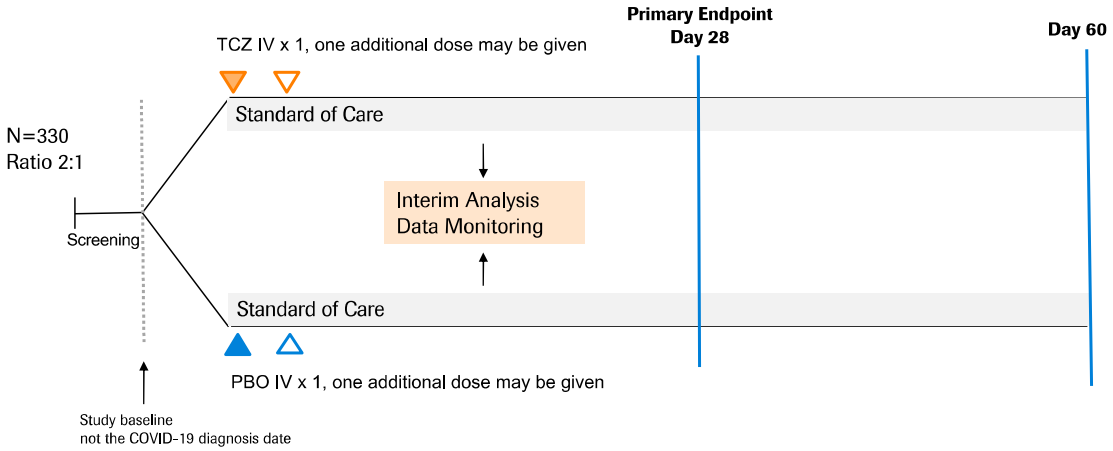
Patients will be followed up for a total of 60 days after first dose of study medication.

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 3: Schedule of Activities: After Day 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.

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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:	3
EUDRACT NUMBER:	2020-001154-22
IND NUMBER:	148225
NCT NUMBER:	NCT04320615
TEST PRODUCT:	Tocilizumab (RO4877533)
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
11-Jun-2020 19:02:50	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
2	14 April 2020
1	18 March 2020

PROTOCOL AMENDMENT, VERSION 3:
RATIONALE

Protocol WA42380 has been amended to better align with the statistical analysis plan (SAP). Changes to the protocol, along with a rationale for each change, are summarized below:

- An additional secondary efficacy endpoint of time to recovery was added to facilitate comparison with other trials of treatments for COVID-19 (Sections 2.1.2 and 6.4.2).
- Text on the sample size and power calculation was updated to incorporate the increased enrollment target to maintain 90% power for the primary endpoint, as described in the SAP (Sections 3.1, 4.1, 6.1, 9.5). The potential for an increase in enrollment was included in Version 2 of the protocol, and the confirmation of increased enrollment was communicated to sites, Agencies, and ethics committees in the week of 4 May 2020.
- The geographic stratification factors were updated to address the inclusion of only North American and Europe because no sites outside of these regions were included in the study (Sections 3.1, 4.2.1, 6.1, 6.4.2).
- Text on the reporting of pregnancies in partner of male patients was removed to align with the informed consent form and recommendations for tocilizumab in other indications (Section 5.4.3).
- The method of analysis for the primary endpoint was updated to utilize a non-parametric method that was determined to be a more appropriate method, as described in the SAP (Sections 6.1 and 6.4.1).
- The method of analysis for the secondary endpoint of clinical status at additional timepoints was updated to utilize a non-parametric method that was determined to be a more appropriate method, as described in the SAP (Section 6.4.2).
- Selected secondary efficacy endpoints were specified as key secondary endpoints to address Type I error control, as described in the SAP (Section 6.4.2).
- For clarity and as described in the SAP, language on the planned interim analyses was updated to address the increased enrollment target to maintain 90% power for the primary endpoint and the criteria for not conducting the interim analyses (Section 6.9).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF TOCILIZUMAB IN PATIENTS WITH SEVERE COVID-19 PNEUMONIA**
PROTOCOL NUMBER:	WA42380
VERSION NUMBER:	*3*
EUDRACT NUMBER:	2020-001154-22
IND NUMBER:	148225
IND NUMBER:	NCT04320615
TEST PRODUCT:	Tocilizumab (RO4877533)
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.

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
- 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). For patients entering the study already in ICU or on mechanical ventilation, clinical failure is defined as a one-category worsening on the ordinal scale, withdrawal or death.
- Mortality rate at Days 7, 14, 21, 28, and 60
- Time to hospital discharge or "ready for discharge" (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen)
- *Time to recovery, defined as discharged or "ready for discharge" (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen); OR, in a non-ICU hospital ward (or "ready for hospital ward") not requiring 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
- Organ failure-free days to Day 28

Safety Objective

The safety objective for this study is to evaluate the safety of TCZ compared with placebo in combination with SOC for the treatment of 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
- SARS-CoV-2 (COVID-19) 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, 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 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 and in both blood- and tissue-derived samples

STUDY DESIGN

Description of the Study

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of TCZ in combination with SOC compared with matching placebo in combination with SOC in hospitalized adult patients with severe COVID-19 pneumonia. The Sponsor intends to enroll approximately 450 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 SARS-CoV-2 (COVID-19) infection per WHO criteria, including a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have $SpO_2 \leq 93\%$ 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 and Europe) and mechanical ventilation (yes, no). The proportion of patients who are on a mechanical ventilator at the time of randomization will be capped at no more than 50% of the overall study population.

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, 8–24 hours after the initial infusion.

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

The 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.

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

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

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

Number of Patients

This study aims to enroll approximately 450 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 $\geq$ 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 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

  If a patient is on supplemental oxygen with $SpO_2 > 93\%$, but desaturation to $\leq 93\%$ on lower supplemental oxygen or ambient air is documented during screening, the inclusion criterion is met.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

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

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

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

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

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

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

Exclusion Criteria

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

- Known severe allergic reactions to TCZ or other monoclonal antibodies

- 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 3 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 (according to local laboratory reference ranges)
- ANC $<$ 1000/μL at screening (according to local laboratory reference ranges)
- Platelet count $<$ 50,000/μL at screening (according to local laboratory reference ranges)
- Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
- Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (investigational COVID-19 antivirals may be permitted 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 6 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 estimand is the difference in distributions between TCZ plus SOC and placebo plus SOC, which will be tested using a non-parametric method, the Van Elteren test, including the stratification factors at randomization (region [North America, Europe] and mechanical ventilation [yes, no]). The median ordinal scale result for each treatment group and the corresponding 95% CI for the median will be presented along with the Van Elteren p-value, as well as the difference in medians and a 95% CI for the difference.

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

As an additional analysis, 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] and mechanical ventilation [yes, no]). The odds ratio, p-value, and 95% confidence interval will be presented.

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 for the primary endpoint of comparison of clinical status based on a 7-category ordinal scale at Day 28 using *the Van Elteren test*.

The total mITT sample size of *450* with a 2:1 randomization of TCZ to placebo patients provides approximately *90*% power to detect a *difference in distribution between the treatment groups of the ordinal scale at Day 28 using a two-sided Van Elteren test at the 5% significance level* under the following assumptions of the expected probability distribution of patients in the placebo arm:

1 (discharge)	2	3	4	5	6	7 (death)
0.58	0.05	0.09	0.09	0.02	0.02	0.15

And, assuming proportional odds with an odds ratio of 2, the expected distribution in the TCZ arm with would be:

1 (discharge)	2	3	4	5	6	7 (death)
0.734	0.039	0.064	0.058	0.012	0.012	0.081

In addition, this sample size provides approximately 90% power to detect a ratio of 2 (TCZ to PBO) for the odds of being in a category or a better using a proportional odds model with a two-sided p-value at the 5% significance level.

Assuming proportional odds and the given distribution of the placebo group, the smallest odds ratio that could be statistically significant would be approximately *1.5*.

This sample size also provides *approximately 90%* power to detect a 10% absolute difference in mortality rate under the assumption of a 15% mortality rate in the placebo group.

Planned Interim Analyses

Up to three interim looks for efficacy 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 *111, 222, and 333* patients are enrolled, but all interims are subject to change depending on enrollment. If the sample size is increased during the study, the remaining efficacy interims will be performed at similar proportions of information to the original planned efficacy interim analyses.

The first efficacy interim analysis will be conducted when approximately *111* patients (*74* TCZ and *37* 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 the study is at least 90% enrolled within 5 weeks (28 days follow up plus 1 week to perform the analysis) of the 111th patient being enrolled, then no interim analyses will be conducted.*

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 (three interim looks and final analysis) are *4.364, 2.986, 2.377, and 2.011*.

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

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

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

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

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 CRS in the European Union and certain other countries.

1.4 REAL WORLD EXPERIENCE WITH TOCILIZUMAB IN COVID-19 PNEUMONIA

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

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

- Severe disease: dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation (SpO_2) ≤ 93%, PaO2/FiO_2 ratio (the ratio between the blood pressure of the oxygen [partial pressure of oxygen, 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).

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

Results from 21 Patients Treated with Tocilizumab in China

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

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

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

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

The study authors concluded that TCZ is an effective treatment for patients with severe COVID-19 (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 $\leq$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
- 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). For patients entering the study already in ICU or on mechanical ventilation, clinical failure is defined as a one-category worsening on the ordinal scale, withdrawal or death.
- Mortality rate at Days 7, 14, 21, 28, and 60
- Time to hospital discharge or “ready for discharge” (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or $\leq$2L supplemental oxygen)

- *Time to recovery, defined as discharged or "ready for discharge" (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen); OR, in a non-ICU hospital ward (or "ready for hospital ward") not requiring 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
- Organ failure-free days to Day 28

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of TCZ compared with placebo in combination with SOC for the treatment of 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
- SARS-CoV-2 (COVID-19) 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, 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

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 450 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 SARS-CoV-2 (COVID-19) infection per WHO criteria, including a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have $SpO_2 \leq 93\%$ 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 and Europe) and mechanical ventilation (yes, no). The proportion of patients who are on a mechanical ventilator at the time of randomization will be capped at no more than 50% of the overall study population.

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; see Section 4.5.10), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion.

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

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

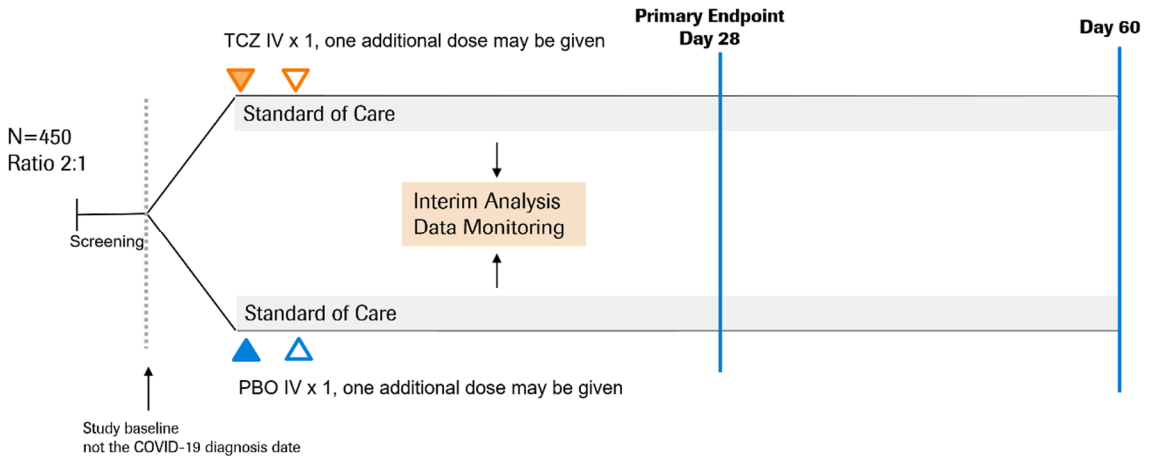
Patients will be followed up for a total of 60 days after first dose of study medication.

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

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 6 months.

Patients with evidence of lung fibrosis will be referred to their regular healthcare provider for further follow up.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Tocilizumab Dose and Schedule

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

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

infusions of TCZ (with at least 8 hours in between infusions) are allowed for CAR-T induced CRS, the proposed additional one infusion if clinical signs/symptoms worsen or do not improve is justified.

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

3.3.2 Rationale for Patient Population

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

Given the significant unmet need in 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 patients with severe COVID-19 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 450 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 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

  If a patient is on supplemental oxygen with $SpO_2 > 93\%$, but desaturation to $\leq 93\%$ on lower supplemental oxygen or ambient air is documented during screening, the inclusion criterion is met.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

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

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

(e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

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

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

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

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

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

4.1.2 Exclusion Criteria

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

- Known severe allergic reactions to TCZ or other monoclonal antibodies
- 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) within the past 3 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 (according to local laboratory reference ranges)
- ANC < 1000/μL at screening (according to local laboratory reference ranges)

- Platelet count $<$ 50,000/μL at screening (according to local laboratory reference ranges)
- Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
- Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (investigational COVID-19 antivirals may be permitted if approved by Medical Monitor)
- Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study

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 and Europe) and mechanical ventilation (yes, no). The proportion of patients who are on a mechanical ventilator at the time of randomization will be capped at no more than 50% of the overall study population.

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). In addition, Roche monitors, project statisticians, and the project team will be blinded from PK and

PD results (including IL-6, sIL-6R, and CRP) until the primary analysis. Study centers may be unblinded after the final study results are reported.

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

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

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMP) for this study are tocilizumab IV and its 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). One additional infusion of blinded treatment of TCZ or placebo can be given 8–24 hours after the initial infusion.

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

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

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

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

4.3.3 Investigational Medicinal Product Handling and Accountability

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

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

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

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

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

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

4.3.4 Continued Access to Tocilizumab

Since the TCZ treatment is not intended for continued therapy, the Sponsor does not have any plans to provide 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, investigational anti-viral agents, blood products) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

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

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

Clinical management guidelines from WHO recommend against the use of corticosteroids in patients with COVID-19 pneumonia. However, country- and region-specific guidelines recommend considering corticosteroids in some COVID-19 patients. This protocol allows the use of low-dose steroids as part of local SOC. If

steroids are given, the Sponsor recommends a dose of no more than 1 mg/kg methylprednisolone or equivalent for no more than 5 days.

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

4.4.2 Cautionary Therapy

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

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

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

4.4.2.2 Herbal Therapies

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

4.4.3 Prohibited Therapy

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

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

- Plasmapheresis or extracorporeal photopheresis during the study
- Immunization with a live or attenuated vaccine for the duration of the patient's study participation.

4.5 STUDY ASSESSMENTS

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

1. Efficacy assessments: clinical status, clinical signs and symptoms, oxygen saturation
2. Safety assessments: vital signs, review of adverse events, concomitant medications
3. Laboratory samples: on days when study drug is administered, all samples (including predose PK, safety and biomarkers) must be taken within 4 hours 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)

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

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

4.5.1 Informed Consent Forms and Screening Log

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

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. 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). If it is not feasible to weigh bed-bound patients, historical body weight may be used.

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 twice per day, with approximately 12 hours in between, 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. If vital signs or oxygen saturation are measured more than once during a 12-hour period, the worst values (highest temperature, respiratory rate, and heart rate; lowest blood pressure, oxygen saturation, and consciousness level) during that period should be recorded on the eCRF. Following hospital discharge these

parameters should be recorded once at each return visit to the clinic. Vital signs and oxygen saturation will not be recorded if follow-up visits are conducted by telephone.

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

4.5.5 Assessments Specific to National Early Warning Score 2

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

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, D-dimer, and ferritin
- Pregnancy test

  All women of childbearing potential will have a pregnancy test at screening (urine or serum). If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- SARS-CoV-2 (COVID-19) PCR (screening): nasopharyngeal swab, 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
- Serum samples for SARS-CoV-2 antibody titer
- Nasopharyngeal swabs and BAL (if applicable) for SARS-CoV-2 virology tests (viral load and exploratory analysis)
- 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, serum viral load, 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.

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

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

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

4.5.9 Electrocardiograms

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

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

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

4.5.10 Ordinal Scale Determination

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

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

Patients who are ready to be discharged but are still hospitalized (e.g., due to non-medical or administrative reasons) will be assigned an ordinal scale category of 1. Patients in a non-ICU hospital ward who are eligible for ICU care based on clinical presentation but are awaiting ICU care will be assigned an ordinal scale category of 4. Patients in an ICU for administrative or non-medical reasons who are ready for a non-ICU hospital ward will be assigned an ordinal scale category of 2 (if not requiring supplemental oxygen), 3 (if requiring supplemental oxygen), or 4 (if requiring non-invasive ventilation or high-flow oxygen).

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

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

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

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

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

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

4.6.2 Patient Discontinuation from the Study

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

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

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

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

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

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

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

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events and laboratory abnormalities, including criteria for 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. It is recommended that neutropenic patients (ANC $< 1000/\mu L$) undergo weekly surveillance blood cultures during the study.

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

5.1.1.3 Gastrointestinal Perforations

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

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

5.1.1.4 Hematologic Abnormalities

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

5.1.1.5 Demyelinating Disorders

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

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

5.1.1.6 Elevated Liver Enzymes

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

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

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

5.1.1.7 CYP450 Enzyme Normalization

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

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

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

Mobile Telephone No.: [redacted]

Alternate Medical Monitor Contact Information for All Sites

Medical Monitor: [redacted], M.D.

Mobile Telephone No.: [redacted]

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

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

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

5.4.3.2 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.

5.4.3.3 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 for the primary endpoint of comparison of clinical status based on a 7-category ordinal scale at Day 28 using *the Van Elteren test*.

The total mITT sample size of *450* with a 2:1 randomization of TCZ to placebo patients provides approximately *90*% power to detect a *difference in distribution between the treatment groups of the ordinal scale at Day 28 using a two-sided Van Elteren test at the 5% significance level* under the following assumptions of the expected probability distribution of patients in the placebo arm:

1 (discharge)	2	3	4	5	6	7 (death)
0.58	0.05	0.09	0.09	0.02	0.02	0.15

And, assuming proportional odds with an odds ratio of 2, the expected distribution in the TCZ arm would be:

1 (discharge)	2	3	4	5	6	7 (death)
0.734	0.039	0.064	0.058	0.012	0.012	0.081

In addition, this sample size provides approximately 90% power to detect a ratio of 2 (TCZ to PBO) for the odds of being in a category or a better using a proportional odds model with a two-sided p-value at the 5% significance level.

