PROTOCOL

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF REMDESIVIR PLUS TOCILIZUMAB COMPARED WITH REMDESIVIR PLUS PLACEBO IN HOSPITALIZED PATIENTS WITH SEVERE COVID-19 PNEUMONIA**
PROTOCOL NUMBER:	WA42511
VERSION NUMBER:	6
EUDRACT NUMBER:	2020-002275-34
IND NUMBER:	148225
NCT NUMBER:	NCT04409262
TEST PRODUCTS:	Tocilizumab (RO4877533) Remdesivir
MEDICAL MONITOR:	[redacted], M.D., M.S.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
22-Feb-2021 00:20:00	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
5	10 December 2020
4	21 September 2020
3	1 July 2020
2	21 May 2020
1	27 April 2020

PROTOCOL AMENDMENT, VERSION 6: RATIONALE

Protocol WA42511 has been amended in response to health authority feedback. Changes have been made to the planned data analyses and do not affect the Schedule of Activities or data collected in the study. Changes to the protocol are summarized below:

- The derivation of the primary endpoint was updated (Section 2.1.1).
- Two additional secondary endpoints were added (Section 2.1.2):
  - Proportion of patients discharged or "ready for discharge" up to Day 28
  - Proportion of patients who require initiation of mechanical ventilation postbaseline or die up to Day 28 and up to Day 60
- The definition of the mITT population was clarified as all patients randomized in the study who received any amount of tocilizumab/placebo (Section 6.4).
- Time to event endpoints were changed from "time from administration of tocilizumab/placebo" to "time from randomization" (Sections 2.1.1, 2.1.2, 2.1.3, 6.4.1, 6.4.2, and 6.4.3).
- Analysis timepoints were defined for all efficacy endpoints (Sections 2.1.1, 2.1.2, 2.1.3, 6.4.1, 6.4.2, and 6.4.3).
- It was clarified that SARS-CoV-2 viral load is not limited to respiratory samples and will also be analyzed in serum samples (Sections 2.1.3 and 6.4.3).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

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PHASE:	Phase III
INDICATION:	Severe COVID-19 pneumonia
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of combination therapy with remdesivir plus tocilizumab compared with remdesivir plus placebo in hospitalized patients with severe coronavirus disease 2019 (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 the remdesivir plus tocilizumab arm compared with the remdesivir plus placebo arm for the treatment of severe COVID-19 pneumonia on the basis of the following endpoint:

- Time from *randomization* to hospital discharge or "ready for discharge" *up to Day 28*

  Hospital discharge or "ready for discharge" is defined as a score of 1 on the 7-*category* ordinal scale.

Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of the remdesivir plus tocilizumab arm compared with the remdesivir plus placebo arm for the treatment of severe COVID-19 pneumonia on the basis of the following endpoints:

- Time to mechanical ventilation or death *up to Day 28*, defined as the time from *randomization* to the first occurrence of mechanical ventilation or death (whichever occurs first)
- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status *up to Day 28*
- Clinical status as assessed by the investigator using a 7-category ordinal scale of clinical status on Days 7, 14, 21, 28, and 60

- Proportion of patients requiring initiation of mechanical ventilation postbaseline up to Day 28 and Day 60 (patients who do not require mechanical ventilation at baseline)
- Proportion of patients who are alive and free of respiratory failure *at* Day 28 and Day 60 (patients requiring mechanical ventilation at baseline)
- Duration of mechanical ventilation (patients who require mechanical ventilation at baseline) *up to Day 28*
- Time to death up to Day 28 and Day 60
- Mortality on Days 14, 28, and 60 *(proportions at specified time points)*
- Time to recovery *up to Day 28*, defined as time from *randomization* to the time when a category of 2 *on the 7-category ordinal scale* (non-ICU hospital ward or "ready for hospital ward" not requiring supplemental oxygen), or better is observed
- *Proportion of patients who are discharged or "ready for discharge" up to Day 28*
- *Proportion of patients who require initiation of mechanical ventilation postbaseline or die up to Day 28*

A pre-defined meta-analysis may be performed on mortality as well as the primary and selected secondary endpoints with results of Studies WA42380 and ML42528.

Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of the remdesivir plus tocilizumab arm compared with the remdesivir plus placebo arm for the treatment of severe COVID-19 pneumonia on the basis of the following endpoints:

- Time to clinical improvement (TTCI) *up to Day 28*, defined as time from *randomization* to National Early Warning Score 2 (NEWS2) score of ≤ 2 maintained for 24 hours:
- Time to clinical failure *up to Day 28*, defined as the time from randomization to the first occurrence of mechanical ventilation, ICU admission, death, or withdrawal *from study prior to discharge* (whichever occurs first)

  For patients entering the study already on mechanical ventilation, clinical failure is defined as a one-category worsening on the ordinal scale, withdrawal *from study* prior to discharge, or death.
- Proportion of patients requiring initiation of ICU care postbaseline up to Day 28 and Day 60
- Duration of ICU stay *up to Day 28*
- Duration of supplemental oxygen use *up to Day 60*
- Proportion of patients requiring initiation of vasopressor use postbaseline *up to Day 28*
- Duration of vasopressor use *up to Day 28*
- Proportion of patients requiring initiation of extracorporeal membrane oxygenation (ECMO) postbaseline *up to Day 28 and up to Day 60*
- Duration of ECMO *up to Day 28*
- Organ failure-free days from *randomization* to Day 28
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load up to Day 28 and Day 60
- Time to reverse-transcriptase polymerase chain reaction (RT-PCR) SARS-CoV-2 virus negativity *up to Day 60 (respiratory samples) or Day 14 (serum samples)*

Safety Objective

The safety objective for this study is to evaluate the safety of the remdesivir plus tocilizumab arm compared with the remdesivir plus placebo arm 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, Version 5.0 (NCI CTCAE v5.0)
- Proportion of patients with any post-treatment infection at specified timepoints
- Change from baseline in targeted clinical laboratory test results

Pharmacokinetic Objective

The pharmacokinetic (PK) objective for this study is to characterize the PK profile of remdesivir and metabolite(s) in patients with severe COVID-19 pneumonia on the basis of the following endpoint:

- Plasma concentration of remdesivir and metabolite(s) 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 remdesivir plus tocilizumab combination treatment (i.e., predictive biomarkers), may serve as early surrogates of efficacy or be associated with 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 provide further evidence of tocilizumab pharmacological activity (i.e., pharmacodynamic biomarkers), or could overall increase our knowledge and understanding of disease pathogenesis and drug safety, on the basis of the following endpoint:

- Relationship between biomarkers in serum, peripheral blood mononuclear cells (PBMCs), blood, and tissue and efficacy or safety endpoints

STUDY DESIGN

Description of the Study

This is a Phase III, randomized, double-blind, multicenter study to assess the efficacy and safety of remdesivir plus tocilizumab compared with remdesivir plus placebo in hospitalized patients with severe COVID-19 pneumonia. The Sponsor intends to enroll patients who have been diagnosed with severe COVID-19 pneumonia and meet the entry criteria in centers globally. Enrollment may be up to 800 patients but will target approximately 650 patients.

In addition to the randomized patients from this study, patients from the Phase III studies WA42380 and ML42528 will be included in a meta-analysis of the primary and secondary endpoints. This analysis will assist in the interpretation of the effect of tocilizumab in combination with remdesivir compared with tocilizumab alone.

Patients must be at least 12 years of age and hospitalized with confirmed 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 require supplemental oxygen >6 L/min to maintain $SpO_2 > 93\%$.

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 an initial 2:1 ratio to receive blinded treatment of either remdesivir plus tocilizumab or remdesivir plus placebo. Study treatment will be given in combination with standard supportive care. The randomization will be stratified by geographic region (North America, Europe, Other) and a 2-level factor based on the assessment of the 7-category ordinal scale of clinical status at screening, with levels 4–5 and 6. The proportion of randomized patients in the scale $=6$ stratum will also be no more than 25%.

Patients assigned to the remdesivir plus tocilizumab (RDV + TCZ) arm will receive remdesivir as a 200 mg IV loading dose followed by one infusion of tocilizumab 8 mg/kg (maximum dose of 800 mg) on Day 1. Patients will subsequently be administered a 100 mg once-daily IV

maintenance dose of remdesivir from Days 2–10. Remdesivir will be discontinued at the time of hospital discharge even if 10 days of remdesivir dosing have not been completed.

Remdesivir dosing must be adjusted for patients that enter the study having received prior remdesivir. Patients who received remdesivir prior to randomization must not exceed 10 days of dosing in total (including remdesivir received prior to the study and during the study). If a patient received 1 dose of remdesivir (200-mg loading dose) prior to Day 1, the patient should receive remdesivir 100 mg on Days 1–9. If a patient received 2 doses of remdesivir (200-mg loading dose followed by 100-mg maintenance dose) prior to Day 1, the patient should receive remdesivir 100 mg on Days 1–8. Patients who received remdesivir prior to trial entry must not receive a second 200-mg loading dose on Day 1. The same sequence and timing of remdesivir and tocilizumab will be followed on Days 1 and 2 regardless of whether the patient has received remdesivir prior to randomization.

For both arms, if the patient has a sustained fever or clinically significant worsening of signs or symptoms (e.g., an increased supplemental oxygen requirement), one additional infusion of blinded tocilizumab/placebo can be given 8–24 hours after the first tocilizumab/placebo infusion. The second dose of blinded tocilizumab must not be given if the patient develops an adverse event or laboratory abnormalities that warrant discontinuation of tocilizumab.

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

The study assessments to be conducted include the following: physical examination, vital signs, oxygen saturation, assessment of consciousness, presence and absence of respiratory support, chest X-ray, ECG, 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 drug.

If patients are discharged from hospital prior to Day 28, follow-up visits should be conducted on Day 14, Day 21, and Day 28 (± 2 days). Follow-up visits on Day 14 and Day 21 may be conducted as telephone visits. Patients should return to the site for the Day 28- visit, if at all possible. 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 for discharged patients. Patients should return to the site for the Day 60 visit, if at all possible.

Number of Patients

The target enrollment for the study is approximately 650 hospitalized patients with severe COVID-19 pneumonia, but up to 800 patients may be enrolled to achieve approximately 520 patients discharged by Day 28.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Documented informed consent to participate in the study
- Signed Assent Form when appropriate, as determined by the patient's age and individual site and country standards
- Age ≥ 12 years at time of informed consent
- 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

  The PCR test must be collected ≤ 7 days before randomization.
- Requiring >6 L/min supplemental oxygen to maintain $SpO_2 > 93\%$
- Agrees to not participate in another clinical trial for the treatment of COVID-19 while participating in this study

- 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.

  Hormonal contraceptive methods must be supplemented by a barrier method.

  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 tocilizumab or other monoclonal antibodies
- Known hypersensitivity to remdesivir, the metabolites, or formulation excipients
- 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
- Treatment with immunosuppressive or immunomodulatory therapy (including tocilizumab) within the past 3 months
- Concurrent treatment with other agents with actual or possible direct-acting antiviral activity against SARS-CoV-2 within 24 hours prior to study drug dosing

  In addition, patients with prior or current treatment with >2 doses remdesivir for COVID-19 are excluded.
- Participating in another drug clinical trial
- Estimated glomerular filtration rate (eGFR) <30 mL/min (including patients receiving hemodialysis or hemofiltration), using the equation described in the FDA EUA Fact Sheet for remdesivir

- ALT or AST $>5\times$ upper limit of normal (ULN) detected within 24 hours of screening (according to local laboratory reference ranges)
- ANC $<$ 1000/μL at screening
- Platelet count $<$50,000/μL at screening
- Body weight $<$40 kg
- Pregnant or breastfeeding, or positive pregnancy test in a predose examination
- Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization
- Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study

End of Study

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

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

Length of Study

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

Investigational Medicinal Products

Test Products (Investigational Drugs)

The investigational medicinal products (IMPs) for this study are remdesivir IV, tocilizumab IV, and placebo for tocilizumab IV

Patients assigned to the remdesivir plus tocilizumab (RDV + TCZ) arm will receive remdesivir loading dose followed by one infusion of tocilizumab on Day 1, and once-daily maintenance dose of remdesivir from Days 2–10.

