Official Title: A Randomized, Double-Blind, Placebo-controlled, Multicenter Study to Evaluate The Efficacy And Safety of Tocilizumab in Hospitalized Patients With Covid-19 Pneumonia

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STATISTICAL ANALYSIS PLAN

TITLE: **A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TOCILIZUMAB IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA**

PROTOCOL NUMBER: ML42528

STUDY DRUG: Tocilizumab (RO4877533)

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PLAN PREPARED BY: [redacted]

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STATISTICAL ANALYSIS PLAN APPROVAL

Company Signatory:

Approval Date:
August 31, 2020

[redacted]

DocuSigned by:
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Statistical Analysis Plan Update Rationale

The statistical analysis plan ML42528 Version 2 includes the following updates from Version 1:

- Key secondary endpoints were updated
- The Type I error control section was added to specify a hierarchy for testing of the primary endpoint followed by testing of the predefined key secondary endpoints
- Cumulative Incidence Function plots were specified for time to 'improvement' secondary endpoints
- The censoring rules for the time to event endpoints were updated
- Derivation of the time to clinical failure endpoint was clarified
- Pre-specification of the stratified efficacy analyses to include only the age randomization strata
- Definition of baseline was added
- Additional subgroup analyses for race/ethnicity combined category and elevated CRP were added
- Appendices 1, 2, and 3 were updated to be consistent with the current protocol version 3

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
BIPAP	bilevel positive airway pressure
CoV	coronaviruses
CPAP	continuous positive airway pressure
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic Case Report Form
ECMO	extracorporeal membrane oxygenation
FiO_2	fraction of inspired oxygen
hs-CRP	high sensitivity C-reactive protein
ICU	intensive care unit
IL-6	interleukin 6
IMC	Internal Monitoring Committee
IxRS	interactive voice or web-based response system
LPLV	last patient, last visit
mITT	modified intent-to-treat
NCI	National Cancer Institute
PaO_2	partial pressure of oxygen
SARS-CoV	severe acute respiratory syndrome
SOC	standard of care
SpO_2	blood oxygen saturation
TB	tuberculosis
TCZ	tocilizumab
ULN	upper limit of normal
WHO	World Health Organization

1. BACKGROUND

This Statistical Analysis Plan (SAP) provides details of the planned analyses and statistical methods for the clinical efficacy and clinical safety for Study ML42528.

There are currently no drugs approved for the treatment of patients with SAS-CoV-2 (COVID-19). Given the results of studies (Xu et al. 2020), tocilizumab (TCZ), along with standard of care (SOC) treatment, could provide efficacy, offering the potential to treat COVID-19 in hospitalized populations more effectively than current SOC alone. Extensive safety data have previously been generated on the use of TCZ in other indications. Therefore, a placebo-controlled study in combination with SOC to assess safety and efficacy of TCZ in hospitalized patients with COVID-19 pneumonia is justified to address the high unmet need.

2. STUDY DESIGN

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

Patients must be at least 18 years of age with confirmed SARS-CoV-2 (COVID-19) infection per WHO criteria, including a positive PCR of any specimen (e.g., respiratory, blood, urine, stool, other bodily fluid). At the time of enrollment, patients must have SpO2<94% on ambient air and be on SOC, which may include anti-viral treatment, low dose systemic corticosteroids, and supportive care.

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

Eligible patients per study eligibility criteria will be randomly allocated in a 2:1 ratio to receive double-blind treatment with TCZ or placebo within 96 hours of hospital admission. Randomization will be stratified by country and age (≤60 and >60 years). The first dose of study drug will be administered within approximately 4 hours after randomization along with local SOC.

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

If the clinical signs or symptoms worsen or do not improve (reflected by sustained fever or at least a one-category worsening on the 7-category ordinal scale of clinical status),

one additional double-blind infusion of TCZ or placebo can be given, 8–24 hours after the initial infusion. Note: Pre-dose assessments must be repeated and reviewed before an additional infusion of blinded treatment of TCZ or placebo is administered.

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

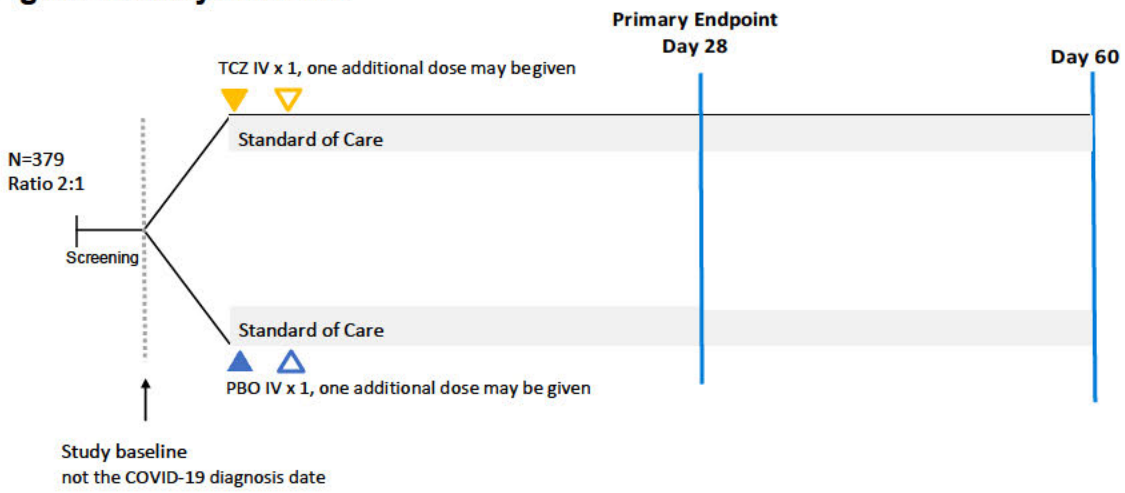
Safety and efficacy will be assessed according to the SOA (see Appendix 2 and Appendix 3).