Assuming proportional odds and the given distribution of the placebo group, the smallest odds ratio that could be statistically significant would be approximately 1.*5*.

This sample size also provides *approximately 90%* power to detect a 10% absolute difference in mortality rate under the assumption of a 15% mortality rate in the placebo group.

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 SOC compared with placebo plus SOC 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 ≤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 estimand is the difference in distributions between TCZ plus SOC and placebo plus SOC, which will be tested using a non-parametric method, the Van Elteren test, including the stratification factors at randomization (region [North America, Europe] and mechanical ventilation [yes, no]). The median ordinal scale result for each treatment group and the corresponding 95% CI for the median will be presented along with the Van Elteren p-value, as well as the difference in medians and a 95% CI for the difference.

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

As an additional analysis, 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] and mechanical ventilation [yes, no]). The odds ratio, p-value, and 95% confidence interval will be presented.

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 mechanical ventilation (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.

- Time to clinical improvement (TTCI)

  Defined as time from *first dose of study drug* to NEWS2 of ≤2 maintained for 24 hours

- Time to improvement in ordinal clinical status *(key secondary endpoint)*

  Defined as time from *first dose of study drug* 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. For patients entering the study already in ICU or on mechanical ventilation, clinical failure is defined as a one-category worsening on the ordinal scale, withdrawal or death.

- Time to hospital discharge or "ready for discharge" *(key secondary endpoint)*

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

- *Time to recovery*

  Defined as discharged or "ready for discharge" (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen); OR, in a non-ICU hospital ward (or "ready for hospital ward") not requiring 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 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.

- Incidence of mechanical ventilation by Day 28
- Incidence of intensive care unit (ICU) stay by Day 28
- Difference in mortality rate at Day 28 *(key secondary endpoint)*

  In addition, mortality rates at Days 7, 14, 21, and 60 will be summarized descriptively.

Comparison of clinical status according to the 7-category ordinal scale (as detailed for the primary endpoint at Day 28) *will* also be analyzed *at Day 14 (key secondary endpoint)*.

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

Other secondary endpoints include:

- Ventilator-free days to Day 28 *(key secondary endpoint)*
- Duration of ICU stay
- Duration of supplemental O2

Duration endpoints will be summarized descriptively using the medians, with 95% CIs for the medians by treatment group.

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.

Organ failure-free days to Day 28 will be summarized descriptively using the median, with 95% CI for the medians by treatment group.

Organ failure is defined as present on any date when the most abnormal vital signs/abnormal lab value meets the definition of clinically significant organ failure according to the Brussels Organ Failure Table (Vincent 2006). Cardiovascular, pulmonary and central nervous system function will be assessed through blood pressure and requirement for pressors (instead of responsiveness to fluids), PaO_2:FiO_2 (or SpO_2:FiO_2 if arterial blood gases were not measured) ratio and the alert, verbal, pain, unresponsive scale (AVPU; instead of Glasgow Coma Scale), respectively. Renal, hepatic and coagulation parameters will be assessed via blood tests in order that the presence of clinically significant organ failure can be determined. Any day that a patient is alive and free of all 5 organ failures (pulmonary, cardiovascular, renal, hepatic, central nervous system) will be considered organ failure-free days. Days without organ failure will be summarized through Day 28 during hospitalization.

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.

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) SARS-CoV-2 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, 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 three interim looks for efficacy 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 *111, 222, and 333* patients are enrolled, but all interims are subject to change depending on enrollment. If the sample size is increased during the study, the remaining efficacy interims will be performed at similar proportions of information to the original planned efficacy interim analyses.

The first efficacy interim analysis will be conducted when approximately *111* patients (*74* TCZ and *37* 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 the study is at least 90% enrolled within 5 weeks (28 days follow up plus 1 week to perform the analysis) of the 111th patient being enrolled, then no interim analyses will be conducted.*

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 (three interim looks and final analysis) are *4.364, 2.986, 2.377, and 2.011*.

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 14-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

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

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

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of

the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

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

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

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

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

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

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a

separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

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

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

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior

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

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 60 sites globally will participate to enroll approximately 450 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.

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, b]	Baseline			
Study Day	−2 to 0	1		2	
Time Post Initial Treatment (Assessment Window)		0 Pre-dose (−4 hrs)	15 min After end of infusion (+1 hr)	24 hrs (±4 hrs)	36 hrs (±4 hrs)
Informed consent	x				
Inclusion/exclusion criteria	x	x			
Demographic data	x				
Randomization		x			
Medical history		x			
Complete physical examination [c]	x				
Weight		x			
COVID-19 diagnosis [d]	x				
Chest X-ray/CT scan [e]	x				
ECG	x				
Pregnancy test [f]	x				
PaO_2/FiO_2 [g]	x	← Optional →			
SpO_2 [h]	x	x	x	x	x
Vital signs [h]	x	x	x	x	x
Ordinal scoring [i]		x		x	
Adverse events [j]		x		x	
Concomitant medications [k]		x		x	

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

	Screening [a, b]	Baseline			
Study Day	−2 to 0	1		2	
Time Post Initial Treatment (Assessment Window)		0 Pre-dose (−4 hrs)	15 min After end of infusion (+1 hr)	24 hrs (±4 hrs)	36 hrs (±4 hrs)
Hematology [l]	x	x		x	
Chemistry [m]	x	x		x	
Study drug administration [n]		x			
Central Labs					
Serum PD (CRP, IL-6, sIL-6R)		x [o]	x [o]	x	x
Serum PK [p]		x [q]	x [q]	x	x
Serum sample for exploratory biomarkers		x		x	
SARS-CoV-2 viral load [r]		x		x	
Serum SARS-CoV-2 antibody titer		x			
Cryopreserved PBMCs [s]		x		x	
Whole blood in PAXgene® tubes for RNA analyses [t]		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 48 hours before randomization may be used; such tests do not need to be repeated for screening.

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

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

[d] COVID-19 test (SARS-CoV2 PCR) to confirm diagnosis should be performed within 7 days of randomization.

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

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

[g] If arterial blood gases are measured.

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

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

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

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

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

[m] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and/or AST, uric acid, LDH, ferritin, and D-dimer.

[n] Study drug should be administered after collection of all samples for pharmacodynamic and exploratory biomarker analyses. The initial study drug infusion should be given within 4 hours of randomization. If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion.

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

[p] Patents receiving a second infusion of study drug should provide an extra PK sample prior to and 15 minutes (to 1 hour) after the end of the infusion, on the opposite arm as the infusion.

[q] On Day 1, PK samples should be drawn 0–4 hours before the start of infusion and then within 15 minutes (to 1 hour) after the end of the infusion, on the opposite arm as the infusion.

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

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

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

Appendix 2
Schedule of Activities: Days 3–28

	Days 3–28 [a]																								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	
Chest X-ray/CT scan					x							x							x							x	x
Vital signs [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PaO_2/FiO_2 [c]	← Optional →																										Optional
SpO_2 [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ordinal scoring [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [f]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hematology [g]	x				x			x				x							x							x	x
Chemistry [h]	x				x			x				x							x							x	x
Central Labs																											
Serum PD (CRP, IL-6, sIL-6R)	x				x							x							x							x	x
Serum PK					x							x							x							x	x
Serum sample for exploratory biomarkers	x				x							x							x							x	x
SARS-CoV-2 viral load [i]	x	x	x	x	x			x				x							x							x	x
Serum SARS-CoV-2 antibody titer																										x	x
Cryopreserved PBMCs [j]	x				x							x							x							x	x

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

	Days 3–28 [a]																								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 [k]	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: For patients who have been discharged, all assessments should be performed within ±3 days of the scheduled onsite visit.

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

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

[c] If arterial blood gases are measured.

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

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

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

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

[h] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and/or AST, uric acid, LDH, ferritin, and D-dimer.

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

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

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

Appendix 3
Schedule of Activities: After Day 28

			Study Completion
Study Day (Assessment Window)	35 [a] (±3 days)	45 [a] (±3 days)	60 (±3 days)
Chest X-ray/CT scan			x
SARS-CoV-2 viral load [b]	x	x	x
Vital signs [c]	x	x	x
SpO_2 [c]	x	x	x
Ordinal scoring [d]	x	x	x
Adverse events [e]	x	x	x
Concomitant medications [f]	x	x	x
Hematology [g]	x	x	x
Chemistry [h]	x	x	x
Central Labs			
Serum PD (CRP, IL-6, sIL-6R)	x		x
Serum PK	x		x
Serum sample for exploratory biomarkers	x		x
Serum SARS-Cov-2 antibody titer			x

CRP = c-reactive protein; CT = computed tomography; PK = pharmacokinetic; SpO_2 = peripheral capillary oxygen saturation.

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

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

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

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

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

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

[g] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes), and lymphocyte subsets (T cells, B cells, and NK cells). Hematology labs will not be performed if follow-up visits are conducted by telephone.

[h] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and/or AST, uric acid, LDH, ferritin, and D-dimer. Chemistry labs will not be performed if follow-up visits are conducted by telephone.

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.

Appendix 4: National Early Warning Score 2 (NEWS2) (cont.)

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.

List of Protocol Amendments

Protocol WA42380 was amended to better align with the statistical analysis plan (SAP). Changes to the protocol, along with a rationale for each change, are summarized below:

- An additional secondary efficacy endpoint of time to recovery was added to facilitate comparison with other trials of treatments for COVID-19 (Sections 2.1.2 and 6.4.2).
- Text on the sample size and power calculation was updated to incorporate the increased enrollment target to maintain 90% power for the primary endpoint, as described in the SAP (Sections 3.1, 4.1, 6.1, 9.5). The potential for an increase in enrollment was included in Version 2 of the protocol, and the confirmation of increased enrollment was communicated to sites, Agencies, and ethics committees in the week of 4 May 2020.
- The geographic stratification factors were updated to address the inclusion of only North American and Europe because no sites outside of these regions were included in the study (Sections 3.1, 4.2.1, 6.1, 6.4.2).
- Text on the reporting of pregnancies in partner of male patients was removed to align with the informed consent form and recommendations for tocilizumab in other indications (Section 5.4.3).
- The method of analysis for the primary endpoint was updated to utilize a non-parametric method that was determined to be a more appropriate method, as described in the SAP (Sections 6.1 and 6.4.1).
- The method of analysis for the secondary endpoint of clinical status at additional timepoints was updated to utilize a non-parametric method that was determined to be a more appropriate method, as described in the SAP (Section 6.4.2).
- Selected secondary efficacy endpoints were specified as key secondary endpoints to address Type I error control, as described in the SAP (Section 6.4.2).
- For clarity and as described in the SAP, language on the planned interim analyses was updated to address the increased enrollment target to maintain 90% power for the primary endpoint and the criteria for not conducting the interim analyses (Section 6.9).

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

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STATISTICAL ANALYSIS PLAN

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

STUDY DRUG: Tocilizumab (RO4877533)

VERSION NUMBER: 1

IND NUMBER: 148225

EUDRACT NUMBER: 2020-001154-22

SPONSOR: F. Hoffmann-La Roche Ltd.

PLAN PREPARED BY: [redacted]

DATE FINAL: See electronic date stamp below

STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
24-Apr-2020 18:24:49	Company Signatory	[redacted]

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GLOSSARY OF ABBREVIATIONS

AE	adverse event
AEGT	adverse event grouped term
AESI	adverse event of special interest
BAL	bronchoalveolar lavage
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus 2019/ SAS-CoV-2
CRP	C-reactive protein
DMC	data monitoring committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic Case Report Form
ICU	intensive care unit
IL-6	interleukin 6
iDMC	independent data monitoring committee
ISAP	interim statistical analysis plan
IxRS	interactive voice or web-based response system
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEWS2	National Early Warning Score 2
PaO_2/FiO_2	Ratio between the blood pressure of the oxygen (partial pressure of oxygen, PaO_2) and the percentage of oxygen supplied (fraction of inspired oxygen, FiO_2)
PBO	placebo
PCR	polymerase chain reaction
PD	phamacodynamic
PK	pharmacokinetic
PT	preferred term
RT-PCR	reverse-transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
sIL-6R	soluble interleukin-6 receptor
SMQ	Standard MedDRA Query

SMT	study management team
SOC	standard of care / system organ class
SoC	scientific oversight committee
SpO2	blood oxygen saturation
TB	tuberculosis
TCZ	tocilizumab
TTCI	time to clinical improvement
VFDs	ventilator-free days
WHO	World Health Organisation

1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for the clinical efficacy and clinical safety for Study WA42380. Any analyses of biomarkers will be covered by a separate analysis plan. Analyses of pharmacokinetic data will be covered by a separate analysis plan.

There are currently no drugs licensed for the treatment of patients with SAS-CoV-2 (COVID-19). Based on the results from an initial 21-patient retrospective observational study, in which patients with severe or critical COVID-19 pneumonia were treated with tocilizumab (TCZ) off-label (Xu et al. 2020), TCZ, along with standard of care (SOC) treatment, could provide efficacy, offering the potential benefit to treat COVID-19 in hospitalized populations; with the limitation for this observational study of a lack of a proper control as a comparator. Extensive safety data have previously been generated on the use of TCZ in other indications. Therefore, a randomized 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. STUDY DESIGN

Study WA42380 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 (PBO) 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. A blinded sample size re-estimation may be considered during the study if the assumptions made on the distribution of patients across the ordinal scale do not hold. The sample size may be increased up to a maximum of 450 patients in order to adequately power the study.

Patients must be at least 18 years of age with confirmed SARS-CoV-2 (COVID-19) infection per WHO criteria, including a positive polymerase chain reaction (PCR) of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have blood oxygen saturation (SpO_2) ≤ 93% or PaO_2/FiO_2 (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 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 at a 2:1 ratio to receive blinded treatment of either TCZ or a matching placebo, respectively. Study treatment will be given in combination with SOC per local practice. The randomization will be stratified by geographic region (North America, Europe, and other) and mechanical ventilation (yes, no). The proportion of patients on a mechanical ventilator will be capped at no more than 50% of the overall study population.

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.

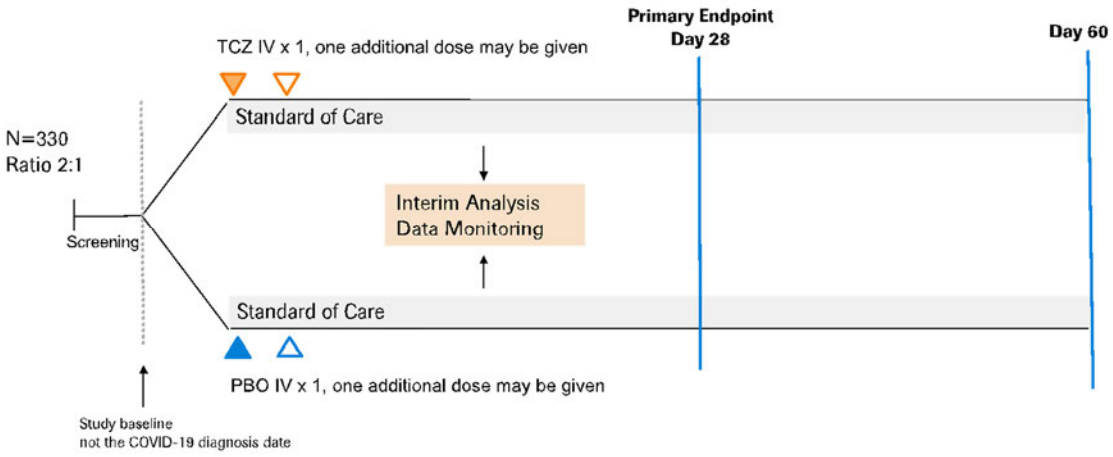
For both arms, if the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion. The investigator will record the reasons for screen failure in the screening log.

The study assessments to be conducted include the following: physical examination, vital signs, oxygen saturation, assessment of consciousness, presence and absence of respiratory support, adverse events, concomitant therapies, clinical laboratory tests, and nasopharyngeal swabs. Please see Appendix 2, Appendix 3 and Appendix 4 for details concerning the timing of these assessments.

Figure 1 presents an overview of the study design. The Schedule of Assessments is provided in Appendix 2, Appendix 3 and Appendix 4.

Figure 1 Study WA42380 Schema



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

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2, Appendix 3 and Appendix 4.

2.2 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.

2.2.1 Primary Efficacy Endpoints

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

  The ordinal scale categories are as follows:

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

4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen
5. ICU, requiring intubation and mechanical ventilation
6. ICU, requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support (e.g. vasopressors, renal replacement therapy)
7. Death

2.2.2 Secondary Efficacy 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
- Incidence of intensive care unit (ICU) stay
- Duration of ICU stay
- Clinical status assessed using a 7-category ordinal scale at Day 14
- Time to clinical failure, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first). For patients entering the study already in ICU or on mechanical ventilation, clinical failure is defined as a one-category worsening on the ordinal scale, withdrawal or death.
- Mortality 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 ≤2L supplemental oxygen)
- Duration of supplemental oxygen

2.2.2.1 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", which can include other forms of ventilation to maintain oxygen saturation (see Appendix 5).

NEWS2 values will be calculated by the Sponsor based on vital sign parameters and NEWS2 related assessments recorded by the investigator in the appropriate electronic Case Report Form (eCRF).

2.2.3 Exploratory Efficacy Endpoints

- Incidence of vasopressor use

- Duration of vasopressor use
- Incidence of extracorporeal membrane oxygenation (ECMO)
- Duration of ECMO
- Organ failure-free days

2.2.4 Pharmacodynamic Efficacy Endpoints

- Serum concentrations of interleukin 6 (IL-6), soluble interleukin-6 receptor (sIL-6R), ferritin, and C-reactive protein (CRP) at specified time points as shown in the schedule of assessments (see Appendix 2, Appendix 3 and Appendix 4).