Patients assigned to the remdesivir plus placebo (RDV + placebo) arm will receive remdesivir as loading dose followed by one infusion of tocilizumab-placebo on Day 1, and once-daily maintenance dose of remdesivir from Days 2–10.

For both arms, if the patient has a sustained fever or clinically significant worsening of signs or symptoms (e.g., an increased supplemental oxygen requirement), one additional infusion of blinded tocilizumab/placebo can be given 8–24 hours after the first tocilizumab/placebo infusion. The second dose of blinded tocilizumab must not be given if the patient develops an adverse event or laboratory abnormalities that warrant discontinuation of tocilizumab.

Administration of study treatments will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Statistical Methods

Primary Analysis

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

- Time from randomization to hospital discharge or "ready for discharge" *up to Day 28*

  Hospital discharge or "ready for discharge" is defined as a score of 1 on the 7-*category* ordinal scale. *Patients will meet the endpoint at the time of discharge or the time that they achieve category 1 of the 7-category ordinal scale, provided that they do not have any further ordinal scale assessments > category 1 on or prior to Day 28, they are not re-hospitalized on or prior to Day 28 and they do not die on or prior to Day 28.*

The distribution of time from *randomization* to hospital discharge (or ready for discharge) will be compared with the remdesivir plus tocilizumab arm and the remdesivir plus placebo arm up to Day 28. Patients discharged after Day 28 will be administratively censored. The distributions will be compared using an appropriate method for comparing censored event distributions *such as the Cox model. Kaplan-Meier and* cumulative incidence plots will be presented as well as median time to discharge (or ready for discharge), with 95% confidence intervals for the remdesivir plus tocilizumab arm and the remdesivir plus placebo arm.

Determination of Sample Size

The primary endpoint, time to discharge or "ready for discharge," is event driven. Based on the severe cohort receiving 10 days of remdesivir in Gilead's SIMPLE trial (Study GS-US-540-5773), the median time to discharge or "ready for discharge" was 11 days. Assuming a median time to discharge or "ready for discharge" of 11 days in the remdesivir plus placebo arm, a hazard ratio of 1.3 or an approximately 2.5-day reduction in median time for remdesivir plus tocilizumab versus remdesivir plus placebo, and a 2:1 randomization to remdesivir plus tocilizumab or remdesivir plus placebo, approximately 650 patients are needed to accrue approximately 520 events to achieve approximately 80% power. A reduction of at least 2 days in median time to discharge was considered clinically meaningful and the sample size was increased to ensure that a minimum effect size could be detected. Further sample size adjustments may be considered during the study based on external information. The sample size may be increased up to a maximum of approximately 800 randomized patients if fewer events than expected are observed or further shifts in standard of care warrant reassessing sample size assumptions.

Interim Analyses

There will be up to three optional interim analyses. The first interim analysis can occur after approximately one-third to one-half of the patients have been assessed for the primary endpoint on Day 28, depending on enrollment rate. There may be up to two additional unplanned interim analyses, and these will be considered if there are major changes to the study design following the first interim analysis.

Full statistical details of any optional interim analyses, along with the rationale and timing will be documented in an interim SAP, which will be made available to the relevant health authorities before the data snapshot for the first interim analysis. Only the Data Monitoring Committee (DMC) will be unblinded and decision criteria will be specified in the interim SAP. Should an unblinded interim analysis occur, any necessary adjustment to the type 1 error rate will be specified in the SAP prior to unblinding the study.

The optional interim analysis will be based on the time to discharge (or ready for discharge) and mortality. Questions to be addressed at the interim analysis might include futility as well as potential efficacy.

The DMC will also evaluate safety according to policies and procedures detailed in the DMC Charter. Regular safety reviews will begin after approximately 45 patients (15 remdesivir plus placebo and 30 remdesivir plus tocilizumab) have been enrolled and have reached 14 days of 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 DMC initially consisted of Sponsor representatives not involved in any operational aspects of the study and a Scientific Oversight Committee of external experts (responsibilities and operating principles of the DMC are described in a charter, the Internal Monitoring Committee and Scientific Oversight Committee Agreement). The DMC responsibilities transitioned to a fully independent Data Monitoring Committee (iDMC) prior to the third scheduled safety review after approximately 300 patients reached Day 28 of follow-up. The iDMC will also conduct a fourth scheduled safety data review when at least 450 patients have reached Day 28. Data processing will be handled by a Sponsor statistician and statistical programmer independent of the study management team. Details are reported in the iDMC Charter.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ARDS	acute respiratory distress syndrome
CAR	chimeric antigen receptor
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
CRS	cytokine-release syndrome
CT	computed tomography (scan)
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
ECMO	extracorporeal membrane oxygenation
EDC	electronic data capture
FDA	(U.S.) Food and Drug Administration
FiO_2	fraction of inspired oxygen
GCA	giant cell arteritis
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
ICU	intensive care unit
iDMC	*independent Data Monitoring Committee*
IL-6	interleukin 6
IL-6R	interleukin-6 receptor
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IQR	interquartile range
IRB	Institutional Review Board
IxRS	interactive voice or web-based response system
MERS-CoV	Middle East respiratory syndrome corona virus
mITT	modified intent-to-treat (population)
MOD	multiple-organ dysfunction
MOF	multi-organ failure
NCI	National Cancer Institute
NEWS2	National Early Warning Score 2
PaO_2	partial pressure of oxygen

Abbreviation	Definition
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PCT	procalcitonin
pJIA	polyarticular juvenile idiopathic arthritis
PK	pharmacokinetic
PO	proportional odds
PY	patient years
QD	once a day
RA	rheumatoid arthritis
RDV	remdesivir
RT-PCR	reverse-transcriptase polymerase chain reaction
SAP	Statistical Analysis Plan
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBECD	sulfobutylether-beta-cyclodextrin
sIL6-R	soluble interleukin-6 receptor
sJIA	systemic juvenile idiopathic arthritis
SOC	standard of care
SpO_2	peripheral capillary oxygen saturation
TAK	Takayasu arteritis
TB	tuberculosis
TCZ	tocilizumab
TTCI	time to clinical improvement
ULN	upper limit of normal

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 corona virus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV).

Coronavirus disease 2019 (COVID-19), is caused by a novel coronavirus strain (SARS-CoV-2) and was newly named on 11 February 2020 by the 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. The WHO subsequently declared a pandemic on 11 March 2020.

According to the WHO, as of 19 May 2020 more than 4,500,000 cases of COVID-19 infection were reported in more than 200 countries and territories worldwide, with more than 300,000 deaths (WHO 2020a). 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). Approximately 20% of patients who seek medical care go on to experience complications related to COVID-19 pneumonia, which may progress to acute respiratory distress syndrome (ARDS) and/or multi-organ failure (MOF) and death (WHO 2020a). To date, there is no vaccine effective in preventing COVID-19 disease.

1.2 BACKGROUND ON REMDESIVIR

Remdesivir is a broad-spectrum nucleotide prodrug that inhibits RNA-dependent RNA polymerase activity among a diverse group of RNA viruses including filoviruses (e.g., Ebola, Sudan, Marburg), paramyxoviruses (e.g., Nipah, Hendra), and pathogenic coronaviruses (Warren et al. 2016; Lo et al. 2017, 2019). Multiple nonhuman primate studies demonstrated the therapeutic efficacy of remdesivir against Ebola virus (Warren et al. 2016; Lo et al. 2019). Remdesivir was used in a randomized clinical trial for Ebola (the PALM study; NCT03719586) (Mulangu et al. 2019). While remdesivir was demonstrated to be inferior to investigational treatment with monoclonal antibodies MAb114 and REGN-EB3 in the PALM study, the lack of a control arm limits interpretation of the clinical efficacy of remdesivir. Studies in human airway epithelial cell assays demonstrated that remdesivir inhibits replication of coronaviruses, including MERS-CoV (Sheahan et al. 2017). In mouse infection models, remdesivir had therapeutic efficacy against SARS-CoV and MERS-CoV (Sheahan et al. 2017, 2020). An in vitro study with mouse hepatitis virus (a murine coronavirus) found that remdesivir inhibits coronavirus replication through interference with the viral polymerase, despite the presence of a viral proofreading exoribonuclease (Agostini et al. 2018). In that study, coronaviruses that were partially resistant to inhibition by remdesivir were still sensitive

to higher concentrations of remdesivir, and fitness was impaired in the resistant viruses as compared with wild-type MERS-CoV. In a recent non-human primate study, therapeutic remdesivir treatment initiated 12 hours post inoculation with MERS-CoV provided clinical benefit with a reduction in clinical signs, reduced virus replication in the lungs, and decreased presence and severity of lung lesions (de Wit et al. 2013, 2020). Activity of remdesivir against SARS-CoV-2 at low-micromolar concentration was recently confirmed in cell culture assays (Wang et al. 2020). Finally, interim analysis data of a randomized, placebo-controlled trial showed that remdesivir was associated with a shorter time to recovery compared with placebo in patients with severe COVID-19 disease (FDA 2020a).

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

1.3 EXPERIENCE WITH REMDESIVIR IN COVID-19 PNEUMONIA

A compassionate use case series evaluating remdesivir as a possible treatment of COVID-19 was conducted at hospitals in North America, Europe, and Asia between January and March 2020 (Grein et al. 2020). This case series evaluated off-label treatment with remdesivir in a cohort of patients hospitalized due to COVID-19. All patients had a peripheral capillary oxygen saturation (SpO_2) $\leq$94% while breathing ambient air or were receiving oxygen support. Patients were administered remdesivir 200 mg IV on the first day of treatment, followed by remdesivir 100 mg IV on the next 9 consecutive days.

A total of 61 patients received at least one dose of remdesivir in this case series and 40 patients completed the full 10-day course of remdesivir. Over a median follow-up of 18 days (interquartile range [IQR]: 13–23 days) after receiving the first dose of remdesivir, 36 of 53 patients (68%) showed an improvement in oxygen support, and 8 of 53 patients (15%) showed worsening. Improvement was observed in all 12 patients who were breathing ambient air or receiving low-flow supplemental oxygen at start of treatment and in 5 of 7 patients (71%) who were receiving non-invasive oxygen support. In addition, 17 of 30 patients (57%) who were receiving invasive mechanical ventilation were extubated, and 3 of 4 patients (75%) who were receiving extracorporeal membrane oxygenation (ECMO) stopped receiving it. After 28 days of follow-up, the cumulative incidence of clinical improvement, as defined by either a decrease of two or more points on the six-point ordinal scale or live discharge, was 84%.

Seven of the 53 patients (13%) who completed 10 days of remdesivir treatment died. The median time to death was 15 days after initiation of remdesivir (IQR: 9–17 days). Six of 34 patients (18%) who received invasive ventilation died compared with 1 of 19 patients (5%) who did not receive invasive ventilation. Adverse events were reported in 32 patients (60%), the most common of which were increased hepatic enzymes (23%), diarrhea (9%), rash (8%), renal impairment (8%), and hypotension (8%). Twelve patients (23%) had serious adverse events and the most common

events—multiple-organ-dysfunction (MOD) syndrome, septic shock, acute kidney injury, and hypotension—were reported in patients who were receiving intensive ventilation at baseline (Grein et al. 2020).