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

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

Figure 1 presents an overview of the study design.

Figure 1 Study Schema



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

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1.

2.2 ENDPOINTS

2.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is:

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

2.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

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

2.2.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

- Change from baseline at Day 28/discharge/early dropout in inflammatory markers levels (hs-CRP/CRP, D-dimer, and ferritin)
- Time to first requiring CPAP or BIPAP

2.2.4 Safety Endpoints

The safety endpoints are as follows:

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

2.3 DETERMINATION OF SAMPLE SIZE

A total of approximately 379 patients will be randomized in this study. Patients will be randomly allocated in a 2:1 ratio to receive TCZ and or placebo, in addition to local SOC.

The sample size of 379 patients provides approximately 80% power using a logrank test to detect a 15% difference between treatment arms in the cumulative proportions of patients with death or mechanical ventilation by Day 28 under the following assumptions: cumulative survival (i.e., alive and not requiring mechanical ventilation) rates of 75% in the TCZ group and 60% in placebo group by Day 28, using a two-sided 5% alpha, and 10% dropout rate in each arm. Sample size re-estimation may be considered during the study based on updated assumptions of the treatment effect.

2.4 ANALYSIS TIMING

No interim efficacy analyses have been planned. Safety data will be reviewed by an Internal Monitoring Committee (IMC) during the study. The IMC will consist of Sponsor representatives who will not be blinded to study data. The planned safety interim review will occur when the first 30 patients have completed the Day 14 study visit. See Section 3.2 for further details.

The primary analysis of Day 28 outcomes will occur when the last patient either has withdrawn or completed the Day 28 visit. A snapshot of this data will be taken and the primary and key secondary efficacy analyses will be performed.

There will be one additional analyses on the final data when all patients have either reached Day 60 or withdrawn from study, all data from the study are in the database, and the database is locked.

3. STUDY CONDUCT

3.1 RANDOMIZATION

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

Patients will be randomly assigned to one of two treatment arms: TCZ in combination with SOC or placebo in combination with SOC. Randomization will occur in a 2:1 ratio through use of a permuted-block randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified by country (US, Peru, Brazil, Mexico, Kenya, South Africa) and age ($\leq$60 and $>$60 years).

3.2 DATA MONITORING

An IMC will evaluate safety according to procedures and guidelines detailed in the IMC agreement. The IMC will consist of Sponsor representatives who are not members of the study management team and will not be blinded to study data.

The first IMC safety review will occur after approximately 30 patients (20 in TCZ and 10 in PBO) have completed the Day 14 visit. There will be further IMC meetings when

approximately half of the targeted number of patients (i.e., n=189) have been enrolled; but all interim analyses are subject to change depending on enrollment and as appropriate.

The IMC will review unblinded summaries and listings of overall rates of death, serious adverse events (SAEs), and all adverse events (AEs) as well as other key safety data. All enrolled patients will be included in the interim safety summaries as there may be a lag time for obtaining treatment exposure data.

Deaths and serious infections will be reviewed in an expedited manner. The Study Medical director, Safety Scientist or IMC Chair may request additional meetings if concerns arise.

The unblinded safety summaries will be conducted by the IMC-Statistician and statistical programmer independent from the study management team. The list of the planned safety summary tables and listings are provided in the IMC agreement. Communications and recommendations from the IMC will be carried out as specified in the IMC agreement.

4. STATISTICAL METHODS

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

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

4.1 ANALYSIS POPULATIONS

Disposition summaries will be based on an All Patient population (all patients randomized regardless of whether study drug was received). Efficacy analyses will be based on the mITT population, if not otherwise specified. Analysis of safety data will be based on the safety population.

4.1.1 mITT Population

The mITT population is defined as all randomized patients in the study who received any amount of study medication, with patients grouped according to the treatment assignment at randomization.

4.1.2 Safety Population

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

4.2 DATA HANDLING CONVENTIONS

4.2.1 Definition of Study Day

Based on the protocol, study treatment must be given within approximately 4 hours after randomization. Therefore, the first treatment dose date will be used as Day 1 in all analyses. The day immediately following the first treatment dose date is study Day 2 and so on.

The detailed analysis windows for inflammatory markers, vital signs, and laboratory data will be defined in the specifications of the planned tables, listings, and graphs.