2.2.5 Biomarkers

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 AEs or could lead to improved adverse event (AE) 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:

- Exploratory analysis of individual biomarkers in relation to efficacy, safety, exposure (listed in Section “Laboratory, Biomarker, and Other Biological Samples” of the protocol) and in both blood- and tissue-derived samples will be defined in a separate SAP.

2.2.6 Safety Endpoints

- Incidence and severity of AEs, 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 DETERMINATION OF SAMPLE SIZE

The estimated sample size was determined for the primary endpoint of comparison of clinical status based on a 7-category ordinal scale at Week 4 using the Van Elteren test. Table 1 shows the assumed distribution of the ordinal scale in the PBO plus SOC group. Table 2 shows the expected distribution in the TCZ plus SOC group with an odds ratio of 2 (assuming proportional odds). Under these assumptions, the total modified intent to treat (mITT) sample size of 330 with a 2:1 randomization of TCZ to placebo patients

provides approximately 80% power to detect a difference in distribution between the treatment groups of the ordinal scale at Week 4 using a two-sided Van Elteren test at the 5% significance level.

In addition this sample size provides approximately 80% power to detect a ratio of 2 (TCZ to PBO) for the odds of being in a category or a better category under the assumptions of the expected probability distribution of patients in the placebo arm in Table 1 , using a proportional odds model with a two-sided p-value at the 5% significance level.

Assuming proportional odds and the given distribution of the placebo group, the smallest odds ratio that could be statistically significant would be approximately 1.6.

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 blinded sample size re-estimation may be considered during the study if the assumptions made on the distribution of patients across the ordinal scale do not hold. The sample size may be increased up to a maximum of 450 patients in order to adequately power the study.

Table 1 Distribution of Ordinal Scale in the Placebo Group

1 (discharge)	2	3	4	5	6	7 (death)
0.58	0.05	0.09	0.09	0.02	0.02	0.15

Assuming proportional odds the expected distribution in the TCZ arm with an odds ratio of 2 would be:

Table 2 Distribution of the Ordinal scale in the Tocilizumab Group

1 (discharge)	2	3	4	5	6	7 (death)
0.734	0.039	0.064	0.058	0.012	0.012	0.081

2.4 ANALYSIS TIMING

Up to three interim looks for efficacy prior to the primary analysis will be carried out on the data with mortality rate at 4 Weeks (secondary endpoint) evaluated for interim efficacy analyses. The interim looks will occur after roughly 75, 150 and 225 patients have been enrolled and have reached the Day 28 follow-up time point, but all interims are subject to change depending on the enrollment rate. If the sample size is increased during the study then the remaining efficacy interims will be performed at similar proportions of information to the original planned efficacy interim analyses. For additional information about interim analyses, refer to Section 4.8.

If efficacy is declared based on an interim analysis of mortality, the data will be cleaned, a snapshot taken and the data in the snapshot will be reported. There will then be a final snapshot when all patients either reach Day 60, or have withdrawn.

If the study does not meet the efficacy criteria at one of the interim looks no reports for interim data, other than for the data monitoring committee (DMC), will be prepared; a snapshot of the data will be taken and the primary analysis will occur when the last patient either has withdrawn or completed the Day 28 visit. Formal efficacy analyses based on this snapshot will use data included in the Week 4 time window (see Section 4.5.1). A clinical study report (CSR) based on these analyses from this snapshot will be produced.

There will be an additional analysis on the final data when all patients have either reached Day 60 or withdrawn. Analyses from the first reporting event, restricted to data up to Week 4, will not be updated based on the final snapshot.

3. STUDY CONDUCT

The plan is to enroll approximately 330 patients that have been diagnosed with COVID-19 pneumonia and meet the entry criteria in centers globally. Patients will be randomized 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 standard of care. For both arms, if the clinical signs or symptoms worsen or do not improve, one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion.

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

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

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

3.1 RANDOMIZATION, STRATIFICATION AND BLINDING

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); and will occur through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. The proportion of patients who are on a mechanical ventilator at the time of randomization will be capped at no more than 50% of the overall study population.

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, interactive voice or web-based response system (IxRS) service provider, and Data Monitoring Committee (DMC) members and statistical programming analysts working with the DMC.

While pharmacokinetic (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 [SAE] 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 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.

3.2 DATA MONITORING

A DMC will monitor the incidence of all SAEs, adverse events of special interest (AESI) and any anticipated events during the study.

The DMC 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 14-day follow-up. Early stopping criteria will be detailed in the DMC charter and a separate interim statistical analysis plan (ISAP). Further details of efficacy interims are provided in Section 4.8. Interim analyses will 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 will initially consist of Sponsor representatives not directly involved in the study management team (SMT) and a scientific oversight committee (SoC) of external experts (responsibilities and operating principles of the DMC are described in a charter, the Internal Monitoring Committee and Scientific Oversight Committee Agreement). If feasible during study conduct the DMC responsibilities may transition to a fully independent data monitoring committee (iDMC).

4. STATISTICAL METHODS

All primary and secondary efficacy endpoints will be analyzed in the mITT population, with patients grouped according to the treatment assignment at randomization.

In all safety and pharmacodynamic analyses patients will be grouped according to the treatment that the patients actually received rather than the treatment assigned at randomization.

4.1 ANALYSIS POPULATIONS

Disposition summaries will be based on an All Patient population (all patients randomized and/or receiving study drug). Efficacy analyses will be based on the mITT population, if not otherwise specified. Analysis of safety data and pharmacodynamic (PD) data will be based on the safety population.

4.1.1 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.

4.1.2 Safety Population

Safety population will consist of all patients who receive any amount of study medication. In all safety and pharmacodynamic analyses, patients will be grouped according to the treatment that the patients first received rather than the treatment assigned at randomization.

4.2 ANALYSIS OF STUDY CONDUCT

The number of patients enrolled, discontinued, or who complete the study will be summarized to week 4 and to the end of the study. Reasons for premature study discontinuation will be listed and summarized to Week 4; and additionally to the end of the study. Listing of randomized patients and a listing of investigators will be produced.

The number of patients discharged from hospital will also be summarized by visit.

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

A listing by treatment group and patient of missed assessments for the primary endpoint will be produced through to Day 28, including study day of missed assessment, study day of discharge and /or death, if any.

The patients excluded from the safety and mITT populations will be summarized, including the reason for exclusion by treatment group. A summary of enrollment by country and investigator name will be produced.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (including, but not limited to, age, sex, race, geographic region, NEWS2, ordinal scale for clinical status, IL-6, sIL-6R, 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.

4.3.1 Demographics

- Sex
- Age
- Weight
- Race
- Ethnicity
- Geographic region
- Female fertility status

4.3.2 Disease Characteristics

- Smoking history (Never, Current, Former)
    - Former/current user: number of years subject smoked (years), Nicotine exposure in pack years
    - e-cigarettes use (Yes/No)

- NEWS2
- Ordinal scale for clinical status
- IL-6
- sIL-6R
- Mechanical ventilation (levels 5-6 of ordinal scale for clinical status)
- Steroid use at Day 1 (to be derived from concomitant medication)
- Anti-viral treatment at Day 1 (to be derived from concomitant medication)
- Symptoms at time of COVID 19 diagnosis
    - Fever
    - Cough
    - Shortness of breath
    - gastrointestinal symptoms (e.g. diarrhea, nausea, loss of appetite)
    - Headache
    - Fatigue
    - Other
- Number of days from first COVID-19 symptom at baseline
- COVID-19 diagnosis based on PCR of specimen type
- Number of days from COVID-19 diagnosis at baseline
- Specimen type at screening
- PCR result (Negative, positive)
- Quantitative PCR result

4.3.3 Medical history

Medical history data will be summarized descriptively by treatment group using the safety population. A glossary showing the mapping of investigator verbatim terms to diseases will be produced for the medical history data.

4.3.4 Surgeries and Procedures

A listing of any previous or ongoing surgeries and procedures will be produced for the safety population.

4.3.5 Previous and Concomitant Medications

Previous and concomitant treatments will be summarized descriptively by treatment group for the safety population. Previous treatments that have been stopped prior to study Day 1 will be summarized separately. There will be a summary of all concomitant treatments, including those that were initiated prior to study day 1. In addition there will be a summary of all treatments with the indication given as ‘COVID-19’.

Previous and concomitant treatments will be listed, with treatments for COVID-19 listed separately.

A glossary showing the mapping of investigator verbatim terms to medication coded terms will be produced for previous or concomitant medication.

4.4 VISIT LABELS

For summaries of data not collected by visit, such as AEs, medical history and concomitant medications all data up to the end of study will be included. Exceptions to these are death and discharge; which will be summarized weekly in descriptive summaries, following the time windowing approach described below.

Deaths will also be captured on the ordinal scale of clinical status. Deaths confirmed by public record are also captured in the eCRF, which may not have been captured as AEs for patients withdrawn from the study. These events will also be incorporated into the windowing for death.

Table 3 Time Windows for Assigning Assessment Study Days to Study Visits Labels for Deaths and Discharge

Scheduled study day	Efficacy time window
1 (Baseline)	< 1
7 (Week 1)	1 to 7
14 (Week 2)	>7 to ≤ 14
21 (Week 3)	> 14 to ≤ 21
28 (Week 4)	> 21 to ≤ 28
35 (Week 5)	> 28 to ≤ 35
45	> 35 to ≤ 45
60	> 45 to ≤ 67

Patient assessments that are collected at scheduled visits will be assigned to a study visit using the actual study day of the assessment; this includes data from withdrawal visits and any unscheduled visits. Time windows will be continuous from the midpoint between two consecutive study visits to the next midpoint, and will be dependent on the schedule of assessments for each variable independently. An example of time windowing for the PD parameters (CRP, IL-6, sIL-6R) is shown below.

Table 4 Time Windows for Assigning Assessment Study Days to Study Visits for PD parameters

Scheduled study day	[a]Efficacy time window
1 (Baseline)	≤ 1
Day 2	2
Day 3	3
7 (Week 1)	> 3 to ≤ 10
14 (Week 2)	> 10 to ≤ 17
21 (Week 3)	> 17 to ≤ 24
28 (Week 4)	> 24 to ≤ 28
35 (Week 5)	> 28 to ≤ 38
Day 45	> 38 to ≤ 52
Day 60	> 52 to ≤ 67

a From Week 1 onwards use value nearest to scheduled study day.

Where there is more than one efficacy assessment within a time window, then the nearest non-missing assessment will be assigned to that visit. If two or more assessments are equidistant from the scheduled time point, then the latest assessment will be used for efficacy (other than death where the assessment prior to the visit week will be used).

For safety parameters such as laboratory parameters and vital signs the 'worst case' will be used.

The last value from screening will be used for baseline assessments if there is no baseline (study Day 1) value. Pretreatment assessments will be used preferentially on study Day 1 for baseline.

4.5 EFFICACY ANALYSIS

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 withdrawals) may be conducted and are described in this SAP in each relevant section.

Descriptive subgroup analyses to evaluate the consistency of results across pre-specified subgroups may also be conducted as specified in Section 4.5.5.

4.5.1 Primary Efficacy Endpoint

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

- Clinical status assessed using a 7-category ordinal scale at Week 4

Assessment of patient status using this ordinal scale will be recorded at baseline and once daily in the morning (between 8 am and 12 pm) while hospitalized.

The primary estimand attributes are:

– Population: Patients with severe COVID-19 pneumonia as per the inclusion/exclusion criteria specified in the protocol (mITT)

– Primary endpoint: Clinical status at Week 4

– Treatments: TCZ plus SOC versus Placebo plus SOC

– Intercurrent events: Study withdrawal

– Handling of intercurrent events: last observed post-baseline value (except if the patient has been discharged [without re-admittance] or has died up to and including Day 28, then the death or discharge will override the Week 4 value or be imputed for a missing Week 4 value).

– Summary measure: medians (95% CI) PBO plus SOC and TCZ plus SOC

Intercurrent events are those that occur after treatment initiation and either preclude observation of the variable or affect its interpretation. For patients who withdraw before Week 4, their last post baseline ordinal category prior to withdrawal will be used in the primary analysis, unless death within the time frame was captured from public records or otherwise; in which case death will be used in the analysis.

The estimand is the difference in distributions between Tocilizumab plus SOC and Placebo plus SOC which will be tested using a non-parametric method, the Van Elteren test, including the stratification factors at randomization (region [North America, Europe, Other] and mechanical ventilation [yes, no]). The median ordinal scale result for each treatment group and the corresponding 95% CI for the median will be presented along with the Van Elteren P-value.

Additionally, for patients that withdraw prior to Week 4 on the TCZ arm, the 50th percentile of the TCZ data will be imputed from those that complete the study to Week 4, and on the placebo arm the 50th percentile will be imputed from the placebo data.

For patients that withdraw prior to Week 4 on the TCZ arm the 75th percentile will be imputed from those that complete the study to Week 4, and on the placebo arm the 25th percentile will be imputed from the placebo data.

In addition, the clinical status according to the 7-category ordinal scale will be compared between the TCZ group and the placebo group at Week 4, using a proportional odds

model accounting for stratification factors at randomization in the model (region [North America, Europe, Other] and mechanical ventilation [yes, no] using the mITT population. The odds ratio, p-value, and 95% confidence interval will be presented.

The assumption of proportional odds will be evaluated by visually comparing the fitted proportions of patients across the ordinal scale from the model with the observed data.

In addition to imputing the ordinal scale at Week 4 with an earlier death or discharge (without re-admittance), this imputation rule will also be followed at earlier time points. A death or discharge (unless the patient is re-admitted) will always be carried forward to all subsequent assessments regardless of what is recorded for the ordinal scale.

The ordinal scale will be summarized by Week and treatment showing n and percentage in each category, as well as missing data. Comparison of clinical status according to the 7-category ordinal scale (detailed for the primary endpoint at Week 4) will be analyzed using a proportional odds model at additional time points including but not limited to Week 2.

Stacked bar charts of the ordinal scale will be produced by treatment group, the bars will total to 100% and the categories, including 'missing', will be shown. At Week 4, a side by side comparison of the treatment groups by stacked bar chart will be shown.

4.5.2 Controlling for Type I Error

The following are key secondary endpoints for the study:

- Difference in Mortality at Week 4
- Ventilator-free days at Week 4
- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status to Week 4
- Clinical status assessed using a 7-category ordinal scale at Week 2

A treatment effect may be observed that may not meet statistical significance, but may still be considered clinically meaningful. For example, for difference in the proportion of deaths by Week 4, assuming a death rate of 15% on PBO plus SOC, the minimal difference that could be statistically significant is approximately 8%, whereas a smaller difference would be considered clinically important. Therefore all four of the key secondary endpoints will be tested in addition to the primary endpoint in order to help inform prescribers by potentially providing this information in the label if clinically meaningful.

4.5.3 Secondary Endpoints

4.5.3.1 Time to Event Analyses

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) and mechanical ventilation (yes, no) included as the stratification factors at Day 28 using the mITT population. The Kaplan-Meier plot, median time to response, and their 95% CIs, and a p-value will be presented. In addition, the treatment groups will be compared descriptively using a Cox proportional hazards model adjusting for the stratification factor applied at randomization. Hazard ratios and a 95% CI will be produced.

Time to event endpoints include:

- Time to clinical improvement in hours

Defined as time from randomization to NEWS2 of ≤ 2 maintained for 24 hours

The estimand is the difference in distributions between Tocilizumab plus SOC and Placebo plus SOC using the log rank test as described above.

Intercurrent events are those that occur after treatment initiation and either preclude observation of the variable or affect its interpretation. Intercurrent events, such as patients who are lost to follow-up, die or discontinue for any reason prior to achieving the event or do not have the event, will be accounted for through censoring rules, as described in Table 5 below.

Partial date times may be imputed based on available data, following a conservative approach. The NEWS2 is to be assessed twice daily, with approximately 12 hours between each assessment. Three consecutive scheduled assessments with a score of <=2 covering a span of at least 21.5 hours, with no missed scheduled assessments, will be required to meet the criterion.

Table 5 Time to clinical improvement and Censoring

Event	Censor	Date and Time
Hospital discharge prior to clinical improvement criterion met	Yes	Hospital discharge
Hospital discharge and hospital re-admission within 12 hours and continue study	No	Not Applicable
Death prior to clinical improvement criterion met	Yes	last scheduled vital sign assessment prior to death
Discontinuation for any reason prior to clinical improvement criterion met	Yes	last scheduled vital sign assessment prior to discontinuation
No clinical improvement	Yes	last vital sign assessment within Week 4 time window

NEWS2=National early warning score 2.

Other time to event endpoints include:

- Time to improvement in ordinal clinical status (days)

Defined as time from randomization to the time when at least a 2-category improvement in the 7-category ordinal scale is observed. For patients in category 2 at baseline, discharge will be considered as meeting the threshold. For patients that are discharged and the ordinal scale assessment has not been completed at discharge, they will be assumed to be in category one of the ordinal scale at the point of discharge, unless they are re-admitted within 12 hours. Intercurrent events, such as patients who are lost to follow-up, die or discontinue for any reason prior to achieving the event or do not have the event, will be accounted for through censoring rules, as described in Table 6 below.

Table 6 Time to improvement in Ordinal Clinical Status and Censoring

Event	Censor	Date and Time
Hospital discharge and hospital re-admission within 12 hours and continue study	No	Not Applicable
Death prior to improvement in Ordinal clinical status criterion met	Yes	Death
Discontinuation for any reason prior to improvement in Ordinal clinical status criterion met	Yes	last Ordinal scale assessment prior to discontinuation
No improvement in Ordinal clinical status	Yes	last Ordinal scale assessment within Week 4 time window

- Time from randomization to hospital discharge or “ready for discharge” (hours)

Ready for discharge; defined as normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen (ordinal scale category one)

Intercurrent events, such as patients who are lost to follow-up, die or discontinue for any reason prior to achieving the event or do not have the event, will be accounted for through censoring rules, as described in Table 7 below.