A Phase III study evaluating remdesivir in patients with mild-to-moderate COVID-19 was initiated in China in February 2020 but was suspended in April 2020 due to lack of eligible patients (NCT04252664). A study in patients with severe COVID-19 in China was also terminated in April due to lack of eligible patients (NCT04257656). However, a number of trials are still ongoing outside of China. A randomized, Phase III study is evaluating response to treatment with a 5- or 10-day course of remdesivir plus standard of care (SOC) in patients with severe COVID-19 (NCT04292899). A further randomized Phase III study is assessing 5- and 10-day dosing of remdesivir plus SOC compared with SOC in patients with moderate COVID-19 (NCT04292730). The safety and efficacy of remdesivir is also being assessed in several adaptive trials alongside other novel therapeutic agents in hospitalized adults diagnosed with COVID-19 (NCT04280705, NCT04321616, NCT04315948, and NCT04280705). Favorable interim results of one of these trials formed the basis for the Emergency Use Authorization for the use of remdesivir in hospitalized patients with severe COVID-19 disease in the US (FDA 2020a).

1.4 BACKGROUND ON TOCILIZUMAB

Tocilizumab is a recombinant humanized, anti-human monoclonal antibody of the IgG1 subclass directed against soluble interleukin-6 receptor (sIL-6R) and membrane-bound IL-6R. Tocilizumab binds specifically to both sIL-6R and membrane-bound IL-6R and has been shown to inhibit both soluble and membrane-bound IL-6R–mediated signaling. Interleukin-6 (IL-6) is a pleiotropic pro-inflammatory multifunctional cytokine produced by a variety of cell types and has been shown to be involved in diverse 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, 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 tocilizumab has been approved in the European Union and certain other countries.

Tocilizumab 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 Development International Birth Date (28 April 1997) until 10 April 2019 (the data lock point for the Periodic Benefit–Risk Evaluation Report) was 24,826 patients (40154.98 patient years [PY]). Since the International Birth Date (11 April 2005), the estimated cumulative market exposure to tocilizumab until 10 April 2019 was 1,301,050 patients (1,053,779 PY). The combined cumulative postmarketing 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.

1.5 TOCILIZUMAB TREATMENT IN CYTOKINE-RELEASE SYNDROME OF CAR T-CELL THERAPY

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

On 30 August 2017, the FDA 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 tocilizumab was based on a retrospective analysis of data for patients treated with tocilizumab who developed CRS after treatment with tisagenlecleucel (Kymriah®) or axicabtagene ciloleucel (Yescarta®) in prospective clinical trials, (Le et al. 2018). Of the 45 patients, 31 patients (69%) from the tisagenlecleucel series achieved a response (defined as being afebrile and off vasopressors for at least 24 hours within 14 days of the first dose of tocilizumab, if no more than two tocilizumab doses were given without use of additional treatment other than corticosteroids), 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, sex, race, ethnicity, grade of CRS at first dose of tocilizumab, and duration of CRS prior to treatment with tocilizumab. There were no reports of adverse reactions attributable to tocilizumab.

Pharmacokinetic (PK) data were available for 27 patients after the first dose of tocilizumab and for 8 patients after a second dose of tocilizumab. Based on 131 PK observations, the geometric mean (% coefficient variation) maximum concentration of tocilizumab 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 tocilizumab than healthy volunteers and other patient populations, and simulations showed that exposure was considered acceptable with up to four doses of tocilizumab at least 8 hours apart in patients with CRS.

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

1.6 EXPERIENCE WITH TOCILIZUMAB IN COVID-19 PNEUMONIA

Physicians in China initiated the off-label use of tocilizumab in the treatment of patients with 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 tocilizumab (Xu et al. 2020), an ongoing investigator-sponsored randomized, controlled trial ($n = 188$) has been initiated in the same population in China, testing the same tocilizumab dose regimen, with approximately 70 patients enrolled. At present, the 21-patient publication (Xu et al. 2020) is the only robust published clinical data the Sponsor is aware of regarding the use of tocilizumab in the treatment of patients with severe COVID-19 pneumonia.

On 3 March 2020, tocilizumab 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 patients with 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, $SpO_2 \leq 93\%$, partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio (the ratio between the blood pressure of the oxygen [PaO_2] and the 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 MOD or MOF

  This occurred in 5% of cases (Wu et al. 2020).

Because body weight measurement is not always feasible in urgent circumstances, the dosing regimen used in China is a single, fixed dose of tocilizumab 400 mg 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. Tocilizumab

treatment is not permitted for people with active infections including tuberculosis (TB), bacterial, or fungal.

Results from 21 Patients Treated with Tocilizumab in China

In February 2020, 21 patients with severe or critical COVID-19 pneumonia were treated with tocilizumab 400 mg IV plus SOC. 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 4 patients (19.0%) were assessed as critical. Most patients (85%) presented with lymphopenia. C-reactive protein (CRP) levels were increased in all 20 patients evaluated (mean: 75.06 [±66.80] mg/L). The median procalcitonin (PCT) value was 0.33 (±0.78) ng/mL, and only 2 of 20 patients (10.0%) presented with an abnormal value. Mean IL-6 level before tocilizumab was 132.38 (±278.54) pg/mL (normal <7 pg/mL).

SOC consisted of lopinavir, methylprednisolone, other symptom relievers, and oxygen therapy as recommended by the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia* (Trial Version 6) (China National Health Commission 2020). All 21 patients had received routine SOC treatment for a week before deteriorating with sustained fever, hypoxemia, and chest computed tomography (CT) image worsening.

Eighteen patients (85.7%) received tocilizumab once, and 3 patients (14.3%) had a second dose due to fever within 12 hours. According to the authors, after tocilizumab treatment, fever returned to normal and all other symptoms improved remarkably. Fifteen of the 20 patients (75.0%) had lowered their oxygen intake, and 1 patient needed no oxygen therapy. CT scans showed significant remission of opacities in both lungs in 19 of 20 patients (90.5%) after treatment with tocilizumab. The percentage of lymphocytes in peripheral blood, which was decreased in 17 of 20 patients (85%) before treatment (mean: 15.52 [±8.89]%), returned to normal in 10 of 19 patients (52.6%) on the fifth day after treatment. Abnormally elevated CRP decreased significantly in 16 of 19 patients (84.2%). No adverse drug reactions and no subsequent pulmonary infections were reported.

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

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

A randomized, double-blind, Phase III study evaluating the safety and efficacy of tocilizumab administered intravenously compared with placebo plus SOC therapy in hospitalized patients with severe COVID-19 pneumonia is currently ongoing (NCT04320615).

1.7 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

There are currently no drugs licensed for the treatment of patients with COVID-19 pneumonia, but the FDA has recently issued an Emergency Use Authorization for the use of remdesivir in hospitalized patients with severe COVID-19 disease (FDA 2020a). Given the results of studies outlined above, remdesivir in combination with tocilizumab could provide better efficacy, offering the potential to treat COVID-19 pneumonia in hospitalized populations more effectively than remdesivir alone. Extensive safety data have previously been generated on the use of tocilizumab in other indications. In addition, data for remdesivir and tocilizumab in patients with severe COVID-19 pneumonia have shown both agents to be well tolerated in this patient population. Therefore, a study investigating the safety and efficacy of combination therapy with remdesivir plus tocilizumab compared with remdesivir alone 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 and safety of combination therapy with remdesivir plus tocilizumab compared with remdesivir plus placebo 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 the remdesivir plus tocilizumab arm compared with the remdesivir plus placebo arm for the treatment of severe COVID-19 pneumonia on the basis of the following endpoint:

- Time from *randomization* to hospital discharge or "ready for discharge" *up to Day 28*
  - Hospital discharge or "ready for discharge" is defined as a score of 1 on the 7-*category* ordinal scale.

2.1.2 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of the remdesivir plus tocilizumab arm compared with the remdesivir plus placebo arm for the treatment of severe COVID-19 pneumonia on the basis of the following endpoints:

- Time to mechanical ventilation or death *up to Day 28*, defined as the time from *randomization* to the first occurrence of mechanical ventilation or death (whichever occurs first)
- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status *up to Day 28*

- Clinical status as assessed by the investigator using a 7-category ordinal scale of clinical status on Days 7, 14, 21, 28, and 60
- Proportion of patients requiring initiation of mechanical ventilation postbaseline up to Day 28 and Day 60 (patients who do not require mechanical ventilation at baseline)
- Proportion of patients who are alive and free of respiratory failure *at* Day 28 and Day 60 (patients requiring mechanical ventilation at baseline)
- Duration of mechanical ventilation (patients who require mechanical ventilation at baseline*) up to Day 28*
- Time to death up to Day 28 and Day 60
- Mortality on Days 14, 28, and 60 *(proportions at specified time points)*
- Time to recovery *up to Day 28*, defined as time from *randomization* to the time when a category of 2 *on the 7-category ordinal scale* (non-ICU hospital ward or "ready for hospital ward" not requiring supplemental oxygen), or better is observed
- *Proportion of patients discharged or "ready for discharge" up to Day 28*
- *Proportion of patients who require initiation of mechanical ventilation postbaseline or die up to Day 28*

A pre-defined meta-analysis may be performed on mortality as well as the primary and selected secondary endpoints with results of Studies WA42380 and ML42528.

2.1.3 Exploratory Efficacy Objective

The exploratory efficacy objective for this study is to evaluate the efficacy of the remdesivir plus tocilizumab arm compared with the remdesivir plus placebo arm for the treatment of severe COVID-19 pneumonia on the basis of the following endpoints:

- Time to clinical improvement (TTCI) *up to Day 28*, defined as time from *randomization* to National Early Warning Score 2 (NEWS2) score of≤2 maintained for 24 hours
- Time to clinical failure *up to Day 28*, defined as the time from *randomization* to the first occurrence of death, mechanical ventilation, ICU admission or withdrawal *from study prior to discharge* (whichever occurs first)

  For patients entering the study already on mechanical ventilation, clinical failure is defined as a one-category worsening on the ordinal scale, withdrawal *from study* prior to discharge, or death.
- Proportion of patients requiring initiation of ICU care postbaseline up to Day 28 and Day 60
- Duration of ICU stay *up to Day 28*
- Duration of supplemental oxygen use *up to Day 60*
- Proportion of patients requiring initiation of vasopressor use postbaseline *up to Day 28*

- Duration of vasopressor use *up to Day 28*
- Proportion of patients requiring initiation of ECMO postbaseline *up to Day 28 and Day 60*
- Duration of ECMO *up to Day 28*
- Organ failure-free days from *randomization* to Day 28
- SARS-CoV-2 viral load up to Day 28 and Day 60
- Time to reverse-transcriptase polymerase chain reaction (RT-PCR) SARS-CoV-2 virus negativity *up to Day 14 (serum samples) or Day 60 (respiratory samples)*

2.2 SAFETY OBJECTIVE

The safety objective for this study is to evaluate the safety of the remdesivir plus tocilizumab arm compared with the remdesivir plus placebo arm 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, Version 5.0 (NCI CTCAE v5.0)
- Proportion of patients with any post-treatment infection at specified timepoints
- Change from baseline in targeted clinical laboratory test results

2.3 PHARMACOKINETIC OBJECTIVE

The PK objective for this study is to characterize the PK profile of remdesivir and metabolite(s) in patients with severe COVID-19 pneumonia on the basis of the following endpoint:

- Plasma concentration of remdesivir and metabolite(s) at specified timepoints

2.4 BIOMARKER OBJECTIVE

The exploratory biomarker objectives for this study are to identify and/or evaluate biomarkers that could be predictive of response to remdesivir plus tocilizumab combination treatment (i.e., predictive biomarkers), may serve as early surrogates of efficacy or be associated with 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 provide further evidence of tocilizumab pharmacological activity (i.e., pharmacodynamic biomarkers), or could overall increase our knowledge and understanding of disease pathogenesis and drug safety, on the basis of the following endpoint:

- Relationship between biomarkers in serum, peripheral blood mononuclear cells (PBMCs), blood, and tissue (listed in Section 4.5.6) and efficacy or safety endpoints

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase III, randomized, double-blind, multicenter study to assess the efficacy and safety of remdesivir plus tocilizumab compared with remdesivir plus placebo in hospitalized patients with severe COVID-19 pneumonia. The Sponsor intends to enroll patients who have been diagnosed with severe COVID-19 pneumonia and meet the entry criteria in centers globally. Enrollment may be up to 800 patients but will target approximately 650 patients.