Table 7 Time to hospital discharge or "ready for discharge" and censoring

Event	Censor	Date and Time
Hospital discharge and hospital re-admission within 12 hours and continue study	No	Not Applicable
Death prior to discharge	Yes	Death
Discontinuation for any reason prior to discharge or "ready for discharge" criterion met	Yes	last Ordinal scale assessment prior to discontinuation
Not discharged or " ready for discharge"	Yes	last Ordinal scale assessment within Week 4 time window

- Time to clinical failure (days)

Defined as the time from randomization to first occurrence on study of death, mechanical ventilation, ICU admission or withdrawal (discontinuation from study), whichever occurs first. For patients entering the study already in ICU or on mechanical ventilation, clinical failure is defined as a one-category worsening on the ordinal scale, withdrawal or death.

Intercurrent events, such as patients who are lost to follow-up or discontinue for any reason prior to the event or do not have the event, will be accounted for through censoring rules, as described in Table 8 below.

Table 8 Time to Clinical Failure and censoring

Event	Censor	Date and Time
Hospital discharge not followed by death	Yes	Hospital discharge
Hospital discharge and hospital re-admission within 12 hours and continue study	No	Not Applicable
Clinical failure criterion not met	Yes	last of scheduled vital sign assessments or ordinal scale assessments within Week 4 time window

The NEWS2 score and clinical failure status as defined above will be summarized descriptively by visit.

4.5.3.2 Incidence endpoints

Secondary efficacy incidence 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) using the mITT population, unless stated otherwise. The weighted difference in proportions for the treatment group comparison will be presented with a p-value, together with a 95% CI (see Appendix 6).

- Incidence of mechanical ventilation by Week 4

Mechanical ventilation refers to invasive mechanical ventilation only, and/or ECMO.

- Incidence of ICU stay by Week 4

For incidence of mechanical ventilation or incidence of intensive care stay by Week 4 for patients that have withdrawn or died prior to Week 4, the non-responder rule will be applied, i.e. it will be assumed that the patient required mechanical ventilation, or has had an ICU stay by Week 4 in the analysis. Patients without either mechanical ventilation or intensive care stay respectively prior to discharge, will be assumed to be responders in the analysis, unless the patient is readmitted to hospital within 12 hours, or the patient dies by Week 4.

The number and proportion of patients requiring mechanical ventilation or an ICU stay will be summarized descriptively by study week.

- Difference in mortality at Week 4

The difference in proportion of patients that have died by Day 28 will be compared using the CMH test as described above as the main analysis method. In addition, a Fisher's exact test at Day 28 along with a p-value and a 95% CI for the difference using an exact method will be performed. The proportion in each group will also be presented along with a 95% CI for the proportion in each group using the Clopper-Pearson method. All deaths post discontinuation and discharge will be included in these analysis.

Deaths occurring between each visit, and cumulative deaths by visit will be summarized descriptively to Day 60.

4.5.3.3 Duration endpoints

- Ventilator-free days

The number of Ventilator-free days (VFDs) during hospitalization (prior to and including study day of death or discharge) is defined as the number of days from day 1 to day 28 when the patient is alive and breathes without invasive assistance of the mechanical ventilator. VFDs will be derived from the vital signs and oxygen saturation log; if invasive mechanical ventilation or ECMO is recorded for any part of the day, the day will not be counted as a VFD.

For patients withdrawn early from the study but not discharged, if patients were on invasive-mechanical ventilation at the point of discontinuation it will be assumed that the

remainder of days to Week 4 were not VFDs. For patients not using invasive mechanical ventilation at point of withdrawal it will be assumed the period to Week 4 are VFDs. Day 28 will be imputed as the final day of the hospitalization period for discontinued patients, unless the patient dies following discontinuation prior to Day 28, in which case Day of death will be used.

The rate of VFDs during hospitalization will be analyzed using a Poisson regression with duration in hospital as the offset, adjusting for baseline stratification factors.

VFDs during hospitalization will also be summarized descriptively using the medians, with 95% CIs for the medians and means with 95% CI by treatment group. The total number of days patients are hospitalized will be displayed as well as the ventilator-free days during hospitalization.

- Duration of supplemental O2 (days)

Duration of supplemental O2 (days) during hospitalization (prior to and including study day of death or discharge) will also be derived from the vital signs and oxygen saturation log, where study days with 'supplemental oxygen or other forms of ventilation' will be summed up to and including Week 4. Patients without any supplemental O2 use will assigned a duration of zero days. For patients withdrawn early from the study but not discharged, if the patients were on supplemental oxygen at the point of withdrawal it will be assumed that the remainder of days to Week 4 were on supplemental oxygen. For patients not using supplemental oxygen at point of withdrawal it will be assumed supplemental oxygen is not required to Week 4. Day 28 will be imputed as the final day of the hospitalization period for discontinued patients, unless the patient dies following discontinuation prior to Day 28, in which case Day of death will be used.

Days of supplemental O2 use during hospitalization will be analyzed and summarized descriptively in a similar method to VFDs. In addition number and the proportion of patients on supplemental oxygen using the observed data will be summarized by visit to Day 60.

- Duration of ICU stay (hours)

Duration of ICU stay (hours) during hospitalization will be calculated as the sum of the number of hours spent in ICU up to and including Week 4, based on the admission and discharge date times from the ICU stay information log; (ICU discharge datetime – ICU admission datetime). Multiple periods of ICU stay will be summed. Patients without any ICU stays will be assigned a duration of zero hours.

Partial admission and discharge times may be imputed based on available data, following a conservative approach. For patients that die or are discharged, any ongoing ICU stays without an end date will be imputed from date of death/ date of discharge as appropriate. For patients not in the ICU at the point of withdrawal from study it will be assumed that the period to Week 4 (or earlier death) has no incidences of ICU stay post

withdrawal. For patients in ICU on the day of withdrawal it will be assumed that they are in the ICU throughout the period to Week 4 (or earlier death). Day 28 will be imputed as the final day of the hospitalization period for discontinued patients, unless the patient dies following discontinuation prior to Day 28, in which case Day of death will be used.

Hours of ICU stay during hospitalization will be analyzed and summarized descriptively in a similar method to VFDs.

4.5.4 Exploratory Efficacy Endpoints

Incidence of vasopressor use (from concomitant medication records) and incidence of extracorporeal membrane oxygenation (ECMO) by Week 4 (and separately to Day 60) will be summarized descriptively.

Duration of vasopressor use (days) and ECMO (days) to Week 4 will be summarized using the median along with 95 % CIs for the median by treatment group. ECMO is collected daily and the total number of days of ECMO use will be totaled. Vasopressor duration will use start and stop dates from the concomitant medication records. A concomitant medication record that is ongoing at Week 4 will use the upper bound of the Week 4 time window as the end date for the duration.

Days without organ failure during hospitalization will be summarized descriptively through Week 4.

Organ failure is defined as present on any day when the most abnormal vital signs/abnormal lab value meets the definition of clinically significant organ failure according to the Brussels Organ Failure Table (Vincent 2006). Cardiovascular, pulmonary and central nervous system function will be assessed through blood pressure and pH (and responsiveness to fluids), PaO2:FiO2 ratio and alert, verbal, pain, unresponsive scale (AVPU; instead of Glasgow Coma Scale), respectively. Renal, hepatic and coagulation parameters will be assessed via blood tests in order that the presence of clinically significant organ failure can be determined. Each day a patient is alive and free of a given clinically significant organ failure will be scored as a failure-free day. Any day that a patient is alive and free of all 5 organ failures (pulmonary, cardiovascular, renal, hepatic, central nervous system) will be considered organ failure-free days.

4.5.5 Subgroup Analyses

The odds ratio for mortality for TCZ versus PBO at day 28 will be analyzed by logistic regression, including covariates of interest as well as the stratification factors in the model. The odds ratio for the treatment effect by gender, age (18-64 years, 65-84 years, 85 years and over), region and mechanical ventilation will be determined. Other subgroup analyses may also be performed.

4.6 PHARMACODYNAMIC ANALYSES

The PD analysis population will be identical to the safety population.

Summary tables for serum concentration of IL-6, sIL-6R, CRP and ferritin (mean, standard deviation, median, minimum, and maximum) will be produced by visit/ time point and treatment arm.

Individual patient data and descriptive statistics (i.e. median and interquartile range) will be plotted by visit/ time point for each treatment arm.

4.7 SAFETY ANALYSES

Safety assessments will be performed on the safety population. In all safety analyses, patients will be grouped according to the treatment that the patients first received rather than the treatment assigned at randomization.

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

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

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. The number and proportion of patients negative and positive will be displayed, and for those positive the quantitative result will be summarized.

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

4.7.1 Exposure of Study Medication

Exposure to study drug will be summarized including number of patients with one or two doses and number of patients with dose modification by treatment group.

A listing of patients by treatment group will be prepared detailing dosing of study drug, volume administered and any dose modification.

4.7.2 Adverse Events

Medical Dictionary for Regulatory Activities (MedDRA) will be used as the thesaurus for AEs and disease codes, and the WHO Drug Global B3 Format dictionary will be used for treatments. A glossary of these codes will be produced.

Only treatment-emergent AEs will be summarized. Treatment-emergent events are defined as those AEs with observed or imputed onset date on or after the start date of trial treatment. Only where the most extreme intensity is greater than the initial intensity (or if most extreme intensity is not missing and initial intensity is missing) will events with an onset date prior to the start of trial treatment be considered treatment-emergent. An AE with a completely missing start date will be assumed to be treatment-emergent unless the AE has a complete non-imputed end date that is prior to study Day 1.

Adverse events will be coded and tabulated by system organ class (SOC), and/or preferred term (PT) and treatment arm. In tabulations, PTs and their associated SOC will be presented in order of descending frequency summed across the treatment arms.

Adverse events will also be tabulated by severity, as graded according to NCI CTCAE v5.0 scale, and relationship to study medication as indicated by the investigator.

The following will also be summarized:

- serious adverse events
- adverse events leading to withdrawal of study drug
- adverse events leading to discontinuation from the study
- adverse events leading to death
- hypersensitivity adverse events (adverse events occurring immediately after or within 24 hours of the end of an infusion that are not deemed “unrelated” to study treatment)
- anaphylactic reactions

Adverse events of special interest will be defined using SOC, published Standard MedDRA Queries (SMQs) or AE Grouped Terms (AEGTs) defined by Roche Drug Safety. The groupings of AEs will include but may not be limited to the following:

- Infections (Infections and Infestations SOC)
- Opportunistic infections (Roche Standard AEGT Basket)
- Malignancies (Malignant or Unspecified tumors SMQ Narrow)
- Hepatic events (Hepatic failure, Fibrosis, and Cirrhosis and Other Liver Damage-related Conditions SMQ Wide or Hepatitis, non-infectious SMQ Wide)
- Stroke (Ischemic Cerebrovascular Conditions SMQ Wide or Hemorrhagic Cerebrovascular SMQ Wide)
- Myocardial infarction [MI] (MI SMQ Wide)
- Hypersensitivity Reactions (Hypersensitivity SMQ Narrow)

- Anaphylactic reaction events (utilizing Roche Standard AEGT Basket according to Sampson's criteria) [Sampson et al. 2006] occurring immediately after or within 24 hours of injection of tocilizumab; and a separate summary using the Anaphylactic Reaction SMQ Narrow for events occurring immediately after or within 24 hours of injection of tocilizumab
- Gastrointestinal perforations (Gastrointestinal perforation SMQ Wide)
- Bleeding events (Hemorrhages SMQ Wide)
- Demyelinating events (Demyelination SMQ Narrow)
- Severe cutaneous adverse reactions (Severe Cutaneous Adverse Reactions SMQ Wide)
- Accidents and Injuries (Accidents and Injuries SMQ Wide)
- Acute Pancreatitis (Acute Pancreatitis SMQ Narrow)
- Haematopoietic Thrombocytopenia (Haematopoietic Thrombocytopenia SMQ Narrow)
- Hypertension (Hypertension SMQ Narrow)
- Infectious biliary disorders (Infectious biliary disorders SMQ Narrow)
- Interstitial lung disease (ILD SMQ Wide)
- Liver related investigations, signs and symptoms (Liver related investigations, signs and symptoms SMQ Wide)
- Drug-induced Liver Injury (Roche Standard AEGT Basket)
- Lipid Lab Parameters (Roche Standard AEGT Basket)
- Neutropenia and associated complications (Obinutuzumab Roche Standard AEGT Basket)
- Pneumonia (Roche Standard AEGT Basket)
- Cholestasis and jaundice of hepatic origin (Cholestasis and jaundice of hepatic origin SMQ Narrow)
- Hepatocellular damage and hepatitis NEC (Hepatocellular damage and hepatitis NEC HLT)

A glossary showing the mapping of investigator verbatim terms to preferred terms will be produced for all AEs included in the analysis. For each AE of special interest table based on SMQs/AEGTs, a corresponding listing of the preferred terms that comprise the SMQ will be produced.

Listings of AEs and SAEs will be produced. Adverse events of special interest will also be listed.

AEs and SAEs will summarized by age category (18-64 years, 65-84 years, 85 years and over).

The exposure duration on study (exposure duration is the date of the last safety assessment or death if present, minus the date of the first dose of TCZ plus one divided by 365.25) will be summarized.

4.7.3 Laboratory Data

Laboratory values will be converted to Système International units, and data will be transformed to a common Roche Standard Reference Range.

Summary tables will detail the actual values and changes from baseline of the laboratory parameters over visits by treatment arm. Arterial blood gases will be summarized separately. Summaries of the number of patients by CTC grade for hematology, hepatic lab parameters (Alkaline phosphatase [ALP], Alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), and total bilirubin) and lipids (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) will be produced (for summaries referring to NCI CTCAE grading).

For neutrophils, platelets, lymphocytes, hepatic lab parameters and lipids, the number of patients will be summarized by CTCAE grade category for baseline and worst post baseline result.

Patients with values outside the reference will be listed, with an indication of the direction of the abnormality (High, Low).

A listing of all pregnancies will be presented.

4.7.4 Vital Signs

Summary statistics on absolute values and their change from baseline for all observed vital signs (diastolic blood pressures, systolic blood pressures, respiratory rate, pulse rate, body temperature and peripheral oxygen saturation) will be presented over time by treatment group. Baseline is defined as the last assessment prior to treatment. Additionally, a graphical representation of means over time of oxygen saturation and temperature (daily to Week 4) will be presented.

For patients requiring supplemental oxygen, summary statistics on absolute values of the oxygen flow rate (L/min) and/or fraction of inspired oxygen (FiO2) will be produced by visit/ time point and treatment group.

The level of consciousness will be summarized over time.

The number and proportion of patients requiring oxygen supplementation or other form of ventilation will be summarized over time, including type of support given. Non-invasive mechanical ventilation will be summarized overall as well as by its component types (continuous positive airway pressure [CPAP], bi-level positive airway pressure [BiPAP], other). Invasive mechanical ventilation will also be summarized overall and by component types (Endotracheal tube, tracheostomy tube).

A listing of patients with chest X-ray, CT scans and ECGs (as a separate listing) with clinically significant abnormalities will be produced.

4.7.5 Other Safety Endpoints

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.

4.8 INTERIM ANALYSES

Up to three efficacy interim analyses will be carried out on the data with mortality rate at 28 days (secondary endpoint) evaluated for efficacy. The interim looks will occur after roughly 75, 150, 225, patients are enrolled and have reached 28 days follow up, but all interims are subject to change depending on the enrollment rate. If the sample size is increased during the study, the remaining efficacy interims will be performed at similar proportions of information to the original planned efficacy interim analyses.

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). Up to two further interim efficacy analyses will occur after roughly 150 and 225 patients have reached the 28-day follow-up time point. 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 be eligible receive open-label TCZ. At this point, efficacy will be declared. Recruitment into the TCZ arm will continue until 220 patients have been enrolled.

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 (three interim analyses and primary analysis) are 4.6, 3.13, 2.49 and 2.00. The one-sided local significance levels at the three efficacy interim analyses are 0.000002581, 0.0008847 and 0.006351.

Additional information regarding the efficacy interim analyses is detailed in 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 be reviewed by a 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 DMC 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 14-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 directly involved in the SMT. If feasible during study conduct, the responsibilities may transition to a fully independent DMC (iDMC).

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Appendix 1 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**
PROTOCOL NUMBER:	WA42380
VERSION NUMBER:	2
EUDRACT NUMBER:	2020-001154-22
IND NUMBER:	148225
IND NUMBER:	NCT04320615
TEST PRODUCT:	Tocilizumab (RO4877533)
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.

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
- 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). For patients entering the study already in ICU or on mechanical ventilation, clinical failure is defined as a one-category worsening on the ordinal scale, withdrawal or death.
- Mortality rate at Days 7, 14, 21, 28, and 60
- Time to hospital discharge or "ready for discharge" (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or $\leq$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
- Organ failure-free days to Day 28

Safety Objective

The safety objective for this study is to evaluate the safety of TCZ compared with placebo in combination with SOC for the treatment of 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
- SARS-CoV-2 (COVID-19) 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, 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 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 and in both blood- and tissue-derived samples

STUDY DESIGN

Description of the Study

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of TCZ in combination with SOC compared with 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. Enrollment may be increased to 450 patients if a sample size re-estimation is performed.

Patients must be at least 18 years of age with confirmed SARS-CoV-2 (COVID-19) infection per WHO criteria, including a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have $SpO_2 \leq 93\%$ 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). The proportion of patients who are on a mechanical ventilator at the time of randomization will be capped at no more than 50% of the overall study population.

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, 8–24 hours after the initial infusion.

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

The 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.

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

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

Day 45 visits may be conducted by telephone or by home visits for discharged patients, while the Day 60 visit should be conducted onsite.

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

Number of Patients

This study aims to enroll approximately 330 hospitalized patients with severe COVID-19 pneumonia. Enrollment may be increased to 450 patients if a sample size re-estimation is performed.