In addition to the randomized patients from this study, results from the Phase III studies WA42380 and ML42528 will be included in a meta-analysis of the primary and secondary endpoints. This analysis will assist in the interpretation of the effect of tocilizumab in combination with remdesivir compared with tocilizumab alone.

Patients must be at least 12 years of age and hospitalized with confirmed 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 require >6 L/min supplemental oxygen to maintain $SpO_2 > 93\%$.

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 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 remdesivir plus tocilizumab or remdesivir plus placebo. Study treatment will be given in combination with standard supportive care. The randomization will be stratified by geographic region (North America, Europe, Other) and a 2-level factor based on the assessment of the 7-category ordinal scale of clinical status at screening, with levels 4–5 and 6. The proportion of randomized patients in the scale $= 6$ stratum will also be no more than 25%.

Patients assigned to the remdesivir plus tocilizumab (RDV + TCZ) arm will receive remdesivir as a 200 mg IV loading dose followed by one infusion of tocilizumab 8 mg/kg (maximum dose of 800 mg) on Day 1. Patients will subsequently be administered a 100 mg once-daily IV maintenance dose of remdesivir from Days 2–10. Remdesivir will be discontinued at the time of hospital discharge even if 10 days of remdesivir dosing have not been completed.

Patients assigned to the remdesivir plus placebo (RDV + placebo) arm will receive remdesivir as a 200 mg IV loading dose followed by one infusion of tocilizumab-placebo

on Day 1. Patients will subsequently be administered a 100 mg once-daily IV maintenance dose of remdesivir from Days 2–10. Remdesivir will be discontinued at the time of hospital discharge even if 10 days of remdesivir dosing have not been completed.

Remdesivir dosing must be adjusted for patients that enter the study having received prior remdesivir. Patients who received remdesivir prior to randomization must not exceed 10 days of dosing in total (including remdesivir received prior to the study and during the study). If a patient received 1 dose of remdesivir (200-mg loading dose) prior to Day 1, the patient should receive remdesivir 100 mg on Days 1–9. If a patient received 2 doses of remdesivir (200-mg loading dose followed by 100-mg maintenance dose) prior to Day 1, the patient should receive remdesivir 100 mg on Days 1–8. Patients who received remdesivir prior to trial entry must not receive a second 200-mg loading dose on Day 1. The same sequence and timing of remdesivir and tocilizumab will be followed on Days 1 and 2 regardless of whether the patient has received remdesivir prior to randomization (see Appendix 1).

For both arms, if the patient has a sustained fever or clinically significant worsening of signs or symptoms (e.g., an increased supplemental oxygen requirement), one additional infusion of blinded tocilizumab/placebo can be given 8–24 hours after the first tocilizumab/placebo infusion. The second dose of blinded tocilizumab must not be given if the patient develops an adverse event or laboratory abnormalities that warrant discontinuation of tocilizumab as described in Section 5.1.2.

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 as described 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, chest X-ray, ECG, 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.

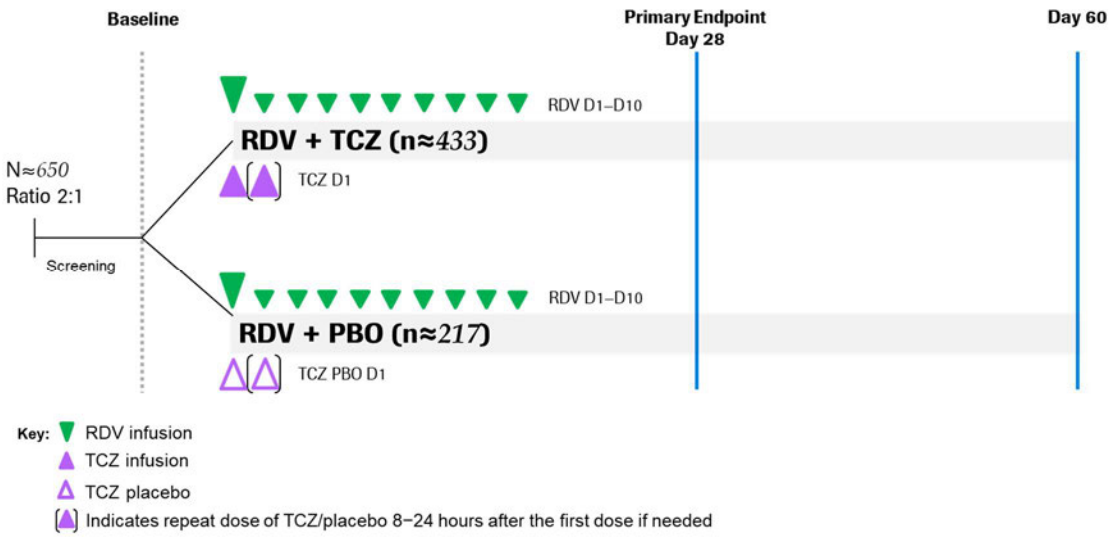
Patients will be followed up for a total of 60 days after first dose of study drug.

If patients are discharged from hospital prior to Day 28, follow-up visits should be conducted on Day 14, Day 21, and Day 28 (± 2 days). Follow-up visits on Day 14 and Day 21 may be conducted as telephone visits. Patients should return to the site for the Day 28-visit, if at all possible. 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 for discharged patients. Patients should return to the site for the Day 60 visit, if at all possible.

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



COVID-19 = coronavirus disease 2019; D = Day; PBO = placebo; RDV = remdesivir; TCZ = tocilizumab.
Notes: Baseline refers to study baseline (not the COVID-19 diagnosis date). Patients who received remdesivir prior to randomization will not exceed 10 days of dosing in total.

3.2 END OF STUDY AND LENGTH OF STUDY

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

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

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

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Remdesivir and Tocilizumab Dose and Schedule

The 10-day remdesivir dosing regimen selected for this study is consistent with the Emergency Use Authorization for remdesivir for treatment of COVID-19 in adults and children hospitalized with severe disease weighing more than 40 kg (FDA 2020b). Patients weighing less than 40 kg will not be permitted into the study, as the remdesivir dosing regimen may not be appropriate for such patients.

The tocilizumab dosing regimen chosen in this study is consistent with the approved tocilizumab dosage for patients with CAR T cell–induced CRS (weight ≥ 30 kg), recent off-label experience in China (one additional infusion if fever not improved within 12 hours), and the permitted use of three additional infusions of tocilizumab (≥ 8 hours between infusions) for CAR T cell–induced CRS. The proposed one additional infusion of tocilizumab if the patient has a sustained fever or clinically significant worsening of signs or symptoms (e.g., an increased supplemental oxygen requirement) is justified based on these data.

Patients will be followed up for a period of 60 days after randomization. In the case series of patients who received compassionate-use remdesivir, a 28-day follow-up period was sufficient time to permit assessment of treatment outcome (Grein et al. 2020). This follow-up duration for tocilizumab-treated patients is supported by historical data from studies performed in healthy subjects and patients with RA (Studies LRO300 and LRO301), where the mean apparent tocilizumab 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 every 4 weeks. Moreover, modeling of free sIL-6R 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 with clinical symptoms due to COVID-19 experience mild disease, require only symptomatic relief, and can recover at home. However, approximately 20% of symptomatic patients require hospitalization due to more severe disease. A study of 138 hospitalized patients with COVID-19 in China found that 26% of patients admitted to hospital required transfer to the 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 showed that 13 of 41 patients (32%) admitted to a hospital were also admitted to an ICU and 6 patients (15%) died (Huang et al. 2020). A recent case series of 393 patients admitted to two hospitals in New York City reported respiratory failure leading to invasive mechanical ventilation in 130 patients (33.1%). Only 43 of these patients (33.1%) had been extubated at the time of publication, while 40 of the patients (10.2%) had died, and the remaining 260 patients (66.2%) had been discharged from the hospital (Goyal et al. 2020).

Given the significant unmet need in patients hospitalized with severe COVID-19, and based on the emerging evidence for remdesivir and tocilizumab use in patients with COVID-19 pneumonia, this study is designed to evaluate the efficacy and safety of remdesivir in combination with tocilizumab compared with remdesivir alone in this population. Morbidity and mortality are particularly high for elderly patients and those

with comorbidities. This study will include both of these groups, with no upper age limit. Furthermore, to align with the patient population studied in the remdesivir Phase III program, adolescent patients aged 12 or older will also be permitted to enroll into the study.

3.3.3 Rationale for Control Group

The study will compare the efficacy and safety of remdesivir plus tocilizumab with remdesivir plus placebo in patients with severe COVID-19 pneumonia.
Placebo-controlled clinical trials to evaluate remdesivir or tocilizumab in patients with severe COVID-19 pneumonia are ongoing and will report the efficacy and safety of each treatment compared with placebo. Based on emerging data, remdesivir can now be considered a standard treatment for severe COVID-19 pneumonia and the control arm of this study will therefore be treatment with remdesivir plus placebo.

3.3.4 Rationale for Biomarker Assessments

COVID-19 is a heterogeneous disease, and patients with severe COVID-19 have shown various levels of IL-6 pathway activation and present at varying stages of viral progression (Xu et al. 2020). Therefore, all patients may not benefit equally from remdesivir plus tocilizumab combination therapy. The exploratory biomarkers will be assessed to understand which patients are most likely to respond to the combination treatment relative to remdesivir monotherapy. Biomarker data assessed in conjunction with both virological and clinical outcome measures should provide a deeper understanding of efficacy as well as progression of COVID-19.

4. MATERIALS AND METHODS

4.1 PATIENTS

The target enrollment for the study is approximately 650 hospitalized patients with severe COVID-19 pneumonia, but up to 800 patients may be enrolled to achieve approximately 520 patients discharged by Day 28.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Documented informed consent to participate in the study
- Signed Assent Form when appropriate, as determined by the patient's age and individual site and country standards
- Age $\geq$ 12 years at time of informed consent
- 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

  The PCR test must be collected $\leq$ 7 days before randomization.

- Requiring >6 L/min supplemental oxygen to maintain $SpO_2 > 93\%$
- Agrees to not participate in another clinical trial for the treatment of COVID-19 while participating in this study
- 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.

  Hormonal contraceptive methods must be supplemented by a barrier method.

  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 tocilizumab or other monoclonal antibodies
- Known hypersensitivity to remdesivir, the metabolites, or formulation excipients
- 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
- Treatment with immunosuppressive or immunomodulatory therapy (including tocilizumab) within the past 3 months
- Concurrent treatment with other agents with actual or possible direct-acting antiviral activity against SARS-CoV-2 within 24 hours prior to study drug dosing

  In addition, patients with prior or current treatment with $>2\ doses\ of$ remdesivir for COVID-19 are excluded.
- Participating in another drug clinical trial
- Estimated glomerular filtration rate (eGFR) <30 mL/min (including patients receiving hemodialysis or hemofiltration), using the equation described in the FDA EUA Fact Sheet for remdesivir (FDA 2020b)
- ALT or AST $>5\times$ upper limit of normal (ULN) detected within 24 hours of screening (according to local laboratory reference ranges)
- ANC $<1000/\mu L$ at screening
- Platelet count $<50{,}000/\mu L$ at screening
- Body weight <40 kg
- Pregnant or breastfeeding, or positive pregnancy test in a predose examination
- Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization
- 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 study. After initial 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 the below listed treatment arms.

- Remdesivir plus tocilizumab (RDV + TCZ)
- Remdesivir plus placebo (RDV + placebo)

Randomization will occur at an initial 2:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm at the specified ratio. The randomization will be stratified by geographic region (North America, Europe, Other) and a 2-level factor based on the assessment of the 7-category ordinal scale of clinical status at screening, 4–5 or 6. The proportion of randomized patients in the scale = 6 stratum will also be no more than 25%.

4.2.2 Blinding

Study site personnel and patients will be blinded to TCZ treatment assignment during the study. The Sponsor and its agents will also be blinded to TCZ 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, unblinded pharmacist (if required), IxRS service provider, and Data Monitoring Committee (DMC) members and support staff as specified in the DMC Charter who may be Roche employees but independent of the study team.

Investigators, site staff, Roche monitors, project statisticians, and the project team will be blinded from PK and pharmacodynamic results (including 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 accessing 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 (IMPs) for this study are remdesivir IV, tocilizumab IV, and placebo for tocilizumab IV.

4.3.1 Study Treatment Formulation and Packaging

4.3.1.1 Remdesivir

Remdesivir will be supplied by the Sponsor as a sterile lyophilized solid containing 100 mg of remdesivir to be reconstituted with 19 mL of sterile water for injection and diluted into IV infusion fluids prior to IV infusion. Following reconstitution, each vial contains a 5 mg/mL remdesivir concentrated solution with sufficient volume to allow withdrawal of 20 mL (100 mg of remdesivir).

For information on the formulation and handling of remdesivir, see the remdesivir pharmacy manual and remdesivir Investigator's Brochure, as well as the fact sheet for use of remdesivir for patients with severe COVID-19 disease (FDA 2020b).

4.3.1.2 Tocilizumab and Placebo

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

Alternatively, due to limitations on placebo supplies, normal saline may be given at an equal volume as a placebo in place of the solution for infusion (requires unblinded pharmacist).

For information on the formulation and handling of tocilizumab, see the tocilizumab 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 Remdesivir

Remdesivir will be administered by IV infusion at doses of 200 mg and 100 mg.

Remdesivir must be administered under close supervision of the investigator in a setting where medications and resuscitation facilities are available.

Ambient vials of the lyophilized formulation of remdesivir should be stored below 30°C (86°F). The lyophilized formulation needs to be reconstituted and then diluted into IV infusion fluids before use. After reconstitution, the total storage time before completion

of administration (including any time before or after dilution) should not exceed 4 hours at room temperature (20°C–25°C [68°F–77°F]) or 24 hours at refrigerated temperature (2°C–8°C [36°F–46°F]).

The remdesivir will be administered at room temperature by controlled infusion into a vein over 30–120 minutes. The infusion rate must be kept steady over the course of the infusion. The entire 100 mL–250 mL content of the infusion bag must be administered. A total of at least 30 mL of normal saline will be administered following the infusion of study treatment to flush the remaining study drug through the IV set.

Remdesivir does not meet the criteria for a hazardous compound as defined by National Institute for Occupational Safety and Health and American Society of Health-System Pharmacists hazard classification systems. The study products may be prepared in a standard hospital pharmacy.

Refer to the Remdesivir Investigator's Brochure for further instructions regarding recommended storage conditions and packaging configuration, as well as the fact sheet for use of remdesivir for patients with severe COVID-19 disease (FDA 2020b).

4.3.2.2 Tocilizumab and Placebo

Tocilizumab/placebo will be administered by IV infusion at doses of 8 mg/kg. The maximum dose of tocilizumab that will be administered is 800 mg. The dose of tocilizumab infusion will be calculated on the basis of body weight (see Appendix 1). One additional infusion of blinded treatment of tocilizumab or placebo can be given 8–24 hours after the first tocilizumab/placebo infusion. The second dose of blinded tocilizumab must not be given if the patient develops an adverse event or laboratory abnormalities that warrant discontinuation of tocilizumab as described in Section 5.1.2.

Tocilizumab/placebo must be administered under close supervision of the investigator in a setting where medications and resuscitation facilities are available. The tocilizumab/placebo infusion must not be started until at least 1 hour after the end of the remdesivir/placebo infusion. Patients should be monitored for at least 2 hours after the tocilizumab infusion is completed.

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

If stored at 2°C–8°C (36°F–46°F), the infusion bag should be allowed to return to room temperature before administration. The tocilizumab will be administered at room temperature by controlled infusion into a vein over a 1-hour period. In exceptional cases this time may be extended up to 6 hours. The infusion rate 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 at least 20 mL of normal saline will be administered following the infusion of study treatment to flush the remaining study drug through the IV set. If a second tocilizumab/placebo infusion is given 8–24 hours after the first tocilizumab/placebo infusion, there must be at least 2 hours after completion of the second tocilizumab/placebo infusion before the Day 2 remdesivir infusion is administered.

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 IMPs (remdesivir and tocilizumab/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 remdesivir and tocilizumab/placebo, and only authorized staff may supply or administer remdesivir and tocilizumab/placebo.

Remdesivir and tocilizumab/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 manuals and/or the remdesivir and tocilizumab Investigator's Brochures for information on IMP handling, including preparation and storage, and accountability.

4.3.4 Continued Access to Remdesivir

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

4.3.5 Continued Access to Tocilizumab

Currently, the Sponsor does not have any plans to provide Roche IMPs (tocilizumab) or any other study treatments to patients who have completed the study.

The Sponsor may evaluate whether to continue providing tocilizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following website:

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

4.4 CONCOMITANT THERAPY

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

4.4.1 Permitted Therapy

All patients will receive standard supportive care for the treatment of severe COVID-19 pneumonia. Use of the following therapies during the study is permitted as described below:

- Non-steroidal anti-inflammatory drugs or antipyretic drugs.
- Acetaminophen and paracetamol
- Azithromycin is permitted if part of the local SOC. Broad-spectrum antibiotics are also permitted when clinically indicated.
- Low-dose corticosteroids are permitted if part of the local SOC. If corticosteroids are given, the Sponsor recommends giving the lowest possible dose and duration of treatment and that the dose should not exceed methylprednisolone 1 mg/kg, or equivalent, for $\leq$10 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 ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, ranitidine), or equivalent medications per local standard practice. Serious infusion-associated events

manifested by, for example, dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

4.4.2 Cautionary Therapy

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

Remdesivir is a substrate for CYP2C8, CYP2D6, and CYP3A4. However, co-administration with inhibitors of these CYP isoforms is unlikely to markedly increase remdesivir levels, as its metabolism is likely to be predominantly mediated by hydrolase activity.

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 tocilizumab, it is expected that the formation of CYP450 enzymes could be normalized. When starting tocilizumab therapy, patients taking medications that are individually dose adjusted and metabolized by means of CYP450, CYP3A4, CYP1A2, or CYP2C9 (e.g., atorvastatin, calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporine, or benzodiazepines) are recommended to be monitored, as doses may need to be adjusted to maintain their therapeutic effect.

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

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is prohibited 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:

- Convalescent plasma or immunoglobulins for treatment of COVID-19
- Chloroquine or hydroxychloroquine
- Lopinavir / ritonavir
- Rifampin
- Treatment with any investigational agent, cell-depleting therapies, anti-viral agents, 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, anti-thymocyte globulin, and azathioprine
- Immunization with a live attenuated vaccine through Day 28

4.5 STUDY ASSESSMENTS

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

1. Clinical assessments: clinical status, clinical signs and symptoms, oxygen saturation, vital signs
2. Safety assessments: 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 prior to the remdesivir infusion, except for postdose samples for PK analyses, which will be obtained after study drug treatment.
4. Review of creatinine and liver function test results before IV infusion of remdesivir: baseline (Day 1) and up to and including Day 10
5. IV infusion of remdesivir: baseline (Day 1) and up to and including Day 10
6. Safety assessments: vital signs post remdesivir administration/pre-tocilizumab or placebo administration (if indicated)
7. IV infusion of tocilizumab/placebo: only at baseline (Day 1) and an additional dose 8–24 hours after the initial infusion (if required)
8. Safety assessments: vital signs post-tocilizumab administration (if indicated)

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

If patients are discharged from hospital prior to Day 28, follow-up visits should be conducted on Days 14, 21, 28, 35, 45, and 60.

- Follow-up visits on Days 14 and 21 may be conducted as telephone visits.
- Follow-up visit on Day 28 should be in person at the site, if at all possible.
- Follow-up visits on Days 35 and 45 may be conducted as telephone visits.
- Follow-up visit on Day 60 should be in person at the site, if at all possible.

Remdesivir will be discontinued at the time of hospital discharge if hospital discharge occurs before completion of 10 days of remdesivir dosing. Patients should remain in the study and complete all follow-up visits as described above (starting from the Day 14 visit).

If patients are discharged from hospital after Day 28, follow-up visits should be conducted on Days 35, 45, and 60 as described above.

4.5.1 Informed Consent Forms and Screening Log

Documented informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Assent should be documented when appropriate, as determined by the patient's age and individual site and country standards. Written informed consent should be obtained,

when possible. In the pandemic situation where access to hospitals is limited, if allowed in accordance with local regulation, verbal consent can be obtained from the patient or 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 prescription medications used by the patient within 7 days prior to first dose of study drug will be recorded. Vitamins, herbal supplements, over-the-counter cold medicines and antipyretics taken at home prior to hospitalization do not need to be recorded. Record all medications administered during the study. Antipyretics and other medications given for symptomatic care can be recorded only once, even if given multiple times during the hospital course, except when given as a treatment for an adverse event where recording is required. At the time of each follow-up visit, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal (GI), 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 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 schedules 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 vital signs. For patients requiring supplemental oxygen, the oxygen flow rate (L/min) and/or FiO_2 should be recorded.

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, approximately every 12 hours, for the duration of the hospitalization during the study. This is to ensure that the measurements reflect the patient's condition over the entire 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 pulse 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 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:

- PaO_2/FiO_2 (if arterial blood gases are measured during screening or follow-up)
- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes), and lymphocyte subsets (T cells, B cells, and natural killer cells; if the test is available at

the site, or if the site can ship the blood sample on the day of collection to the central laboratory for testing)

- Coagulation: INR, PTT, D-dimer, fibrinogen
- Chemistry panel (serum or plasma): bicarbonate , sodium, potassium, chloride, glucose, BUN, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, LDH, PCT, and ferritin
- Pregnancy test

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

- Plasma samples for PK analysis (for sites capable of sample collection)
- Serum samples for exploratory biomarker research
- Serum samples for SARS-CoV-2 antibody titer
- Nasopharyngeal swabs and other respiratory samples (e.g., endotracheal tube aspirates) for SARS-CoV-2 virology tests (viral load and other exploratory analysis including potential viral resistance assessment)
- Blood PAXgene® RNA for RNA sequencing or quantitative PCR
- Blood for PBMC isolation and cryopreservation (for sites capable of sample collection). If PBMC isolation or cryopreservation is not feasible for the site, then blood samples may alternatively be shipped on the day of collection to the central laboratory)
- Blood for lymphocyte subsets (T cells, B cells, and natural killer cells) (for sites capable of sample collection). If not tested in the local laboratory, then the site can ship the blood sample on the day of collection to the central laboratory for testing

Exploratory biomarker research may include, but will not be limited to, analysis of inflammatory mediators and/or cytokines such as IL-6, CRP, ARDS-related variables, anti-SARS-CoV-2 antibody, viral load, and viral resistance 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 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:

- Plasma 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 5 years after the final Clinical Study Report has been completed.
- Serum, PBMCs, blood PAXgene RNA, and tissue-derived samples (nasopharyngeal swabs and other respiratory samples) collected for biomarker research will be destroyed no later than 5 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 Kidney and Liver Function Monitoring

Patients must be assessed for creatinine and liver function prior to each dose of remdesivir, tocilizumab, or tocilizumab placebo. 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. On subsequent days of remdesivir dosing, creatinine and liver function tests will be assessed daily prior to dosing as per the schedules of activities (Appendix 1 and Appendix 2). Results must be reviewed by the investigator before dose administration. Dosing will occur only if the clinical assessment and local laboratory chemistry panel values are acceptable.