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 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

  If a patient is on supplemental oxygen with $SpO_2 > 93\%$, but desaturation to $\leq$ 93% on lower supplemental oxygen or ambient air is documented during screening, the inclusion criterion is met.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

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

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

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

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

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

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

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

Exclusion Criteria

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

- Known severe allergic reactions to TCZ or other monoclonal antibodies
- 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 3 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 (according to local laboratory reference ranges)
- ANC $<$ 1000/μL at screening (according to local laboratory reference ranges)
- Platelet count $<$ 50,000/μL at screening (according to local laboratory reference ranges)
- Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
- Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (investigational COVID-19 antivirals may be permitted 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 6 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.

An additional sensitivity analysis using a stratified Cochran-Mantel-Haenszel (CMH) test will also 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 for the primary endpoint of comparison of clinical status based on a 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 to detect a ratio of 2 (TCZ to placebo) for the odds of being in a category or a better category under the following assumptions of the expected probability distribution of patients in the placebo arm:

1 (discharge)	2	3	4	5	6	7 (death)
0.58	0.05	0.09	0.09	0.02	0.02	0.15

Assuming proportional odds, the expected distribution in the TCZ arm with an odds ratio of 2 would be:

1 (discharge)	2	3	4	5	6	7 (death)
0.734	0.039	0.064	0.058	0.012	0.012	0.081

Assuming proportional odds and the given distribution of the placebo group, the smallest odds ratio that could be statistically significant would be approximately 1.6.

Planned Interim Analyses

Up to three interim looks for efficacy 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, and 225 patients are enrolled, but all interims are subject to change depending on enrollment. If the sample size is increased during the study, the remaining efficacy interims will be performed at similar proportions of information to the original planned efficacy interim analyses.

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 and will utilize an O'Brien-Fleming alpha-spending function. The efficacy boundaries for the z-scores at the four looks (three interim looks and final analysis) are 4.558, 3.126, 2.492 and 1.997.

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 14-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.

Appendix 2 Schedule of Activities: Days 1 and 2

	Screening [a, b]	Baseline			
Study Day	–2 to 0	1		2	
Time Post Initial Treatment *(Assessment Window)*		0 *Pre-dose (–4 hrs)*	*15 min After end of infusion (+1 hr)*	*24 hrs (±4 hrs)*	*36 hrs (±4 hrs)*
Informed consent	x				
Inclusion/exclusion criteria	x	x			
Demographic data	x				
Randomization		x			
Medical history		x			
Complete physical examination [c]	x				
Weight		x			
COVID-19 diagnosis [d]	x				
Chest X-ray/CT scan [e]	x				
ECG	x				
Pregnancy test [f]	x				
PaO_2/FiO_2 [g]	x	← *Optional* →			
SpO_2 [h]	x	x	*x*	*x*	*x*
Vital signs [h]	x	x	*x*	*x*	*x*
Ordinal scoring [i]		x		x	
Adverse events [j]		x		x	
Concomitant medications [k]		x		x	
Hematology [l]	x	x		x	
Chemistry [m]	x	x		x	
Study drug administration [n]		x			

	Screening [a, b]	Baseline			
Study Day	–2 to 0	1		2	
Time Post Initial Treatment *(Assessment Window)*		0 *Pre-dose (–4 hrs)*	*15 min After end of infusion (+1 hr)*	*24 hrs (±4 hrs)*	*36 hrs (±4 hrs)*
Central Labs					
Serum PD (CRP, IL-6, sIL-6R)		x [o]	x [o]	x	x
Serum PK [p]		x [q]	x [q]	x	x
Serum sample for exploratory biomarkers		x		x	
SARS-CoV-2 viral load [r]		*x*		*x*	
Serum SARS-CoV-2 antibody titer		*x*			
Cryopreserved PBMCs [s]		x		x	
Whole blood in PAXgene® tubes for RNA analyses [t]		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 48 hours before randomization may be used; such tests do not need to be repeated for screening.

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

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

[d] COVID-19 test (SARS-CoV2 PCR) to confirm diagnosis should be performed within 7 days of randomization.

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

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

[g] If arterial blood gases are measured.

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

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

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

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

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

[m] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and/or AST, uric acid, LDH, ferritin, and D-dimer.

[n] Study drug should be administered after collection of all samples for pharmacodynamic and exploratory biomarker analyses. The initial study drug infusion should be given within 4 hours of randomization. If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion.

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

[p] Patents receiving a second infusion of study drug should provide an extra PK sample prior to and 15 minutes (to 1 hour) after the end of the infusion, on the opposite arm as the infusion.

[q] On Day 1, PK samples should be drawn 0–4 hours before the start of infusion and then within 15 minutes (to 1 hour) after the end of the infusion, on the opposite arm as the infusion.

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

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

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

Appendix 3 Schedule of Activities: Days 3–28

	Days 3–28 [a]																									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	
Chest X-ray/CT scan					x							x							x							x	x
Vital signs [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PaO_2/FiO_2 [c]	← *Optional* →																										*Optional*
SpO_2 [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ordinal scoring [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [e]	x	x	x	x	x	x	x	x	x	x	x	x	*x*	*x*	*x*	*x*	*x*	*x*	x	*x*	*x*	*x*	*x*	*x*	*x*	x	x
Concomitant medications [f]	x	x	x	x	x	x	x	x	x	x	x	x	*x*	*x*	*x*	*x*	*x*	*x*	x	*x*	*x*	*x*	*x*	*x*	*x*	x	x
Hematology [g]	x				x			x				x							x							x	x
Chemistry [h]	x				x			x				x							x							x	x
Central Labs																											
Serum PD (CRP, IL-6, sIL-6R)	x				x							x							x							x	x
Serum PK					x							x							x							x	x
Serum sample for exploratory biomarkers	x				x							x							x							x	x
SARS-CoV-2 viral load [i]	x	x	x	x	x			x				x							x							x	x
Serum SARS-CoV-2 antibody titer																										*x*	*x*
Cryopreserved PBMCs [j]	x				x							x							x							x	x

	Days 3–28 [a]																									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 [k]	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: For patients who have been discharged, all assessments should be performed within ±3 days of the scheduled onsite visit.

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

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

[c] If arterial blood gases are measured.

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

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

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

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

[h] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and/or AST, uric acid, LDH, ferritin, and D-dimer.

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

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

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

Appendix 4 Schedule of Activities: After Day 28

			Study Completion
Study Day *(Assessment Window)*	35 [a] *(±3 days)*	45 [a] *(±3 days)*	60 *(±3 days)*
Chest X-ray/CT scan			x
SARS-CoV-2 viral load [b]	x	x	x
Vital signs [c]	x	x	x
SpO_2 [c]	x	x	x
Ordinal scoring [d]	x	x	x
Adverse events [e]	x	x	x
Concomitant medications [f]	x	x	x
Hematology [g]	x	x	x
Chemistry [h]	x	x	x
Central Labs			
Serum PD (CRP, IL-6, sIL-6R)	x		x
Serum PK	x		x
Serum sample for exploratory biomarkers	x		x
Serum SARS-Cov-2 antibody titer			*x*

CRP = c-reactive protein; CT = computed tomography; PK = pharmacokinetic; SpO_2 = peripheral capillary oxygen saturation.

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

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

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

Appendix 4 Schedule of Activities: After Day 28 (cont.)

[d] Assessment of clinical 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.

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

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

[g] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes), and lymphocyte subsets (T cells, B cells, and NK cells). Hematology labs will not be performed if follow-up visits are conducted by telephone.

[h] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and/or AST, uric acid, LDH, ferritin, and D-dimer. Chemistry labs will not be performed if follow-up visits are conducted by telephone.

Appendix 5 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.

Appendix 6 National Early Warning Score 2 (NEWS2) (cont.)

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.

Appendix 6 Cochran-Mantel-Haenszel Test

- The weighted difference in proportions is the difference in the response rates in the experimental treatment group compared with the control treatment group, adjusted for any stratification factors. With two stratification factors, the number of patients in each strata is defined as nijk where i is the level of the first stratification factor and j is the level of the second stratification factor and k is treatment group (experimental or control). The number of events in each strata is denoted by xijk, where i, j and k are as above. The proportion of responders in each strata will be calculated by:

$$p_{ijk} = \frac{x_{ijk}}{n_{ijk}}$$ where i, j and k are as above

- The difference in proportions for each strata will then be calculated as the proportion of patients in each strata in the experimental treatment group (EXP) minus the proportion of patients in each strata in the control treatment group (CON) and denoted $d_{ij} = p_{ijEXP} - p_{ijCON}$, for i and j as above.

- The weights for each strata (i, j) will be calculated as follows:

$$w_{ij} = \frac{n_{ijEXP} * n_{ijCON}}{n_{ijEXP} + n_{ijCON}}$$

- Within each strata, the weighted differences in the proportions in each of the treatment groups will be calculated as follows:

$$wd_{ij} = w_{ij} d_{ij}$$

- and then summed:

$$WD = \sum_i \sum_j wd_{ij}$$

- After calculation of the weighted difference in proportions, the calculation of the 95% confidence interval is as follows;

- Continuity-corrected Proportions

$$p^{\#}_{ijk} = \frac{x_{ijk} + 0.5}{n_{ijk} + 1}$$

- Variances

$$Upvar_{ij} = w_{ij}^2 \left[p^{\#}_{ijEXP} \frac{\left(1 - p^{\#}_{ijEXP}\right)}{n_{ijEXP}} + p^{\#}_{ijCON} \frac{\left(1 - p^{\#}_{ijCON}\right)}{n_{ijCON}} \right]$$

Appendix 6
Cochran-Mantel-Haenszel Test (cont.)

- To calculate the sum of the weights and variances over all strata:

Sum over Strata

$$W = \sum_i \sum_j w_{ij}$$ (sum of weights)

$$Var = \sum_i \sum_j Up\,\mathrm{var}_{ij}$$ (sum of variances)

Point Estimate and Standard Error

$$d = \frac{WD}{W}; \quad se = \sqrt{\frac{Var}{W^2}}$$

Stratified 95% Confidence Intervals

$$\text{Lower Limit} = d - 1.96se$$

$$\text{Upper Limit} = d + 1.96se$$

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STATISTICAL ANALYSIS PLAN

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

STUDY DRUG: Tocilizumab (RO4877533)

VERSION NUMBER: 3

IND NUMBER: 148225

EUDRACT NUMBER: 2020-001154-22

SPONSOR: F. Hoffmann-La Roche Ltd.

PLAN PREPARED BY: [redacted]

DATE FINAL: Version 1: 24 April 2020

DATES AMENDED Version 2: 26 May 2020
Version 3: See electronic date stamp below

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

Date and Time(UTC)	Reason for Signing	Name
16-Jul-2020 16:46:46	Company Signatory	[redacted]

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

This Statistical Analysis Plan WA42380 Version 3 was amended from Version 2 as follows:

- Time to event endpoints were changed from “time from randomization” to “time from first dose of study drug”
- The Type I error control section was updated to specify a hierarchy for testing of the primary endpoint followed by testing the difference in mortality
- Cumulative Incidence Function plots were specified for time to ‘improvement’ end points
- The censoring rules for the time to event endpoints were updated
- Derivation of organ failure-free days was clarified
- Laboratory ranges were clarified
- ‘Other’ was removed from the stratification by region as only patients from Europe and North America were randomized.
- The synopsis appended from the protocol was updated to be consistent with protocol version 3.
- A subgroup analysis of the primary endpoint by mechanical ventilation status (as stratified) was added to the primary analysis section

Additional minor changes have been made to improve clarity and consistency.

This Statistical Analysis Plan WA42380 Version 2 was amended from Version 1 as follows:

- The sample size was amended to 450 patients based on powering the study at 90%
- A new secondary endpoint was added ‘Time to Recovery’
- Time to discharge or “ready for discharge” was elevated to one of the key secondary endpoints
- The censoring rules for deaths were changed to right censoring for time to event endpoints, other than for time to clinical failure
- The derivation of vent-free days was modified so that patients that have died are assigned zero vent-free days.
- The list of Adverse Events of Special Interest was modified

Additional minor changes have been made to improve clarity and consistency.

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GLOSSARY OF ABBREVIATIONS

AE	adverse event
AEGT	adverse event grouped term
AESI	adverse event of special interest
BAL	bronchoalveolar lavage
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus 2019/ SARS-CoV-2
CRP	C-reactive protein
DMC	data monitoring committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic Case Report Form
ICU	intensive care unit
IL-6	interleukin 6
iDMC	independent data monitoring committee
ISAP	interim statistical analysis plan
IxRS	interactive voice or web-based response system
LPLV	last patient last visit
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEWS2	National Early Warning Score 2
PaO_2/FiO_2	Ratio between the blood pressure of the oxygen (partial pressure of oxygen, PaO_2) and the percentage of oxygen supplied (fraction of inspired oxygen, FiO_2)
PBO	placebo
PCR	polymerase chain reaction
PD	phamacodynamic
PK	pharmacokinetic
PT	preferred term
RT-PCR	reverse-transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
sIL-6R	soluble interleukin-6 receptor
SMQ	Standard MedDRA Query

SMT	study management team
SOC	standard of care / system organ class
SoC	scientific oversight committee
SpO2	blood oxygen saturation
TB	tuberculosis
TCZ	tocilizumab
TLR	top line report
TTCI	time to clinical improvement
VFDs	ventilator-free days
WHO	World Health Organisation

1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for the clinical efficacy and clinical safety for Study WA42380. Any analyses of biomarkers will be covered by a separate analysis plan. Analyses of pharmacokinetic data will be covered by a separate analysis plan.

There are currently no drugs licensed for the treatment of patients with SARS-CoV-2 (COVID-19). Based on the results from an initial 21-patient retrospective observational study, in which patients with severe or critical COVID-19 pneumonia were treated with tocilizumab (TCZ) off-label (Xu et al. 2020), TCZ, along with standard of care (SOC) treatment, could provide efficacy, offering the potential benefit to treat COVID-19 in hospitalized populations; with the limitation for this observational study of a lack of a proper control as a comparator. Extensive safety data have previously been generated on the use of TCZ in other indications. Therefore, a randomized 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. STUDY DESIGN

Study WA42380 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 (PBO) in combination with SOC in hospitalized adult patients with severe COVID-19 pneumonia. The Sponsor intends to enroll approximately 450 patients that diagnosed with COVID-19 pneumonia that meet the entry criteria in centers globally.

Patients must be at least 18 years of age with confirmed SARS-CoV-2 (COVID-19) infection per WHO criteria, including a positive polymerase chain reaction (PCR) of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have blood oxygen saturation (SpO_2) ≤ 93% or PaO_2/FiO_2 (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 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 at a 2:1 ratio to receive blinded treatment of either TCZ or a matching placebo, respectively. Study treatment will be given in combination with SOC per local practice. The randomization will be stratified by geographic region (North

America, Europe) and mechanical ventilation (yes, no). The proportion of patients on a mechanical ventilator will be capped at no more than 50% of the overall study population.

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.

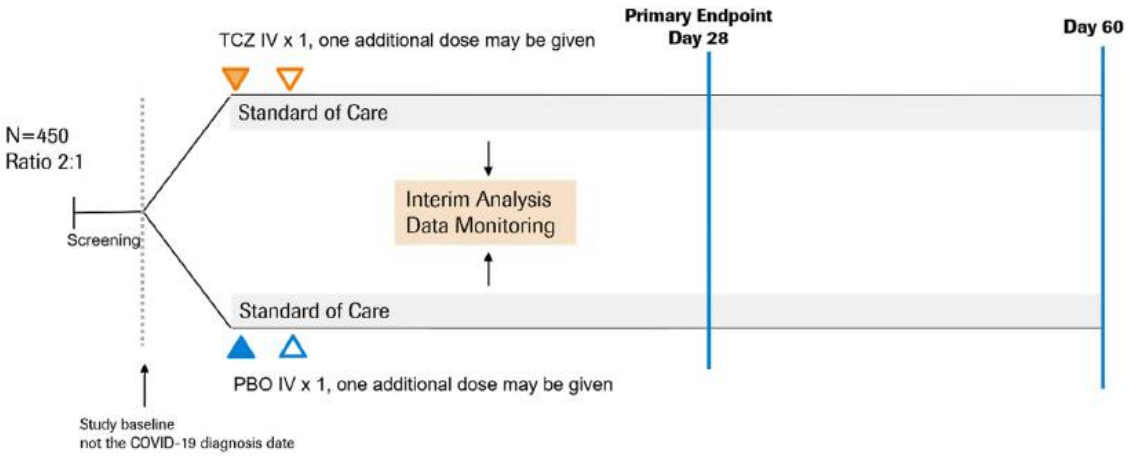
For both arms, if the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion. The investigator will record the reasons for screen failure in the screening log.

The study assessments to be conducted include the following: physical examination, vital signs, oxygen saturation, assessment of consciousness, presence and absence of respiratory support, adverse events, concomitant therapies, clinical laboratory tests, and nasopharyngeal swabs. Please see Appendix 2, Appendix 3 and Appendix 4 for details concerning the timing of these assessments.

Figure 1 presents an overview of the study design. The Schedule of Assessments is provided in Appendix 2, Appendix 3 and Appendix 4.

Figure 1 Study WA42380 Schema



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

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2, Appendix 3 and Appendix 4.

2.2 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.

2.2.1 Primary Efficacy Endpoints

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

  The ordinal scale categories are as follows:

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

2.2.2 Secondary Efficacy 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
- Incidence of intensive care unit (ICU) stay

- Duration of ICU stay
- Clinical status assessed using a 7-category ordinal scale at Day 14
- Time to clinical failure, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first). For patients entering the study already in ICU or on mechanical ventilation, clinical failure is defined as a one-category worsening on the ordinal scale, withdrawal or death.
- Mortality 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 ≤ 2L supplemental oxygen)
- Time to recovery defined as hospital discharge or "ready for discharge" (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen), or Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen
- Duration of supplemental oxygen

2.2.2.1 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", which can include other forms of ventilation to maintain oxygen saturation (see Appendix 5).

NEWS2 values will be calculated by the Sponsor based on vital sign parameters and NEWS2 related assessments recorded by the investigator in the appropriate electronic Case Report Form (eCRF).