4.5.8 Chest X-Rays and CT Scan

Chest X-ray/CT scan findings at baseline should be recorded on the appropriate 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 of clinical status will be recorded at baseline on Day 1 and then again once daily every morning (between 8:00 a.m. and 12:00 p.m.) 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 ≤2 L supplemental oxygen)
2. Non-ICU hospital ward (or “ready for hospital ward”) not requiring supplemental oxygen
3. Non-ICU hospital ward (or “ready for hospital ward”) requiring supplemental oxygen
4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen
5. ICU, requiring intubation and mechanical ventilation
6. ICU, requiring ECMO or mechanical ventilation and additional organ support (e.g., vasopressors, renal replacement therapy)
7. Death

Patients who are ready to be discharged but are still hospitalized (e.g., 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°C–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
- Severe allergic reaction to remdesivir or tocilizumab/placebo
- Discharge from hospital

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 tocilizumab in clinical studies, post-marketing experience with tocilizumab, and experience with remdesivir in clinical trials. The important safety risks for tocilizumab and potential risks for remdesivir are outlined below. Please refer to the Tocilizumab Investigator's Brochure and the Remdesivir Investigator's Brochure for a summary of safety information for the respective molecules. There are no robust data concerning the use of tocilizumab and remdesivir in combination.

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 Potential Risks Associated with Remdesivir

Remdesivir is an investigational therapeutic agent. As of 14 February 2020, 138 healthy adults have been dosed with remdesivir in four Phase I clinical trials. A few subjects to date experienced constipation, heartburn, itching, unusual feelings in the ear, dizziness, loss of appetite, nausea, vomiting, shaking of the leg and arm, headache, loose stool, or upset stomach. These adverse events were temporary, lasting only a few days, and none were serious.

5.1.1.1 Infusion Related Reactions

Infusion-related reactions have been observed during, and/or have been temporally associated with, administration of remdesivir. Signs and symptoms may include hypotension, nausea, vomiting, diaphoresis, and shivering.

5.1.1.2 Elevated Liver Enzymes

In clinical studies, transient elevations in ALT and AST have been observed with single doses of remdesivir up to 225 mg and multiple doses of remdesivir 150 mg once a day (QD) for up to 14 days. Mild (Grade 1) reversible PT prolongation was also noted in some subjects but without any clinically significant change in INR or other evidence of hepatic effects. The mechanism of these elevations is currently unknown. Based on these clinical observations, patients with ALT or AST $> 5 \times$ ULN will not be eligible for study enrollment. Regular laboratory assessments will be performed to monitor hepatic function. Any observed liver function-related laboratory abnormalities or possibly related adverse events will be treated appropriately and followed to resolution.

5.1.1.3 Kidney Toxicity

In nonclinical animal studies, toxicity studies found dose-dependent and reversible kidney injury and dysfunction. In clinical studies, no evidence of nephrotoxicity has been observed with single doses of remdesivir up to 225 mg or multiple doses of remdesivir 150 mg QD for up to 14 days. A 200-mg dose of lyophilized formulations of remdesivir contains 4 g, respectively, of sulfobutylether-beta-cyclodextrin (SBECD), for which the maximum daily recommended daily dose (based on a European Medicines Agency safety review) is approximately 250 mg/kg. Because SBECD is renally cleared, patients with moderate or severe renal impairment may have SBECD exposures greater than patients with less severe renal impairment or normal renal function. Based on this information, patients with an eGFR of less than 30 mL/min (including patients requiring hemodialysis or hemofiltration) will not be eligible for study enrollment.

5.1.1.4 CYP450 Enzyme Normalization

Remdesivir is a substrate for CYP2C8, CYP2D6, and CYP3A4. However, co-administration with inhibitors of these CYP isoforms is unlikely to markedly increase remdesivir levels, as its metabolism is likely to be predominantly mediated by hydrolase activity.

5.1.1.5 Viral Resistance

There is the potential of the SARS-CoV-2 developing resistance to remdesivir, which could result in decreased efficacy. The clinical impact of the development of resistance is not clear at this time.

5.1.2 Risks Associated with Tocilizumab

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

5.1.2.1 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 tocilizumab 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

Tocilizumab infusions will be administered to patients at the site under close supervision. Healthcare professionals administering tocilizumab infusions should be trained in the appropriate procedures for tocilizumab 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 tocilizumab. The patient should be treated according to the SOC for management of the hypersensitivity reaction.

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

5.1.2.2 Serious Infections and Opportunistic Infections

Physicians should exercise caution when considering the use of tocilizumab 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 tocilizumab 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, the second administration of tocilizumab/placebo must not be given

5.1.2.3 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.

The second administration of tocilizumab/placebo must not be given for patients who develop GI perforations.

5.1.2.4 Hematologic Abnormalities

Decreases in neutrophil counts, platelet counts, and fibrinogen levels have been observed following treatment with tocilizumab 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.

5.1.2.5 Demyelinating Disorders

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

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

5.1.2.6 Elevated Liver Enzymes

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

The second infusion of tocilizumab/placebo must not be given in patients with ALT or AST $> 5 \times$ ULN.

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.

5.1.2.7 CYP450 Enzyme Normalization

The expression of hepatic CYP450 enzymes is suppressed by cytokines, such as IL-6, that stimulate chronic inflammation. Tocilizumab normalizes expression of these enzymes. The effect of tocilizumab 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 tocilizumab, patients taking medicinal products that 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.

5.1.3 Management of Patients Who Experience Adverse Events

5.1.3.1 Tocilizumab Dose Modification and Treatment Interruption

If the patient has a sustained fever or clinically significant worsening of signs or symptoms (e.g., an increased supplemental oxygen requirement), one additional infusion of blinded tocilizumab/placebo can be given 8–24 hours after the initial first tocilizumab/placebo infusion. The second dose of blinded tocilizumab must not be given if the patient develops an adverse event or laboratory abnormalities that warrant discontinuation of tocilizumab as described in Section 5.1.2.

5.1.3.2 Remdesivir Treatment Interruption

There are no clinical safety or PK data available for remdesivir in patients with renal and/or hepatic impairment.

If the eGFR decreases to an eGFR <30 mL/min (using the equation described in the FDA EUA Fact Sheet for remdesivir), remdesivir should not be given. Dosing may be resumed if the eGFR returns to ≥ 30 mL/min. Creatinine should be measured daily to assess renal function on remdesivir dosing days. If the patient's renal function worsens to the point that he or she requires hemodialysis or hemofiltration, remdesivir will be discontinued.

If the ALT and/or AST increases to $>5 \times$ ULN, the dose of remdesivir should be held and not be restarted until the ALT and AST $\leq 5 \times$ ULN. Remdesivir dosing should be placed on hold and may be discontinued, following a review of all available clinical data by the medical monitor and discussion with the investigator, if any of the following occurs:

- ALT $>$ 3x ULN and total bilirubin $>$ 2x ULN, confirmed by immediate repeat testing
- ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR
- Suspected drug-related event of hypersensitivity during the infusion (as described in Section 5.5.1). Subjects who have an IV infusion stopped for a safety related issues will not continue with dosing.

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 Section 5.3.5.9 and Section 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 NCI CTCAE v5.0; 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
- 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 until 60 days after the first dose of study drug.

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 a study drug, indicating "yes" or "no" accordingly. For patients in this study who are potentially receiving combination therapy, causality will be assessed individually for each protocol-mandated study drug. The following guidance should be taken into consideration (see also Table 2):

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

Table 2 Causal Attribution Guidance

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

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 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), 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.

5.3.5.3 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 patient, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

5.3.5.4 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.

5.3.5.5 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., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 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).

5.3.5.7 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 and $>2\times$baseline in combination with total bilirubin $>2\times$ULN and $>2\times$baseline
- Treatment-emergent ALT or AST $>3\times$ULN and $>2\times$baseline 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).

5.3.5.8 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.

5.3.5.9 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").

5.3.5.10 Lack of Efficacy or Worsening of Severe 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.

5.3.5.11 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

5.3.5.12 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 tocilizumab or remdesivir (or tocilizumab 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 tocilizumab or remdesivir (or tocilizumab 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.

5.3.5.13 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 Institutional Review Board (IRB)/Ethics Committee (EC).

5.4.1 Medical Monitors and Emergency Medical Contacts

Medical Monitor Contact Information for All Sites (North and South American time zones)

Medical Monitor: [redacted], M.D., M.S.

Mobile Telephone No.: [redacted]

Alternate Medical Monitor Contact Information for All Sites (European time zones)

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 90 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. 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) 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
Remdesivir	Remdesivir 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 who received *any amount of* tocilizumab/placebo and are grouped according to their treatment assignment at randomization: remdesivir plus tocilizumab, or remdesivir plus placebo.

Safety analyses will be performed on the safety-evaluable population, which consists of all patients who receive any amount of study treatment (remdesivir and/or tocilizumab/placebo). 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 primary endpoint, time to discharge or "ready for discharge," is event driven. Based on the severe cohort receiving 10 days of remdesivir in Gilead's SIMPLE trial (Study GS-US-540-5773), the median time to discharge or "ready for discharge" was 11 days. Assuming a median time to discharge or "ready for discharge" of 11 days in the remdesivir plus placebo arm, a hazard ratio of 1.3 or an approximately 2.5-day reduction in median time for remdesivir plus tocilizumab versus remdesivir plus placebo, and a 2:1 randomization to remdesivir plus tocilizumab or remdesivir plus placebo, approximately 650 patients are needed to accrue approximately 520 events to achieve approximately 80% power. A reduction of at least 2 days in median time to discharge was considered clinically meaningful and the sample size was increased to ensure that a minimum effect size could be detected. Further sample size adjustments may be considered during the study based on external information. The sample size may be increased up to a maximum of approximately 800 randomized patients if fewer events than expected are observed or further shifts in standard of care warrant reassessing sample size assumptions.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, are randomized, 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 score, ordinal scale $category$ for clinical status, IL-6, mechanical ventilation) 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 population. The safety population may be presented in a similar fashion if there are differences.

Medical history data, including 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

Efficacy analyses will use the mITT population defined as all randomized patients who have received *any amount* of tocilizumab/placebo. To enable a more comprehensive evaluation of the treatment effect of tocilizumab combined with remdesivir compared with tocilizumab alone, external data *may* be leveraged appropriately in a meta-analysis of this trial combined with WA42380 and ML42528.

Sensitivity analyses to evaluate the robustness of results to the primary analysis methods (e.g., handling of dropouts, etc.) may be conducted and will be described in the SAP. Full details of adjustments to significance levels for hypothesis tests resulting from any interim analyses, and for other instances of multiplicity and/or sequential order of analyses will be predefined in the SAP. *Censoring rules for each endpoint will be predefined in the SAP.* Descriptive subgroup analyses to evaluate the consistency of results across pre-specified subgroups may also be conducted.

6.4.1 Primary Efficacy Endpoint

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

- Time from *randomization* to hospital discharge or “ready for discharge” *up to Day 28*

  Hospital discharge or “ready for discharge” is defined as a score of 1 on the *7- category* ordinal scale. *Patients will meet the endpoint at the time of discharge or the time that they achieve category 1 of the 7-category ordinal scale, provided that they do not have any further ordinal scale assessments > category 1 on or prior to Day 28, they are not re-hospitalized on or prior to Day 28 and they do not die on or prior to Day 28.*

The distribution of time from *randomization* to hospital discharge (or "ready for discharge”) will be compared with the remdesivir plus tocilizumab arm and the remdesivir plus placebo arm up to Day 28. Patients discharged after Day 28 will be administratively censored. The distributions will be compared using an appropriate method for comparing censored event distributions *such as the Cox model. Kaplan-Meier and* cumulative incidence plots will be presented as well as median time to

discharge (or “ready for discharge”), with 95% confidence intervals for the remdesivir plus tocilizumab arm and the remdesivir plus placebo arm.

6.4.2 Secondary Efficacy Endpoints

Time to event secondary endpoints outlined below will be compared between the remdesivir plus tocilizumab arm and the remdesivir plus placebo arm using an appropriate test to compare time to event distributions, *such as the Cox model*. If death is identified as a competing risk then that will be considered in the method chosen *or in the definition of the endpoint*. Tests will appropriately include geographic region (North America, Europe, Other) and the 2-level factor based on the assessment of the 7-category ordinal scale of clinical status at screening (4–5, 6). Details will be addressed in the SAP. The cumulative incidence plot, median time to response, their 95% CIs, and a p-value will be presented for secondary time to event endpoints.

- Time to mechanical ventilation or death *up to Day 28*, defined as the time from *randomization* to the first occurrence of mechanical ventilation or death (whichever occurs first)
- Time to improvement of at least 2 categories relative to baseline on a 7-category ordinal scale of clinical status *up to Day 28*
- Time to death up to Day 28 and Day 60
- Time to recovery *up to Day 28*, defined as time from randomization to the time when a category of 2 *on the 7-category ordinal scale* (non-ICU hospital ward or “ready for hospital ward” not requiring supplemental oxygen), or better is observed

Secondary efficacy incidence endpoints outlined below will be analyzed using the Cochran-Mantel-Haenszel test statistic adjusted by the stratification factors (geographic region [North America, Europe, Other]) and a 2-level factor based on the assessment of the 7-point ordinal scale of clinical status at screening, with levels 4–5, and 6, 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 SAP.

- *Proportion of patients who are discharged or ready for discharge up to Day 28, as defined in Section 6.4.1*
- Proportion of patients requiring initiation of mechanical ventilation postbaseline up to Day 28 and Day 60 (patients who do not require mechanical ventilation at baseline)
- *Proportion of patients who require initiation of mechanical ventilation post baseline or die up to Day 28*
- Proportion of patients who are alive and free of respiratory failure *at* Day 28 and Day 60 (patients requiring mechanical ventilation at baseline)
- Mortality at Days 14, 28, and 60. The difference in proportions for the treatment group comparison will be presented together with a 95% CI using an appropriate method.

Secondary efficacy ordinal endpoints are summarized below. Ordinal data will be analyzed using an appropriate cumulative link model such as PO or a robust alternative such as a variant of Wilcoxon-Mann-Whitney U comparing the remdesivir plus tocilizumab arm and the remdesivir plus placebo arm. The testing approach will account for stratification factors at randomization: geographic region [North America, Europe, Other] and a 2-level factor based on the assessment of the 7-category ordinal scale of clinical status at screening, with levels 4–5 or 6. The appropriate effect size will be presented with p-value and 95% CI as well as descriptively by visit.

- Clinical status as assessed by the investigator using a 7-category ordinal scale of clinical status on Days 7, 14, 21, 28, and 60

Duration endpoints will be summarized descriptively using the *means*, with 95% CIs for the *means and difference in means* by treatment group and/or cumulative incidence plots:

- Duration of mechanical ventilation (patients who require mechanical ventilation at baseline) *up to Day 28*

Primary and selected secondary endpoints *may* be compared across this trial, WA42380, and ML42528 in a meta-analysis using similar approaches. Further details of the secondary endpoint analysis and meta-analysis will be included in the SAP and the *meta-analysis plan*, respectively.

6.4.3 Exploratory Efficacy Endpoints

Exploratory time to event endpoints outlined below will be compared between the remdesivir plus tocilizumab arm and the remdesivir plus placebo arm using an appropriate summary method to compare time to event distributions, if death is identified as a competing risk then that will be considered in the method chosen *or in the definition of the endpoint*. Tests will appropriately include geographic region (North America, Europe, Other) and the 2-level factor based on the assessment of the 7-category ordinal scale of clinical status at screening (4–5, 6). Details *on statistical analysis methods used* and censoring rules will be addressed in the SAP.

- TTCI *up to Day 28*, defined as time from *randomization* to NEWS2 score of ≤2 maintained for 24 hours
- Time to clinical failure up to Day 28, defined as the time from *randomization* to the first occurrence of *death*, mechanical ventilation, ICU admission or withdrawal *from study prior to discharge* (whichever occurs first)
- Proportion of patients requiring initiation of ICU care postbaseline up to Day 28 and Day 60
- Duration of ICU stay (days) *up to Day 28* will be summarized using the *means* along with 95% CIs for the *means* by treatment group.
- Duration of supplemental oxygen use (days) *up to Day 60* will be summarized using the *means* along with 95% CIs for the means by treatment group.

- Proportion of patients requiring initiation of vasopressor use postbaseline *up to Day 28 will* be summarized descriptively.
- Duration of vasopressor use *up to Day 28* will be summarized using the *means* along with 95% CIs for the *means* by treatment group.
- Proportion of patients requiring initiation of ECMO postbaseline *up to Day 28 and Day 60 will be summarized descriptively.*
- Duration of ECMO *up to Day 28* will be summarized using the *means* along with 95% CIs for the *means* by treatment group.
- Organ failure-free days from *randomization* to Day 28 will be summarized descriptively using the *means*, with 95% CI for the *means* by treatment group. In addition, a summary of individual organ failure over time will be provided.
- SARS-CoV-2 viral load over time *up to Day 28 and Day 60* will be summarized descriptively by timepoint and treatment group *for respiratory and serum samples.*
- Time to RT-PCR SARS-CoV-2 virus negativity *up to Day 14 (serum samples) or Day 60 (respiratory samples)* will be analyzed using similar methods to the other time to analyses but account for interval censoring.

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 treatment. In all safety analyses, patients will be grouped according to the treatment that the patients actually received, rather than the treatment assigned at randomization. *Details with respect to grouping will be specified in the SAP.*

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

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.

The proportion of patients with any post-treatment infection will be summarized at time points including Day 60.

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

6.6 PHARMACOKINETIC ANALYSES

Plasma concentrations and PK parameters for remdesivir and metabolite(s) may be listed and summarized using descriptive statistics by group.

For summary statistics, PK concentration values below the limit of quantitation will be treated as zero at predose and one-half of the lower limit of quantitation for sample collected during the remdesivir infusion.

6.7 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.

6.8 INTERIM ANALYSES

There will be up to three optional interim analyses. The first interim analysis can occur after approximately one-third to one-half of the patients have been assessed for the primary endpoint on Day 28, depending on enrollment rate. There may be up to two additional unplanned interim analyses, and these will be considered if there are major changes to the study design following the first interim analysis.

Full statistical details of any optional interim analyses, along with the rationale and timing will be documented in an interim SAP, which will be made available to the relevant health authorities before the data snapshot for the first interim analysis. Only the DMC will be unblinded and decision criteria will be specified in the interim SAP. Should an unblinded interim analysis occur, any necessary adjustment to the type 1 error rate will be specified in the SAP prior to unblinding the study.

The optional interim analysis will be based on the time to discharge (or ready for discharge) and mortality. Questions to be addressed at the interim analysis might include futility as well as potential efficacy.

The DMC will also evaluate safety according to policies and procedures detailed in the DMC Charter. Regular safety reviews will begin after approximately 45 patients (15 remdesivir and 30 combination) have been enrolled and have reached 14 days of 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 DMC initially consisted of Sponsor representatives not involved in any operational aspects of the study and a Scientific Oversight Committee of external experts (responsibilities and operating principles of the DMC are described in a charter, the Internal Monitoring Committee and Scientific Oversight Committee Agreement). The DMC responsibilities transitioned to a fully independent Data Monitoring Committee (iDMC) prior to the third scheduled safety review after approximately 300 patients reached Day 28 of follow-up. The iDMC will also conduct a fourth scheduled safety data review when at least 450 patients have reached Day 28. Data processing will be handled by a Sponsor statistician and statistical programmer independent of the study management team. Details are reported in the iDMC Charter.

6.9 EXTERNAL DATA

Trials WA42380 and ML42528 *may* be included in a meta-analysis of mortality, the primary endpoint, and selected secondary endpoints. Both trials compare 8 mg/kg IV TCZ with placebo. If further relevant studies are identified prior to analysis, they may also be included in the pre-defined meta-analysis. Prior to inclusion, external data will be checked for consistency of measured endpoints so that endpoints can be assessed. Full details of the analysis and trial inclusion criteria will be specified in the *meta-analysis plan*.

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 quality-control 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, health care provider (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 or the patient’s legally authorized representative and this must be documented by the investigator or authorized designee. The case history or clinical records for each patient shall document the informed consent process and that informed consent was obtained prior to participation in the study.

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 with 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 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 9.7).

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

8.4 CONFIDENTIALITY

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

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

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

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

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 100 sites globally will participate to enroll *up to 800* 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 *Study Information* at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application

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

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

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

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

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

9.7 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities: Screening, Days 1 and 2

Study Day	Screening [a, b]	Day 1			Day 2	
	–2 to 0					
Time After Initial Treatment (Assessment Window)		Baseline 0 Predose	1 hour After End of RDV Infusion (+ 2 hrs)	15 min After End of TCZ Infusion (+ 3 hrs)	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 [d]	x					
COVID-19 diagnosis [e]	x					
Chest X-ray/CT scan [f]	x					
ECG	x					
Pregnancy test [g]	x					
PaO_2/FiO_2 [h]	Optional [h]	← Optional →				
SpO_2 [i]	x	x	x	x	x	x
Vital signs [i]	x	x	x	x	x	x
Ordinal scoring [j]		x			x	
Adverse events [k]	x [k]	x [k]	x	x	x	x

Appendix 1: Schedule of Activities: Screening, Days 1 and 2

Study Day	Screening [a, b]	Day 1			Day 2	
	−2 to 0					
Time After Initial Treatment (Assessment Window)		Baseline 0 Predose	1 hour After End of RDV Infusion (+ 2 hrs)	15 min After End of TCZ Infusion (+ 3 hrs)	24 hrs (± 4 hrs)	36 hrs (± 4 hrs)
Concomitant medications [l]	x	x			x	
Hematology [m]	x	x			x	
Chemistry (full panel) [n]	x	x				
Chemistry (only ALT, AST, total bilirubin, ALP, and creatinine)					x	
Coagulation [o]	x	x				
RDV administration [p]		x			x	
TCZ/placebo administration [q]			x			
Central Labs						
Serum sample for exploratory biomarkers [p]		x			x	
Nasopharyngeal swab: SARS-CoV-2 viral load and exploratory biomarkers [r]		x			x [r]	
Serum SARS-CoV-2 antibody titer		x				
Cryopreserved PBMCs [s]		x			x	
Blood in PAXgene® tubes for RNA analyses [t]		x				

Appendix 1: Schedule of Activities: Screening, Days 1 and 2

CT = computed tomography; eCRF = electronic case report form; hrs = hours; min = minute; NEWS2 = National Early Warning Score 2; NK = natural killer (cell); PaO_2/FiO_2 = arterial oxygen partial pressure/fraction of inspired oxygen; PBMCs = peripheral blood mononuclear cells; PCR = polymerase chain reaction; PCT = procalcitonin; RDV = remdesivir; SARS-Cov-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = peripheral capillary oxygen saturation; TCZ = tocilizumab.