2.2.3 Exploratory Efficacy Endpoints

- Incidence of vasopressor use
- Duration of vasopressor use
- Incidence of extracorporeal membrane oxygenation (ECMO)
- Duration of ECMO
- Organ failure-free days

2.2.4 Pharmacodynamic Efficacy Endpoints

- Serum concentrations of interleukin 6 (IL-6), soluble interleukin-6 receptor (sIL-6R), ferritin, and C-reactive protein (CRP) at specified time points as shown in the schedule of assessments (see Appendix 2, Appendix 3 and Appendix 4).

2.2.5 Biomarkers

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 AEs or could lead to improved adverse event (AE) 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:

- Exploratory analysis of individual biomarkers in relation to efficacy, safety, exposure (listed in Section “Laboratory, Biomarker, and Other Biological Samples” of the protocol) and in both blood- and tissue-derived samples will be defined in a separate SAP.

2.2.6 Safety Endpoints

- Incidence and severity of AEs, 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 DETERMINATION OF SAMPLE SIZE

The estimated sample size was determined for the primary endpoint of comparison of clinical status based on a 7-category ordinal scale at Week 4 using the Van Elteren test. Table 1 shows the assumed distribution of the ordinal scale in the PBO plus SOC group. Table 2 shows the expected distribution in the TCZ plus SOC group with an odds ratio of 2 (assuming proportional odds). Under these assumptions, the total modified intent to treat (mITT) sample size of 450 with a 2:1 randomization of TCZ to placebo patients provides approximately 90% power to detect a difference in distribution between the treatment groups of the ordinal scale at Week 4 using a two-sided Van Elteren test at the 5% significance level.

In addition this sample size provides approximately 90% power to detect a ratio of 2 (TCZ to PBO) for the odds of being in a category or a better category under the assumptions of the expected probability distribution of patients in the placebo arm in Table 1, using a proportional odds model with a two-sided p-value at the 5% significance level.

Assuming proportional odds and the given distribution of the placebo group, the smallest odds ratio that could be statistically significant would be approximately 1.5.

This sample size also provides approximately 90% power to detect a 10% absolute difference in mortality rate under the assumption of a 15% mortality rate in the placebo group.

Table 1 Distribution of Ordinal Scale in the Placebo Group

1 (discharge)	2	3	4	5	6	7 (death)
0.58	0.05	0.09	0.09	0.02	0.02	0.15

Assuming proportional odds the expected distribution in the TCZ arm with an odds ratio of 2 would be:

Table 2 Distribution of the Ordinal scale in the Tocilizumab Group

1 (discharge)	2	3	4	5	6	7 (death)
0.734	0.039	0.064	0.058	0.012	0.012	0.081

2.4 ANALYSIS TIMING

Up to three interim looks for efficacy prior to the primary analysis will be carried out on the data with mortality rate at 4 Weeks (secondary endpoint) evaluated for interim efficacy analyses. The interim looks will occur after roughly 111, 222 and 333 patients have been enrolled and have reached the Day 28 follow-up time point, but all interims are subject to change depending on the enrollment rate. For additional information about interim analyses, refer to Section 4.8.

If efficacy is declared based on an interim analysis of mortality, the data will be cleaned, a snapshot taken and the data in the snapshot will be reported. There will then be a final snapshot when all patients either reach Day 60, or have withdrawn.

If the study does not meet the efficacy criteria at one of the interim looks, or the efficacy interim is not performed, no reports for interim data, other than for the data monitoring committee (DMC), will be prepared; a snapshot of the data will be taken and the primary analysis will occur when the last patient either has withdrawn or completed the Day 28 visit. A clinical study report (CSR) and/or a top line report (TLR) based on the analyses from this snapshot will be produced.

There will be an additional analysis on the final data when all patients have either reached Day 60 or withdrawn. Analyses from the first reporting event, restricted to data up to Day 28 (Week 4), will not be updated based on the final snapshot.

3. STUDY CONDUCT

The plan is to enroll approximately 450 patients that have been diagnosed with COVID-19 pneumonia and meet the entry criteria in centers globally. Patients will be

randomized 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 standard of care. For both arms, if the clinical signs or symptoms worsen or do not improve, one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion.

Patients who do not meet the criteria for participation in this study (screen failure) may qualify for one re-screening opportunity (for a total of two screenings per participant) at the investigator's discretion.

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

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

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

3.1 RANDOMIZATION, STRATIFICATION AND BLINDING

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 mechanical ventilation (yes, no); and will occur through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. The proportion of patients who are on a mechanical ventilator at the time of randomization will be capped at no more than 50% of the overall study population.

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, interactive voice or web-based response system (IxRS) service provider, and Data Monitoring Committee (DMC) members and statistical programming analysts working with the DMC.

While pharmacokinetic (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 [SAE] 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 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.

3.2 DATA MONITORING

A DMC will monitor the incidence of all SAEs, adverse events of special interest (AESI) and any anticipated events during the study.

The DMC 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 14-day follow-up. Early stopping criteria will be detailed in the DMC charter and a separate interim statistical analysis plan (ISAP). Further details of efficacy interims are provided in Section 4.8. Interim analyses will 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 will initially consist of Sponsor representatives not directly involved in the study management team (SMT) and a scientific oversight committee (SoC) of external experts (responsibilities and operating principles of the DMC are described in a charter, the Internal Monitoring Committee and Scientific Oversight Committee Agreement). If feasible during study conduct the DMC responsibilities may transition to a fully independent data monitoring committee (iDMC).

4. STATISTICAL METHODS

All primary and secondary efficacy endpoints will be analyzed in the mITT population, with patients grouped according to the treatment assignment at randomization.

In all safety and pharmacodynamic analyses patients will be grouped according to the treatment that the patients actually received rather than the treatment assigned at randomization.

4.1 ANALYSIS POPULATIONS

Disposition summaries will be based on an All Patient population (all patients randomized and/or receiving study drug). Efficacy analyses will be based on the mITT population, if not otherwise specified. Analysis of safety data and pharmacodynamic (PD) data will be based on the safety population.

4.1.1 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.

4.1.2 Safety Population

Safety population will consist of all patients who receive any amount of study medication. In all safety and pharmacodynamic analyses, patients will be grouped according to the treatment that the patients first received rather than the treatment assigned at randomization.

4.2 ANALYSIS OF STUDY CONDUCT

The number of patients enrolled, discontinued, or who complete the study will be summarized to week 4 and to the end of the study. Reasons for premature study discontinuation will be listed and summarized to Week 4; and additionally to the end of the study. Listing of randomized patients and a listing of investigators will be produced.

The number of patients discharged from hospital will also be summarized by visit.

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

A listing by treatment group and patient of missed assessments for the primary endpoint will be produced through to Day 28, including study day of missed assessment, study day of discharge and /or death, if any.

The patients excluded from the safety and mITT populations will be summarized, including the reason for exclusion by treatment group. A summary of enrollment by country and investigator name will be produced.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (including, but not limited to, age, sex, race, geographic region, NEWS2, ordinal scale for clinical status, IL-6, sIL-6R, 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.

4.3.1 Demographics

- Sex
- Age
- Weight
- Race
- Ethnicity
- Geographic region
- Female fertility status

4.3.2 Disease Characteristics

- Smoking history (Never, Current, Former)
  - Former/current user: number of years subject smoked (years), Nicotine exposure in pack years
  - e-cigarettes use (Yes/No)
- NEWS2
- Ordinal scale for clinical status
- IL-6
- CRP
- Ferritin
- sIL-6R
- Mechanical ventilation
- Steroid use at Day 1 (to be derived from concomitant medication)
- Anti-viral treatment at Day 1 (to be derived from concomitant medication)
- Symptoms at time of COVID 19 diagnosis
  - Fever
  - Cough
  - Shortness of breath
  - gastrointestinal symptoms (e.g. diarrhea, nausea, loss of appetite)
  - Headache
  - Fatigue
  - Other
- Number of days from first COVID-19 symptom at baseline

- COVID-19 diagnosis based on PCR of specimen type
- Number of days from COVID-19 diagnosis at baseline
- Specimen type at screening
- PCR result (Negative, positive)
- Quantitative PCR result (viral load)

4.3.3 Medical history

Medical history data will be summarized descriptively by treatment group using the safety population. A glossary showing the mapping of investigator verbatim terms to diseases will be produced for the medical history data.

4.3.4 Surgeries and Procedures

A listing of any previous or ongoing surgeries and procedures will be produced for the safety population.

4.3.5 Previous and Concomitant Medications

Previous and concomitant treatments will be summarized descriptively by treatment group for the safety population. Previous treatments that have been stopped prior to study Day 1 will be summarized separately. There will be a summary of all concomitant treatments, including those that were initiated prior to study day 1. In addition there will be a summary of all treatments with the indication given as 'COVID-19'.

Previous and concomitant treatments will be listed, with treatments for COVID-19 listed separately.

A summary of patients requiring supplemental oxygen post-discharge will be provided. This will be based on "home oxygen" being recorded on the Concomitant Medication page of the eCRF.

A glossary showing the mapping of investigator verbatim terms to medication coded terms will be produced for previous or concomitant medication.

4.4 VISIT LABELS

For summaries of data not collected by visit, such as AEs, medical history and concomitant medications all data up to the end of study will be included. Exceptions to this include death, discharge and ICU stay; which will be summarized weekly in descriptive summaries, following the time windowing approach described below.

Deaths will also be captured on the ordinal scale of clinical status. Deaths confirmed by public record are also captured in the eCRF, which may not have been captured as AEs for patients withdrawn from the study. These events will also be incorporated into the windowing for death.

Table 3 Time Windows for Assigning Assessment Study Days to Study Visits Labels for Deaths and Discharge

Scheduled study day	Efficacy time window
1* (Baseline)	< 1
7 (Week 1)	1 to 7
14 (Week 2)	>7 to ≤ 14
21 (Week 3)	> 14 to ≤ 21
28 (Week 4)	> 21 to ≤ 28
35 (Week 5)	> 28 to ≤ 35
45	> 35 to ≤ 45
60	> 45 to ≤ 67

*Study day 1 is the first day of study drug

Patient assessments that are collected at scheduled visits will be assigned to a study visit using the actual study day of the assessment; this includes data from withdrawal visits and any unscheduled visits. Time windows will be continuous from the midpoint between two consecutive study visits to the next midpoint, and will be dependent on the schedule of assessments for each variable independently. An example of time windowing for the PD parameters (CRP, IL-6, sIL-6R) is shown below.

Table 4 Time Windows for Assigning Assessment Study Days to Study Visits for PD parameters

Scheduled study day	[a]Efficacy time window
1 (Baseline)	≤ 1
Day 2	2
Day 3	3
7 (Week 1)	> 3 to ≤ 10
14 (Week 2)	> 10 to ≤ 17
21 (Week 3)	> 17 to ≤ 24
28 (Week 4)	> 24 to ≤ 28
35 (Week 5)	> 28 to ≤ 38
Day 45	> 38 to ≤ 52
Day 60	> 52 to ≤ 67

a From Week 1 onwards use value nearest to scheduled study day.

Where there is more than one efficacy assessment within a time window, then the nearest non-missing assessment will be assigned to that visit. If two or more assessments are equidistant from the scheduled time point, then the latest assessment will be used for efficacy (other than death or discharge where the assessment prior to the visit week will be used as described previously).

For safety parameters such as laboratory parameters and vital signs the 'worst case' will be used.

The last value from screening will be used for baseline assessments if there is no baseline (study Day 1) value. Pretreatment assessments will be used preferentially on study Day 1 for baseline.

4.5 EFFICACY ANALYSIS

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 withdrawals) may be conducted and are described in this SAP in each relevant section.

Descriptive subgroup analyses to evaluate the consistency of results across pre-specified subgroups may also be conducted as specified in Section 4.5.5.

4.5.1 Primary Efficacy Endpoint

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

- Clinical status assessed using a 7-category ordinal scale at Week 4

Assessment of patient status using this ordinal scale will be recorded at baseline and once daily in the morning (between 8 am and 12 pm) while hospitalized.

The primary estimand attributes are:

– Population: Patients with severe COVID-19 pneumonia as per the inclusion/exclusion criteria specified in the protocol (mITT)

– Primary endpoint: Clinical status at Week 4

– Treatments: TCZ plus SOC versus Placebo plus SOC

– Intercurrent events: Events leading to study withdrawal

– Handling of intercurrent events: last observed post-baseline value (except if the patient has been discharged [without re-admittance] or has died up to and including Day 28, then the death or discharge will override the Week 4 value or be imputed for a missing Week 4 value).

– Summary measure: medians (95% CI) PBO plus SOC and TCZ plus SOC

Intercurrent events are those that occur after treatment initiation and either preclude observation of the variable or affect its interpretation. For patients who withdraw before Week 4, their last post baseline ordinal category prior to withdrawal will be used in the primary analysis, unless death within the time frame was captured from public records or otherwise; in which case death will be used in the analysis.

The estimand is the difference in distributions between Tocilizumab plus SOC and Placebo plus SOC which will be tested using a non-parametric method, the Van Elteren test, including the stratification factors at randomization (region [North America, Europe] and mechanical ventilation [yes, no]). The median ordinal scale result for each treatment group and the corresponding 95% CI for the median will be presented along with the Van Elteren P-value, as well as the difference in medians and a 95% CI for the difference.

Additionally, for patients that withdraw prior to Week 4 on the TCZ arm, the 50th percentile of the TCZ data will be imputed from those that complete the study to Week 4 (deaths and discharges are included as completing to Week 4), and on the placebo arm the 50th percentile will be imputed from the placebo data.

For patients that withdraw prior to Week 4 on the TCZ arm the 75th percentile will be imputed from those that complete the study to Week 4 (deaths and discharges are included as completing to Week 4), and on the placebo arm the 25th percentile will be imputed from the placebo data.

In addition, the clinical status according to the 7-category ordinal scale will be compared between the TCZ group and the placebo group at Week 4, using a proportional odds model accounting for stratification factors at randomization in the model (region [North America, Europe] and mechanical ventilation [yes, no] using the mITT population. The odds ratio, p-value, and 95% confidence interval will be presented.

The assumption of proportional odds will be evaluated by visually comparing the fitted proportions of patients across the ordinal scale from the model with the observed data.

In addition to imputing the ordinal scale at Week 4 with an earlier death or discharge (without re-admittance), captured from ordinal scale or other sources, this imputation rule will also be followed at earlier time points, including the day of death or discharge.

A death or discharge (unless the patient is re-admitted) will always be carried forward to all subsequent assessments regardless of what is recorded for the ordinal scale. If a patient is re-admitted then the ordinal scale data from the point of re-admittance will be used. The ordinal scale will be summarized by Week and treatment showing n and percentage in each category, as well as missing data. Comparison of clinical status according to the 7-category ordinal scale (detailed for the primary endpoint at Week 4) will be analyzed using a proportional odds model at additional time points including but not limited to Week 2.

Stacked bar charts of the ordinal scale will be produced by treatment group, the bars will total to 100% and the categories, including ‘missing’, will be shown. At Week 4, a side by side comparison of the treatment groups by stacked bar chart will be shown.

The primary endpoint will be analysed by the mechanical ventilation status as randomized, as it is considered that this stratification factor may be predictive for response to tocilizumab treatment. The clinical status assessed using a 7-category ordinal scale at Week 4 will be tested in the subgroups split by mechanical ventilation status (yes, no) as stratified using the Van Elteren test for each subgroup. The subgroups will also be analysed using the proportional odds model as specified for the primary endpoint.

4.5.2 Controlling for Type I Error

The following are key secondary endpoints for the study:

- Difference in Mortality at Week 4
- Ventilator-free days at Week 4
- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status to Week 4
- Time to hospital discharge or “ready for discharge”

- Clinical status assessed using a 7-category ordinal scale at Week 2

The primary endpoint (the difference in distributions in clinical status between Tocilizumab plus SOC and Placebo plus SOC at Week 4; Van Elteren test) will be tested at a two-sided 5% significance level. If the primary endpoint is statistically significant the difference in mortality at Week 4 will then be tested at 0.05 (two-sided Cochran-Mantel-Haenszel test). There will be no further multiplicity adjustment for the additional four key secondary endpoints.

A treatment effect may be observed in a key secondary endpoint that may not meet nominal statistical significance, but may still be considered clinically meaningful. Therefore all five of the key secondary endpoints will be tested in addition to the primary endpoint in order to help inform prescribers by potentially providing this information in the label if clinically meaningful.

4.5.3 Secondary Endpoints

4.5.3.1 Time to Event Analyses

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 mechanical ventilation (yes, no) included as the stratification factors at Day 28 using the mITT population. The Kaplan-Meier plot, median time to response, and their 95% CIs, and a p-value will be presented. In addition, the treatment groups will be compared descriptively using a Cox proportional hazards model adjusting for the stratification factor applied at randomization. Hazard ratios and a 95% CI will be produced.

For time to event endpoints, other than time to clinical failure, deaths will be right censored (at Day 28). Consequently, for these endpoints, participants censored on Day 28 reflect two different states, death and failure to meet the improvement outcome criterion. Therefore, it is important to understand the efficacy outcome in the context of the number and timing of deaths by treatment arm. Cumulative incidence function plots for both death and the event of interest will be produced using the non-parametric Aalen–Johansen estimator.

For time to event endpoints that include discharge as an event, the earliest time of discharge or “ready for discharge” from the different sources of discharge will be used in all analyses. If a patient is discharged and re-admitted more than 12 hours later, then the first discharge will be considered as meeting the event. If a patient is readmitted within 12 hours of discharge, then they will not have met the endpoint at this time. If they are discharged later in the study (without re-admittance within 12 hours), then the later time of discharge will be used.

Time to event endpoints include:

- Time to clinical improvement in hours

Defined as time from first dose of study drug to NEWS2 of ≤ 2 maintained for 24 hours

The estimand is the difference in distributions between Tocilizumab plus SOC and Placebo plus SOC using the log rank test as described above.

Intercurrent events are those that occur after treatment initiation and either preclude observation of the variable or affect its interpretation. Intercurrent events, such as patients who are lost to follow-up, die or discontinue for any reason prior to achieving the event or do not have the event, will be accounted for through censoring rules, as described in Table 5 below.

Patients who have a score of ≤2 at baseline will be analysed in the same way as patients with a score that is >2 at baseline.

Partial date times may be imputed based on available data, following a conservative approach. The NEWS2 is to be assessed twice daily, with approximately 12 hours between each assessment. At least two assessments with a score of ≤2 covering a span of at least 21.5 hours will be required to meet the criterion, with a maximum of 26.5 hours between the first and last of these assessments (there must be no assessments with a score >2 in between). If a patient has a score of ≤ 2 and is then discharged from hospital within 26.5 hours, with no subsequent scores > 2 before the discharge they will have met the endpoint.

Table 5 Time to clinical improvement and Censoring

Event	Censor	Date and Time
Hospital discharge prior to clinical improvement criterion met	Yes	Hospital discharge
Hospital discharge and hospital re-admission within 12 hours and continue study	No	Not Applicable
Death prior to clinical improvement criterion met	Yes	Day 28
Discontinuation or lost to follow-up for any reason prior to clinical improvement criterion met	Yes	last scheduled vital sign assessment
No clinical improvement	Yes	last vital sign assessment within Week 4 time window

Other time to event endpoints include:

- Time to improvement in ordinal clinical status (days)

Defined as time from first dose of study drug to the time when at least a 2-category improvement in the 7-category ordinal scale is observed. For patients in category 2 at baseline, discharge or “ready for discharge” will be considered as meeting the threshold. For patients that are discharged and the ordinal scale assessment has not been completed at discharge, they will be assumed to be in category one of the ordinal scale at the point of discharge, unless they are re-admitted within 12 hours. Intercurrent events, such as patients who are lost to follow-up, die or discontinue for any reason prior to achieving the event or do not have the event, will be accounted for through censoring rules, as described in Table 6 below.

Table 6 Time to improvement in Ordinal Clinical Status and Censoring

Event	Censor	Date and Time
Hospital discharge and hospital re-admission within 12 hours and continue study	No	Not Applicable
Death prior to improvement in Ordinal clinical status criterion met	Yes	Day 28
Discontinuation or lost to follow up for any reason prior to improvement in Ordinal clinical status criterion met	Yes	last Ordinal scale assessment
No improvement in Ordinal clinical status	Yes	last Ordinal scale assessment within Week 4 time window

- Time from first dose of study drug to Recovery (days)

Defined as discharged or ready for discharge {normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen} (ordinal scale category one), or Non-ICU hospital ward {or “ready for hospital ward”} not requiring supplemental oxygen (ordinal scale category 2). Patients that are in category 2 at baseline will need to achieve category 1 to meet the endpoint of recovery.

Intercurrent events, such as patients who are lost to follow-up, die or discontinue for any reason prior to achieving the event or do not have the event, will be accounted for through censoring rules, as described in Table 7 below.

Table 7 Time to Recovery and censoring

Event	Censor	Date and Time
Hospital discharge and hospital re-admission within 12 hours and continue study	No	Not Applicable
Death prior to Recovery	Yes	Day 28
Discontinuation or lost to follow up for any reason prior to recovery criterion met	Yes	last Ordinal scale assessment
Not recovered	Yes	last Ordinal scale assessment within Week 4 time window

- Time from first dose of study drug to hospital discharge or “ready for discharge” (days)

Ready for discharge; defined as normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen (ordinal scale category one)

Intercurrent events, such as patients who are lost to follow-up, die or discontinue for any reason prior to achieving the event or do not have the event, will be accounted for through censoring rules, as described in Table 8 below.

Table 8 Time to hospital discharge or “ready for discharge” and censoring

Event	Censor	Date and Time
Hospital discharge and hospital re-admission within 12 hours and continue study	No	Not Applicable
Death prior to discharge	Yes	Day 28
Discontinuation or lost to follow up for any reason prior to discharge or “ready for discharge” criterion met	Yes	last Ordinal scale assessment
Not (discharged or “ ready for discharge”)	Yes	last Ordinal scale assessment within Week 4 time window

- Time to clinical failure (days)

Defined as the time from first dose of study drug to first occurrence on study of death, mechanical ventilation (as collected in the Vital Signs & Oxygen Saturation eCRF), ICU admission or withdrawal (discontinuation from study) prior to discharge, whichever occurs first. For patients entering the study already in ICU or on mechanical ventilation (as collected in the Vital Signs & Oxygen Saturation eCRF), clinical failure is defined as a one-category worsening on the ordinal scale, withdrawal or death. Withdrawals not during hospitalization will not be considered as having met clinical failure and data will be censored at the last vital sign assessment, unless a later death is recorded in which case they will have met the event upon death.

Intercurrent events, such as patients who are lost to follow-up or discontinue for any reason prior to the event or do not have the event, will be accounted for through censoring rules, as described in Table 9 below.

Table 9 Time to Clinical Failure and censoring

Event	Censor	Date and Time
Hospital discharge not followed by death or readmittance	Yes	Last scheduled vital sign assessment (or discharge if no post-discharge vital sign data is available)
Hospital discharge and hospital re-admission within 12 hours and continue study	No	Not Applicable
Lost to follow-up prior to clinical failure criterion met not followed by death	Yes	Last scheduled vital sign assessment or ordinal scale assessment
Clinical failure criterion not met	Yes	last of scheduled vital sign assessments or ordinal scale assessments within Week 4 time window

The NEWS2 score and clinical failure status as defined above will be summarized descriptively by visit.

Sensitivity analyses may be performed considering death as a competitive event (other than for the clinical failure endpoint), using a competing risk model if there is an imbalance between groups in deaths and reason attributed.

4.5.3.2 Incidence endpoints

Secondary efficacy incidence endpoints will be analyzed using the Cochran-Mantel-Haenszel test statistic adjusted by the stratification factors at baseline geographic region (North America, Europe) and mechanical ventilation (yes, no) using the mITT population, unless stated otherwise. The weighted difference in proportions for the treatment group comparison will be presented with a p-value, together with a 95% CI (see Appendix 6).

- Incidence of mechanical ventilation (as collected in the Vital Signs & Oxygen Saturation eCRF) by Week 4 (mechanical ventilation refers to invasive mechanical ventilation only, and/or ECMO).
- Incidence of ICU stay by Week 4

For incidence of mechanical ventilation or incidence of intensive care stay by Week 4 for patients that have withdrawn or died prior to Week 4, the non-responder rule will be applied, i.e. it will be assumed that the patient required mechanical ventilation, or has had an ICU stay by Week 4 in the analysis. Patients without either mechanical ventilation or intensive care stay respectively prior to discharge, will be assumed to be responders in the analysis, unless the patient is readmitted to hospital within 12 hours, or the patient dies by Week 4.

In addition to the analyses based on the mITT, incidence of ICU stay and mechanical ventilation will also be analyzed excluding those patients that were in ICU/mechanically ventilated (according to the stratification), respectively, at baseline.

The number and proportion of patients requiring mechanical ventilation or an ICU stay will be summarized descriptively by study week.

- Difference in mortality at Week 4

The difference in proportion of patients that have died by Day 28 will be compared using the CMH test as described above. All deaths post discontinuation and discharge will be included in this analysis.

Deaths occurring between each visit, and cumulative deaths by visit will be summarized descriptively to Day 60.

4.5.3.3 Duration endpoints

- Ventilator-free days

The number of Ventilator-free days (VFDs) is defined as the number of days from Day 1 to Day 28 when the patient is alive and breathes without invasive assistance of the mechanical ventilator. VFDs will be derived from the vital signs and oxygen saturation log; if invasive mechanical ventilation or ECMO is recorded for any part of the day, the day will not be counted as a VFD.

VFDs will be zero if the patient is mechanically ventilated from Day 1 to Day 28. VFDs will be zero if a patient dies on or prior to Day 28.

For patients withdrawn early from the study but not discharged, if patients were on invasive-mechanical ventilation at the point of discontinuation it will be assumed that the remainder of days to Week 4 were not VFDs. For patients not using invasive mechanical ventilation at point of withdrawal it will be assumed the period from withdrawal to Week 4 are VFDs. For patients that are discharged, days from discharge to Day 28 will be counted as VFDs. If ventilator data is missing for patients that have not withdrawn, died or discharged, then the last observation post-baseline will be carried forward until the next observation.

VFDs will be analysed using the Van Elteren test, including the stratification factors at randomization (region [North America, Europe] and mechanical ventilation [yes, no]). The median VFDs for each treatment group and the corresponding 95% CI for the median will be presented along with the Van Elteren P-value, as well as the difference in medians and a 95% CI for the difference. A cumulative distribution plot of VFDs will be produced.

VFDs will also be summarized descriptively using the medians, along with 95% CIs, by treatment group for those patients alive at Day 28, with a count of the number of patients assigned zero VFDs due to death by Day 28

- Duration of supplemental O2 (days)

Duration of supplemental O2 (days) will also be derived from the vital signs and oxygen saturation log, where study days with 'supplemental oxygen or other forms of ventilation' will be summed up to and including Week 4. Patients without any supplemental O2 use will assigned a duration of zero days. For missing data, the last observation post-baseline will be carried forward until either the next observation or the point of withdrawal/discharge. For patients withdrawn early from the study but not discharged, if the patients were on supplemental oxygen at the point of withdrawal it will be assumed that the remainder of days to Week 4 were on supplemental oxygen. For patients not using supplemental oxygen at point of withdrawal it will be assumed supplemental oxygen is not required to Week 4. For patients that are discharged, days from discharge to Day 28 will be counted as days without supplemental oxygen (unless supplemental oxygen use is recorded on the Concomitant Medications eCRF during follow up visits, in which case all days from the day after discharge to the end date from the Concomitant Medication eCRF will be classed as days with supplemental oxygen). Duration of supplemental oxygen use will be 28 days if a patient dies on or prior to Day 28.

Days of supplemental O2 use will be analyzed and summarized descriptively in a similar method to VFDs.

- Duration of ICU stay (days)

Duration of ICU stay (days) will be calculated as the sum of the number of hours spent in ICU up to and including Week 4 divided by 24, based on the admission and discharge date times from the ICU stay information log; (ICU discharge datetime – ICU admission datetime)/24. Multiple periods of ICU stay will be summed. Patients without any ICU stays will be assigned a duration of zero days.

Partial admission and discharge times may be imputed based on available data, following a conservative approach. For patients that are discharged, any ongoing ICU stays without an end date will be imputed from date of discharge as appropriate and it will be assumed that days from discharge to Day 28 do not involve an ICU stay. For patients not in the ICU at the point of withdrawal from study it will be assumed that the period to Week 4 has no incidences of ICU stay post withdrawal. For patients in ICU on the day of withdrawal it will be assumed that they are in the ICU throughout the period to Week 4. Patients that die on or prior to Day 28 will be assigned a duration from the first dose of study drug to Day 28 23:59:59.

Days of ICU stay will be analyzed and summarized descriptively in a similar method to VFDs.

4.5.4 Exploratory Efficacy Endpoints

Incidence of vasopressor use (from concomitant medication records) and incidence of extracorporeal membrane oxygenation (ECMO) by Week 4 (and separately to Day 60) will be summarized descriptively.

Duration of vasopressor use (days) and ECMO (days) to Week 4 will be summarized using the median along with 95 % CIs for the median by treatment group. ECMO use is collected daily and the number of days of ECMO use will be totaled. Vasopressor duration will use start and stop dates from the concomitant medication records. A concomitant medication record that is ongoing at Week 4 will use the upper bound of the Week 4 time window as the end date for the duration.

Days without organ failure will be summarized descriptively through Week 4. In addition, a summary of individual organ failure over time will be provided.

Organ failure is defined as present on any day when the most abnormal vital signs/abnormal lab value meets the definition of clinically significant organ failure (Bernard et al, 1995; NHLBI ARDS Clinical Trials Network 2014). Cardiovascular organ failure is defined as either systolic BP ≤ 90 mmHg or the need for vasopressor. Renal, hepatic and coagulation parameters will be assessed via blood tests in order that the presence of clinically significant organ failure can be determined. Renal failure is defined as creatinine ≥ 2 mg/dl, hepatic failure is defined as bilirubin ≥ 2 mg/dl and coagulation failure is defined as a platelet count of ≤ 80 $\times 10^3/mm^3$. Each day a patient is alive and free of a given clinically significant organ failure will be scored as a failure-free day for that organ. In the case of no data for a particular organ, the last observation post-baseline will be carried forward until the next observation or discharge. Any day that a patient is alive and free of all 4 organ failures (cardiovascular, renal, hepatic, coagulation) will be considered an organ failure-free day.

If a patient dies on or before Day 28, they will be assigned a value of zero organ failure-free days in the overall summary of organ failure-free days. For patients that are discharged, days from discharge to Day 28 will be counted as organ failure-free days, unless they are readmitted in which case the available data will be used.

4.5.5 Subgroup Analyses

A subgroup analysis of the Clinical status assessed using a 7-category ordinal scale at Week 4 by mechanical ventilation status (yes, no) as stratified will be performed using the Van Elteren test for each subgroup. In addition, a stacked barchart at Day 28, a summary of clinical status at Day 28 and a summary of clinical status over time will be produced by mechanical ventilation status (yes, no) at baseline.

In addition, the clinical status according to the 7-category ordinal scale will be compared between the TCZ group and the placebo group at Week 4 by mechanical ventilation status (yes, no) as stratified, using a proportional odds model accounting for stratification

factors at randomization in the model (region [North America, Europe]) using the mITT population. The odds ratio, p-value, and 95% confidence interval will be presented.

The odds ratio for mortality for TCZ versus PBO at day 28 will be analyzed by logistic regression, including covariates of interest as well as the stratification factors in the model. The odds ratio for the treatment effect by gender, race, age (18-64 years, 65-84 years, 85 years and over), region, mechanical ventilation (as stratified) and ordinal clinical status (categories 1 to 3, vs categories 4 and 5) will be determined. Other subgroup analyses may also be performed. If necessary, where there are small subgroups, categories may be collapsed as appropriate to enable analysis, such as for subgroup analysis by race.

4.6 PHARMACODYNAMIC ANALYSES

The PD analysis population will be identical to the safety population.

Summary tables for serum concentration of IL-6, sIL-6R, CRP and ferritin (mean, standard deviation, median, minimum, and maximum) will be produced by visit/ time point and treatment arm.

Individual patient data and descriptive statistics (i.e. median and interquartile range) will be plotted by visit/ time point for each treatment arm.

4.7 SAFETY ANALYSES

Safety assessments will be performed on the safety population. In all safety analyses, patients will be grouped according to the treatment that the patients first received rather than the treatment assigned at randomization.

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

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

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. The number and proportion of patients negative and positive will be displayed, and for those positive the quantitative result will be summarized.

Time to reverse-transcriptase polymerase chain reaction (RT-PCR) COVID-19 virus negativity will be analyzed using similar methods to the other time to event analyses. There will be an additional analysis limited to patients positive at baseline based on central laboratory results.

4.7.1 Exposure of Study Medication

Exposure to study drug will be summarized including number of patients with one or two doses and number of patients with dose modification by treatment group.

A listing of patients by treatment group will be prepared detailing dosing of study drug, volume administered and any dose modification. If after unblinding a patient has received study drug from more than one treatment group, then the actual dose of TCZ would be calculated from the proportion of TCZ kits received. For example, if a patient received 1 kit of TCZ and 3 kits of PBO then the actual dose of TCZ would be calculated as ¼ of the total recorded dose.

4.7.2 Adverse Events

Medical Dictionary for Regulatory Activities (MedDRA) will be used as the thesaurus for AEs and disease codes, and the WHO Drug Global B3 Format dictionary will be used for treatments. A glossary of these codes will be produced.

Only treatment-emergent AEs will be summarized. Treatment-emergent events are defined as those AEs with observed or imputed onset date on or after the start date of trial treatment. Only where the most extreme intensity is greater than the initial intensity (or if most extreme intensity is not missing and initial intensity is missing) will events with an onset date prior to the start of trial treatment be considered treatment-emergent. An AE with a completely missing start date will be assumed to be treatment-emergent unless the AE has a complete non-imputed end date that is prior to study Day 1.

Adverse events will be coded and tabulated by system organ class (SOC), and/or preferred term (PT) and treatment arm. In tabulations, PTs and their associated SOC will be presented in order of descending frequency summed across the treatment arms.

Adverse events will also be tabulated by severity, as graded according to NCI CTCAE v5.0 scale, and relationship to study medication as indicated by the investigator.

The following will also be summarized:

- serious adverse events
- adverse events leading to withdrawal of study drug
- adverse events leading to discontinuation from the study
- adverse events leading to death
- hypersensitivity adverse events (adverse events occurring during or within 24 hours of the end of an infusion that are deemed “related” to study treatment)

Adverse events of special interest will be defined using SOC, published Standard MedDRA Queries (SMQs) or AE Grouped Terms (AEGTs) defined by Roche Drug Safety. The groupings of AEs will include but may not be limited to the following:

- Infections (Infections and Infestations SOC)
- Opportunistic infections (Roche Standard AEGT Basket)
- Malignancies (Malignant or Unspecified tumors SMQ Narrow)
- Hepatic events (Hepatic failure, Fibrosis, and Cirrhosis and Other Liver Damage-related Conditions SMQ Wide or Hepatitis, non-infectious SMQ Wide)
- Stroke (Ischemic Cerebrovascular Conditions SMQ Wide or Hemorrhagic Cerebrovascular SMQ Wide)
- Myocardial infarction [MI] (MI SMQ Wide)
- Anaphylactic reaction events (utilizing Roche Standard AEGT Basket according to Sampson's criteria) [Sampson et al. 2006] occurring during or within 24 hours of the end of tocilizumab infusion; and a separate summary using the Anaphylactic Reaction SMQ Narrow for events occurring during or within 24 hours of the end of tocilizumab infusion)
- Gastrointestinal perforations (Gastrointestinal perforation SMQ Wide)
- Bleeding events (Hemorrhages SMQ Wide)
- Demyelinating events (Demyelination SMQ Narrow)

Summaries and listings of malignancies and gastrointestinal perforations that were confirmed by medical review will be provided.