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

[a] Results from standard-of-care tests or examinations (including physical exam) performed prior to obtaining informed consent and within 24 hours before screening 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. The screening and baseline visit may be performed on the same day, provided that the patient meets all of the study entry criteria as outlined in Section 4.1.1 and Section 4.1.2 prior to randomization. If the screening and baseline visits occur on the same day, assessments do not need to be repeated.

[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, 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 after randomization should be reported as adverse events (see Section 5.3).

[d] If it is not feasible to weigh bed-bound patients, historical body weight may be used.

[e] COVID-19 test (SARS-CoV-2 PCR) to confirm diagnosis should be collected within 7 days prior to randomization.

[f] Screening chest X-ray or CT scans should be performed within 48 hours prior to randomization.

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

[h] If arterial blood gases are measured.

[i] On Day 1, all vital sign measurements (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressure, and body temperature), oxygen saturation (SpO_2), and NEWS2-specific assessments (i.e., consciousness and presence or absence of oxygen support) must be recorded 1) prior to administration of remdesivir, 2) after administration of remdesivir/prior to administration of tocilizumab/placebo and 3) after administration of tocilizumab/placebo. On Day 2, measurements should be recorded together twice daily approximately every 12 hours. If measured more than once during a 12 hour period on Day 2, 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. For patients requiring supplemental oxygen, the oxygen flow rate (L/min) and/or FiO_2 should be recorded.

[j] Assessment of clinical status using the ordinal scale should be recorded at baseline on Day 1 and again daily every morning (between 8:00 a.m. and 12:00 p.m.) for patients who remain hospitalized. See Section 4.5.10 for additional details.

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

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

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes), and lymphocyte subsets (T cells, B cells, and NK cells; if the test is available at the site, or if the site can ship the blood sample on the day of collection to the central laboratory for testing. Samples are not required if neither of these options is available).

[n] Chemistry panel (serum or plasma) includes bicarbonate, sodium, potassium, chloride, glucose, BUN, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, LDH, ferritin, and PCT.

[o] Coagulation panel includes INR, PTT, D-dimer and fibrinogen.

[p] Remdesivir should be administered after review of hematology and chemistry safety labs and collection of all central lab samples. The initial infusion of remdesivir should be given within 4 hours of randomization. If the patient received remdesivir prior to randomization, the remdesivir dose on Day 1 will be a 100-mg maintenance dose. If a second tocilizumab/placebo infusion is given, there must be at least 2 hours after completion of the second tocilizumab/placebo infusion before the Day 2 remdesivir infusion is administered – in this instance, the visit window on Day 2 at 24 hours may be extended to ±6 hours.

[q] The infusion of tocilizumab/placebo must not be given until at least 60 minutes after the infusion of remdesivir is complete. If the patient has a sustained fever or clinically significant worsening of signs or symptoms (e.g., an increased supplemental oxygen requirement), one additional infusion of blinded tocilizumab/placebo can be given 8–24 hours after the first tocilizumab/placebo infusion (see Section 5.1.3.1).

[r] Viral load will be assessed by nasopharyngeal swab or other respiratory sample (e.g., endotracheal tube aspirate). Sample collection on Day 2 is optional. Where possible the same nostril should be used. Patients who are intubated and undergo bronchoscopy will have samples taken for virological assessment. Genotypic and phenotypic viral resistance may be assessed in exploratory analyses. Other analyses may include evaluation of levels of inflammatory biomarkers.

[s] For sites capable of performing PBMC isolation and cryopreservation. If PBMC isolation or cryopreservation is not feasible for the site, then blood samples may alternatively be shipped on the day of collection to the central laboratory. Samples are not required if neither of these options is available.

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

Appendix 2
Schedule of Activities: Days 3–28

	Days 3–28 [a]																									Study Discontinuation [b]
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	
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
SpO_2 [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]	← Optional →																										Optional
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
Adverse events [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
Concomitant medications [g]	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 [h]	x		x		x			x				x							x							x	x
Chemistry (full panel) [i]	x				x			x				x							x							x	x
Chemistry (only ALT, AST, total bilirubin, ALP and creatinine)		x	x	x		x	x																				
Coagulation [j]					x							x							x							x	x
RDV administration [k]	x	x	x	x	x	x	x	x																			
Central Labs																											
Plasma PK [l]		x			x																						
Serum sample for exploratory biomarkers	x				x							x							x							x	x
Nasopharyngeal swab: SARS-CoV-2 viral load and exploratory biomarkers [m]	x	x [m]	x	x [m]	x			x				x							x							x	x

Appendix 2: Schedule of Activities: Days 3–28

	Days 3–28 [a]																								Study Discontinuation [b]
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	
Serum SARS-CoV-2 antibody titer																										x	x
Cryopreserved PBMCs [n]	x				x							x							x							x	x
Blood in PAXgene® tubes for RNA analyses [o]	x				x																					x	x

NEWS2 = National Early Warning Score 2; NK = natural killer (cell); PaO_2/FiO_2 = arterial oxygen partial pressure/fraction of inspired oxygen; PBMCs = peripheral blood mononuclear cells; PCT = procalcitonin; PK = pharmacokinetic; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = peripheral capillary oxygen saturation.

[a] If patients are discharged from hospital prior to Day 28, follow-up visits should be conducted on Day 14, Day 21 and Day 28 (±2 days). Follow-up visits on Day 14 and Day 21 may be conducted as telephone visits. Vital signs and laboratory testing will not be required for telephone visits. For patients discharged with supplemental oxygen prior to Day 28, SpO_2 measured by the patient at home should be recorded during telephone visits, if available. Patients should return to the site for the Day 28 visit, if at all possible.

[b] Patients who discontinue from study treatment should continue in the study and complete all assessments through Day 60 (as outlined in Appendix 2 and Appendix 3).

[c] All vital sign measurements (i.e., respiratory rate, pulse rate, systolic and diastolic blood pressure, 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 approximately every 12 hours 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.

[d] If arterial blood gases are measured.

[e] Assessment of clinical status using the ordinal scale should be recorded daily every morning (between 8:00 a.m. and 12:00 p.m.) for patients who remain hospitalized. See Section 4.5.10 for additional details.

[f] All adverse events will be reported until 60 days after the first 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, 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.

[h] 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, or if the site can ship the blood sample on the day of collection to the central laboratory for testing. Samples are not required if neither of these options is available). Hematology labs will not be performed if follow-up visits are conducted by telephone.

[i] Chemistry panel (serum or plasma) includes bicarbonate, sodium, potassium, chloride, glucose, BUN, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, LDH, ferritin, and PCT. Chemistry labs will not be performed if follow-up visits are conducted by telephone.

[j] Coagulation panel includes INR, PTT, D-dimer and fibrinogen. Coagulation labs will not be performed if follow-up visits are conducted by telephone.

[k] Remdesivir should be administered after review of chemistry safety labs and collection of all central lab samples. If a patient is discharged from hospital before Day 10, remdesivir will be discontinued at that time. Patients who received remdesivir prior to randomization will not exceed 10 days of remdesivir dosing in total.

[l] On Day 4 and Day 7, PK samples should be drawn prior to the start of remdesivir infusion (predose) and also 30–60 minutes after the start of the remdesivir infusion if possible. All PK samples must be drawn from the opposite arm as the remdesivir infusion. PK samples are not required if collection and processing is not feasible.

[m] Patients who remain in hospital will have viral load assessed by nasopharyngeal swab or other respiratory sample (e.g., endotracheal tube aspirate). Sample collection on Day 4 and Day 6 is optional. Where possible the same nostril should be used. Genotypic and phenotypic viral resistance may be assessed in exploratory analyses. Other analyses may include evaluation of levels of inflammatory biomarkers.

[n] For sites capable of performing PBMC isolation and cryopreservation. If PBMC isolation or cryopreservation is not feasible for the site, then blood samples may alternatively be shipped on the day of collection to the central laboratory. Samples are not required if neither of these options is available.

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

Appendix 3
Schedule of Activities: After Day 28

			Study Completion/ Discontinuation
Study Day (Assessment Window)	35 [a] (±3 days)	45 [a] (±3 days)	60 (±3 days)
Vital signs [b]	x	x	x
SpO_2 [b]	x	x	x
Ordinal scoring [c]	x	x	x
Adverse events [d]	x	x	x
Concomitant medications [e]	x	x	x
Hematology [f]	x	x	x
Chemistry [g]	x	x	x
Coagulation [h]	x	x	x
Central Labs			
Nasopharyngeal swab: SARS-CoV-2 viral load and exploratory biomarkers [i]	x [i]	x [i]	x
Serum sample for exploratory biomarkers	x		x
Serum SARS-CoV-2 antibody titer			x
Cryopreserved PBMCs [j]			x
Blood in PAXgene® tubes for RNA analyses [k]			x

NK = natural killer (cell); PMBCs = peripheral blood mononuclear cells; PCT = procalcitonin; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = peripheral capillary oxygen saturation.

[a] Patients should have follow up visits on Day 35, Day 45, and Day 60 (±3 days). The Day 35 and Day 45 visits may be conducted by telephone for discharged patients. Vital signs and laboratory testing will not be required for telephone visits. For patients discharged with supplemental oxygen, SpO_2 measured by the patient at home should be recorded during telephone visits, if available. Patients should return to the site for the Day 60 visit, if at all possible.

[b] For patients who remain in hospital, vital sign measurements and NEWS2-specific assessments should be conducted twice daily. 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] Assessment of clinical status using the ordinal scale should be recorded daily every morning (between 8:00 a.m. and 12:00 p.m.) for patients who remain hospitalized.

[d] All adverse events will be reported until 60 days after the first 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).

[e] Medication (e.g., prescription drugs, over-the-counter drugs) 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.

[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, or if the site can ship the blood sample on the day of collection to the central laboratory for testing. Samples are not required if neither of these options is available). Hematology labs will not be performed if follow-up visits are conducted by telephone.

[g] Chemistry panel (serum or plasma) includes bicarbonate, sodium, potassium, chloride, glucose, BUN, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST, LDH, ferritin, and PCT. Chemistry labs will not be performed if follow-up visits are conducted by telephone.

[h] Coagulation panel includes INR, PTT, D-dimer, and fibrinogen. Coagulation labs will not be performed if follow-up visits are conducted by telephone.

[i] Patients who remain in hospital will have viral load assessed by nasopharyngeal swab or other respiratory sample (e.g., endotracheal tube aspirate). Sample collection on Day 35 and Day 45 is optional. Where possible the same nostril should be used. Genotypic and phenotypic viral resistance may be assessed in exploratory analyses. Other analyses may include evaluation of levels of inflammatory biomarkers.

[j] For sites capable of performing PBMC isolation and cryopreservation. If PBMC isolation or cryopreservation is not feasible for the site, then blood samples may alternatively be shipped on the day of collection to the central laboratory. Samples are not required if neither of these options is available.

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

Appendix 4
National Early Warning Score 2 (NEWS2)

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

CVPU = confusion, voice, pain, unresponsive; 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). 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 electronic Case Report Form (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 (°C)	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.