A glossary showing the mapping of investigator verbatim terms to preferred terms will be produced for all AEs included in the analysis. For each AE of special interest table based on SMQs/AEGTs, a corresponding listing of the preferred terms that comprise the SMQ will be produced.

Listings of AEs and SAEs will be produced. Adverse events of special interest will also be listed.

AEs and SAEs will summarized by age category (18-64 years, 65-84 years, 85 years and over).

The exposure duration on study (exposure duration is the date of the last safety assessment or death if present, minus the date of the first dose of TCZ plus one divided by 365.25) will be summarized.

4.7.3 Laboratory Data

Laboratory data will use ranges from local laboratories and laboratory values will be converted to Système International units.

Summary tables will detail the actual values and changes from baseline of the laboratory parameters over visits by treatment arm. Arterial blood gases will be summarized separately. Summaries of the number of patients by CTC grade for hematology and hepatic lab parameters (Alkaline phosphatase [ALP], Alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), and total bilirubin) will be produced (for summaries referring to NCI CTCAE grading).

For neutrophils, platelets, lymphocytes, and hepatic lab parameters the number of patients will be summarized by CTCAE grade category for baseline and worst post baseline result.

Patients with values outside the reference will be listed, with an indication of the direction of the abnormality (High, Low).

A listing of all pregnancies will be presented.

4.7.4 Vital Signs

Summary statistics on absolute values and their change from baseline for all observed vital signs (diastolic blood pressures, systolic blood pressures, respiratory rate, pulse rate, body temperature and peripheral oxygen saturation) will be presented over time by treatment group. Baseline is defined as the last assessment prior to treatment. Additionally, a graphical representation of means over time of oxygen saturation and temperature (daily to Week 4) will be presented.

For patients requiring supplemental oxygen, summary statistics on absolute values of the oxygen flow rate (L/min) and/or fraction of inspired oxygen (FiO2) will be produced by visit/ time point and treatment group.

The level of consciousness will be summarized over time.

The number and proportion of patients requiring oxygen supplementation or other form of ventilation will be summarized over time, including type of support given. Non-invasive mechanical ventilation will be summarized overall as well as by its component types (continuous positive airway pressure [CPAP], bi-level positive airway pressure [BiPAP], other). Invasive mechanical ventilation will also be summarized overall and by component types (Endotracheal tube, tracheostomy tube).

A listing of patients with chest X-ray, CT scans and ECGs (as a separate listing) with clinically significant abnormalities will be produced.

4.7.5 Other Safety Endpoints

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.

4.8 INTERIM ANALYSES

Up to three efficacy interim analyses will be carried out on the data with mortality rate at 28 days (secondary endpoint) evaluated for efficacy. The interim looks will occur after roughly 111, 222and 333, patients are enrolled and have reached 28 days follow up, but all interims are subject to change depending on the enrollment rate.

The first efficacy interim analysis will be conducted when approximately 111 patients (74 TCZ and 37 placebo) have reached the 28-day follow-up time point and will be based on the mortality rate at 28 days (secondary endpoint). Up to two further interim efficacy analyses will occur after roughly 222 and 333 patients have reached the 28-day follow-up time point. 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 be eligible receive open-label TCZ. At this point, efficacy will be declared. Recruitment into the TCZ arm will continue until 300 patients have been enrolled.

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 (three interim analyses and primary analysis) are 4.364, 2.986, 2.377 and 2.011. The one-sided local significance levels at the three efficacy interim analyses are 0.000006392, 0.001415 and 0.008718.

Additional information regarding the efficacy interim analyses is detailed in 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 be reviewed by a 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 DMC 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 14-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 directly involved in the SMT. If feasible during study conduct, the responsibilities may transition to a fully independent DMC (iDMC).

5. REFERENCES

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Appendix 1 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**
PROTOCOL NUMBER:	WA42380
VERSION NUMBER:	*3*
EUDRACT NUMBER:	2020-001154-22
IND NUMBER:	148225
IND NUMBER:	NCT04320615
TEST PRODUCT:	Tocilizumab (RO4877533)
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.

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
- 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). For patients entering the study already in ICU or on mechanical ventilation, clinical failure is defined as a one-category worsening on the ordinal scale, withdrawal or death.
- Mortality rate at Days 7, 14, 21, 28, and 60
- Time to hospital discharge or "ready for discharge" (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen)
- *Time to recovery, defined as discharged or "ready for discharge" (as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤2L supplemental oxygen); OR, in a non-ICU hospital ward (or "ready for hospital ward") not requiring 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
- Organ failure-free days to Day 28

Safety Objective

The safety objective for this study is to evaluate the safety of TCZ compared with placebo in combination with SOC for the treatment of 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
- SARS-CoV-2 (COVID-19) 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, 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 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 and in both blood- and tissue-derived samples

STUDY DESIGN

Description of the Study

This is a Phase III, randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of TCZ in combination with SOC compared with matching placebo in combination with SOC in hospitalized adult patients with severe COVID-19 pneumonia. The Sponsor intends to enroll approximately 450 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 SARS-CoV-2 (COVID-19) infection per WHO criteria, including a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have $SpO_2 \leq 93\%$ 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 and Europe) and mechanical ventilation (yes, no). The proportion of patients who are on a mechanical ventilator at the time of randomization will be capped at no more than 50% of the overall study population.

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, 8–24 hours after the initial infusion.

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

The 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.

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

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

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

Number of Patients

This study aims to enroll approximately 450 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 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

  If a patient is on supplemental oxygen with $SpO_2 > 93\%$, but desaturation to $\leq 93\%$ on lower supplemental oxygen or ambient air is documented during screening, the inclusion criterion is met.
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

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

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

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

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

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

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

Exclusion Criteria

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

- Known severe allergic reactions to TCZ or other monoclonal antibodies

- 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 3 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 (according to local laboratory reference ranges)
- ANC $<$ 1000/μL at screening (according to local laboratory reference ranges)
- Platelet count $<$ 50,000/μL at screening (according to local laboratory reference ranges)
- Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
- Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (investigational COVID-19 antivirals may be permitted 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 6 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 estimand is the difference in distributions between TCZ plus SOC and placebo plus SOC, which will be tested using a non-parametric method, the Van Elteren test, including the stratification factors at randomization (region [North America, Europe] and mechanical ventilation [yes, no]). The median ordinal scale result for each treatment group and the corresponding 95% CI for the median will be presented along with the Van Elteren p-value, as well as the difference in medians and a 95% CI for the difference.

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

As an additional analysis, 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] and mechanical ventilation [yes, no]). The odds ratio, p-value, and 95% confidence interval will be presented.

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 for the primary endpoint of comparison of clinical status based on a 7-category ordinal scale at Day 28 using *the Van Elteren test*.

The total mITT sample size of *450* with a 2:1 randomization of TCZ to placebo patients provides approximately *90*% power to detect a *difference in distribution between the treatment groups of the ordinal scale at Day 28 using a two-sided Van Elteren test at the 5% significance level* under the following assumptions of the expected probability distribution of patients in the placebo arm:

1 (discharge)	2	3	4	5	6	7 (death)
0.58	0.05	0.09	0.09	0.02	0.02	0.15

And, assuming proportional odds with an odds ratio of 2, the expected distribution in the TCZ arm with would be:

1 (discharge)	2	3	4	5	6	7 (death)
0.734	0.039	0.064	0.058	0.012	0.012	0.081

In addition, this sample size provides approximately 90% power to detect a ratio of 2 (TCZ to PBO) for the odds of being in a category or a better using a proportional odds model with a two-sided p-value at the 5% significance level.

Assuming proportional odds and the given distribution of the placebo group, the smallest odds ratio that could be statistically significant would be approximately *1.5*.

This sample size also provides *approximately 90%* power to detect a 10% absolute difference in mortality rate under the assumption of a 15% mortality rate in the placebo group.

Planned Interim Analyses

Up to three interim looks for efficacy 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 *111, 222, and 333* patients are enrolled, but all interims are subject to change depending on enrollment. If the sample size is increased during the study, the remaining efficacy interims will be performed at similar proportions of information to the original planned efficacy interim analyses.

The first efficacy interim analysis will be conducted when approximately *111* patients (*74* TCZ and *37* 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 the study is at least 90% enrolled within 5 weeks (28 days follow up plus 1 week to perform the analysis) of the 111th patient being enrolled, then no interim analyses will be conducted.*

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 (three interim looks and final analysis) are *4.364, 2.986, 2.377, and 2.011*.

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 14-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.

Appendix 2 Schedule of Activities: Days 1 and 2

	Screening [a, b]	Baseline			
Study Day	–2 to 0	1		2	
Time Post Initial Treatment *(Assessment Window)*		0 *Pre-dose (–4 hrs)*	*15 min After end of infusion (+1 hr)*	*24 hrs (±4 hrs)*	*36 hrs (±4 hrs)*
Informed consent	x				
Inclusion/exclusion criteria	x	x			
Demographic data	x				
Randomization		x			
Medical history		x			
Complete physical examination [c]	x				
Weight		x			
COVID-19 diagnosis [d]	x				
Chest X-ray/CT scan [e]	x				
ECG	x				
Pregnancy test [f]	x				
PaO_2/FiO_2 [g]	x	← *Optional* →			
SpO_2 [h]	x	x	*x*	*x*	*x*
Vital signs [h]	x	x	*x*	*x*	*x*
Ordinal scoring [i]		x		x	
Adverse events [j]		x		x	
Concomitant medications [k]		x		x	
Hematology [l]	x	x		x	
Chemistry [m]	x	x		x	

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

	Screening [a, b]	Baseline			
Study Day	–2 to 0	1		2	
Time Post Initial Treatment *(Assessment Window)*		0 *Pre-dose (–4 hrs)*	*15 min After end of infusion (+1 hr)*	*24 hrs (±4 hrs)*	*36 hrs (±4 hrs)*
Study drug administration [n]		x			
Central Labs					
Serum PD (CRP, IL-6, sIL-6R)		x [o]	x [o]	x	x
Serum PK [p]		x [q]	x [q]	x	x
Serum sample for exploratory biomarkers		x		x	
SARS-CoV-2 viral load [r]		*x*		*x*	
Serum SARS-CoV-2 antibody titer		*x*			
Cryopreserved PBMCs [s]		x		x	
Whole blood in PAXgene® tubes for RNA analyses [t]		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 48 hours before randomization may be used; such tests do not need to be repeated for screening.

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

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

[d] COVID-19 test (SARS-CoV2 PCR) to confirm diagnosis should be performed within 7 days of randomization.

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

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

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

[g] If arterial blood gases are measured.

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

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

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

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

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

[m] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and/or AST, uric acid, LDH, ferritin, and D-dimer.

[n] Study drug should be administered after collection of all samples for pharmacodynamic and exploratory biomarker analyses. The initial study drug infusion should be given within 4 hours of randomization. If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status), one additional infusion of blinded treatment of TCZ or placebo can be given, 8–24 hours after the initial infusion.

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

[p] Patents receiving a second infusion of study drug should provide an extra PK sample prior to and 15 minutes (to 1 hour) after the end of the infusion, on the opposite arm as the infusion.

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

[q] On Day 1, PK samples should be drawn 0–4 hours before the start of infusion and then within 15 minutes (to 1 hour) after the end of the infusion, on the opposite arm as the infusion.

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

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

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

Appendix 3 Schedule of Activities: Days 3–28

	Days 3–28 [a]																									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	
Chest X-ray/CT scan					x							x							x							x	x
Vital signs [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PaO_2/FiO_2 [c]	← *Optional* →																										*Optional*
SpO_2 [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ordinal scoring [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [e]	x	x	x	x	x	x	x	x	x	x	x	x	*x*	*x*	*x*	*x*	*x*	*x*	x	*x*	*x*	*x*	*x*	*x*	*x*	x	x
Concomitant medications [f]	x	x	x	x	x	x	x	x	x	x	x	x	*x*	*x*	*x*	*x*	*x*	*x*	x	*x*	*x*	*x*	*x*	*x*	*x*	x	x
Hematology [g]	x				x			x				x							x							x	x
Chemistry [h]	x				x			x				x							x							x	x
Central Labs																											
Serum PD (CRP, IL-6, sIL-6R)	x				x							x							x							x	x
Serum PK					x							x							x							x	x
Serum sample for exploratory biomarkers	x				x							x							x							x	x
SARS-CoV-2 viral load [i]	x	x	x	x	x			x				x							x							x	x
Serum SARS-CoV-2 antibody titer																										*x*	*x*

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

	Days 3–28 [a]																								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	
Cryopreserved PBMCs [j]	x				x							x							x							x	x
Whole blood in PAXgene® tubes for RNA analyses [k]	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: For patients who have been discharged, all assessments should be performed within ±3 days of the scheduled onsite visit.

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

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

[c] If arterial blood gases are measured.

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

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

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

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

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

[h] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and/or AST, uric acid, LDH, ferritin, and D-dimer.

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

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

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

Appendix 4 Schedule of Activities: After Day 28

			Study Completion
Study Day *(Assessment Window)*	35 [a] *(±3 days)*	45 [a] *(±3 days)*	60 *(±3 days)*
Chest X-ray/CT scan			x
SARS-CoV-2 viral load [b]	x	x	x
Vital signs [c]	x	x	x
SpO_2 [c]	x	x	x
Ordinal scoring [d]	x	x	x
Adverse events [e]	x	x	x
Concomitant medications [f]	x	x	x
Hematology [g]	x	x	x
Chemistry [h]	x	x	x
Central Labs			
Serum PD (CRP, IL-6, sIL-6R)	x		x
Serum PK	x		x
Serum sample for exploratory biomarkers	x		x
Serum SARS-Cov-2 antibody titer			*x*

CRP = c-reactive protein; CT = computed tomography; PK = pharmacokinetic; SpO_2 = peripheral capillary oxygen saturation.

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

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

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

Appendix 4 Schedule of Activities: After Day 28 (cont.)

[d] Assessment of clinical 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.

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

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

[g] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes), and lymphocyte subsets (T cells, B cells, and NK cells). Hematology labs will not be performed if follow-up visits are conducted by telephone.

[h] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, and/or AST, uric acid, LDH, ferritin, and D-dimer. Chemistry labs will not be performed if follow-up visits are conducted by telephone.

Appendix 5 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.

Appendix 5 National Early Warning Score 2 (NEWS2) (cont.)

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.

Appendix 6 Cochran-Mantel-Haenszel Test

- The weighted difference in proportions is the difference in the response rates in the experimental treatment group compared with the control treatment group, adjusted for any stratification factors. With two stratification factors, the number of patients in each strata is defined as nijk where i is the level of the first stratification factor and j is the level of the second stratification factor and k is treatment group (experimental or control). The number of events in each strata is denoted by xijk, where i, j and k are as above. The proportion of responders in each strata will be calculated by:

$$p_{ijk} = \frac{x_{ijk}}{n_{ijk}}$$ where i, j and k are as above

- The difference in proportions for each strata will then be calculated as the proportion of patients in each strata in the experimental treatment group (EXP) minus the proportion of patients in each strata in the control treatment group (CON) and denoted $d_{ij} = p_{ijEXP} - p_{ijCON}$, for i and j as above.

- The weights for each strata (i, j) will be calculated as follows:

$$w_{ij} = \frac{n_{ijEXP} * n_{ijCON}}{n_{ijEXP} + n_{ijCON}}$$

- Within each strata, the weighted differences in the proportions in each of the treatment groups will be calculated as follows:

$$wd_{ij} = w_{ij} d_{ij}$$

- and then summed:

$$WD = \sum_i \sum_j wd_{ij}$$

- After calculation of the weighted difference in proportions, the calculation of the 95% confidence interval is as follows;

- Continuity-corrected Proportions

$$p^{\#}_{ijk} = \frac{x_{ijk} + 0.5}{n_{ijk} + 1}$$

- Variances

$$Upvar_{ij} = w_{ij}^2 \left[p^{\#}_{ijEXP} \frac{\left(1 - p^{\#}_{ijEXP}\right)}{n_{ijEXP}} + p^{\#}_{ijCON} \frac{\left(1 - p^{\#}_{ijCON}\right)}{n_{ijCON}} \right]$$

Appendix 6
Cochran-Mantel-Haenszel Test (cont.)

- To calculate the sum of the weights and variances over all strata:

Sum over Strata

$$W = \sum_i \sum_j w_{ij}$$ (sum of weights)

$$Var = \sum_i \sum_j Up\,\mathrm{var}_{ij}$$ (sum of variances)

Point Estimate and Standard Error

$$d = \frac{WD}{W}; \quad se = \sqrt{\frac{Var}{W^2}}$$

Stratified 95% Confidence Intervals

$$\text{Lower Limit} = d - 1.96se$$

$$\text{Upper Limit} = d + 1.96se$$

List of SAP Amendments

This Statistical Analysis Plan WA42380 Version 3 was amended from Version 2 as follows:

- Time to event endpoints were changed from “time from randomization” to “time from first
- dose of study drug”
- The Type I error control section was updated to specify a hierarchy for testing of the
- primary endpoint followed by testing the difference in mortality
- Cumulative Incidence Function plots were specified for time to ‘improvement’ end points
- The censoring rules for the time to event endpoints were updated
- Derivation of organ failure-free days was clarified
- Laboratory ranges were clarified
- ‘Other’ was removed from the stratification by region as only patients from Europe and
- North America were randomized.
- The synopsis appended from the protocol was updated to be consistent with protocol
- version 3.
- A subgroup analysis of the primary endpoint by mechanical ventilation status (as
- stratified) was added to the primary analysis section

Additional minor changes have been made to improve clarity and consistency.

This Statistical Analysis Plan WA42380 Version 2 was amended from Version 1 as follows:

- The sample size was amended to 450 patients based on powering the study at 90%
- A new secondary endpoint was added ‘Time to Recovery’
- Time to discharge or “ready for discharge” was elevated to one of the key secondary
- endpoints
- The censoring rules for deaths were changed to right censoring for time to event
- endpoints, other than for time to clinical failure
- The derivation of vent-free days was modified so that patients that have died are
- assigned zero vent-free days.
- The list of Adverse Events of Special Interest was modified

Additional minor changes have been made to improve clarity and consistency.