4.2.2 Definition of Baseline

Baseline value is defined as value from Day 1. The last value from screening will be used for baseline assessment if there is no baseline value. Pretreatment assessments will be used preferentially on study Day 1 for baseline.

4.3 ANALYSIS OF STUDY CONDUCT

The number of patients enrolled, discontinued, or who completed the study up to Day 28 will be summarized. Reasons for premature study discontinuation will be listed and summarized. Listing of randomized patients and listing of investigators will be produced. A summary of enrollment by country and investigator name will be produced.

The number of patients discharged from hospital will be summarized over time.

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

Randomized patients excluded from the safety and mITT populations will be summarized, including the reason for exclusion by treatment arm.

4.4 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (including, but not limited to, age, sex, self-reported race/ethnicity, smoking history) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented by treatment arm based on the mITT population; additional summary may be based on the safety population, as needed.

4.4.1 Demographics and Social Status

- Sex
- Age
- Weight
- BMI
- Race

- Ethnicity
- Race/Ethnicity Combined [Hispanic or Latino, American Indian or Alaska Native, Black or African American, WHITE, Other/unknown]
- Employment status
- Education status
- Primary language
- Living situation (Alone, With Others)
- Smoking history (Never, Current/Former)
- Country group (US, ex-US)

4.4.2 Disease Characteristics

- Ordinal scale for clinical status
- CRP and hs-CRP
  - Elevated CRP (CRP >50 mg/L or hs-CRP >3 mg/L)
- D-dimer
- Ferritin
- Symptoms at time of COVID 19 diagnosis
- Number of days from first COVID-19 symptom at baseline (to be derived from COVID 19 Diagnosis)
- COVID19 diagnosis based on PCR of specimen type
- Number of days from COVID-19 diagnosis at baseline (to be derived from COVID 19 Diagnosis)
- PCR result (Negative, positive)
- ICU admission status at baseline (yes, no)
- Steroid use (part of previous and concomitant medications), including prior (treatment started within 7 days of Day 1) and concurrent treatment (yes, no)
- Antiviral use (part of previous and concomitant medications), including prior (treatment started within 7 days of Day 1) and concurrent treatment (yes, no)

4.4.3 Targeted and General Medical History

Targeted medical history, including Diabetes, hypertension, hyperlipidemia, asthma, COPD, obesity, myocardial infarction, atrial fibrillation, and stroke, will be summarized by treatment arm.

General medical history data will be summarized descriptively by treatment arm. Summaries of the targeted and general medical history will be provided for the safety population. A glossary showing the mapping of investigator verbatim terms to coded disease terms will be produced for the general medical history data.

4.4.4 Surgeries and Procedures

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

4.4.5 Previous and Concomitant Medications

Previous and concomitant treatments will be summarized descriptively by treatment arm for the safety population. Previous treatments that have been stopped prior to study Day 1 will be summarized separately. There will be a summary of all concomitant treatments, including those that were initiated prior to study Day 1.

4.5 EFFICACY ANALYSIS

All efficacy analyses will be performed on the mITT population with patients grouped according to treatment assigned at randomization.

While two-sided unadjusted p-values will be reported, the overall study-level type 1 error will be controlled at a two-sided α=0.05 level according to the type 1 error control plan detailed in Section 4.5.2.

All efficacy analyses will be stratified by age ($\leq$60 and $>$60 years). Country group (US, Peru, Brazil, Mexico, Kenya, South Africa) will not be included as a stratification variable in the efficacy analyses to avoid the likelihood of getting unreliable estimates due to small sample size in a particular stratum (there are only 16 patients in the ex-US countries and age >60 years stratum, with possibly fewer than 10 patients in one of the treatment arms).

Consistent treatment effect in the country group and other prespecified subgroup will be evaluated through subgroup analysis specified in Section 4.5.5.

4.5.1 Primary Efficacy Endpoint

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

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

For this endpoint, mechanical ventilation is defined as mechanical invasive ventilation or ECMO (extracorporeal membrane oxygen). Any patient, who died prior to requiring invasive mechanical ventilation on or prior to Day 28, will be considered as having an event for this endpoint. Time to primary endpoint event is defined as time from Day 1 to the first occurrence of death or requiring mechanical ventilation by Day 28. The cumulative proportions of patients who experienced events by Day 28 will be estimated using the Kaplan-Meier methodology and compared between the TCZ group and the placebo group using the stratified log-rank test with age group as stratification factor.

The cumulative incidence function will be used to estimate and plot the cumulative primary efficacy event rates up to Day 28 for each treatment arm. The estimated cumulative primary efficacy event rates and their 95% confidence intervals (CIs) at Days 7, 14, 21 and 28 will be summarized by treatment arm. The median time to event will also be provided along with the corresponding 95% CIs by treatment arm.

The stratified Cox proportional hazard model, with age group as stratification factor, will be used to estimate the hazard ratio (HR) between the two treatment arms and its 95% CI.

The primary efficacy event and the censoring rules are described in Table 1 below. Death after Day 28 will not be considered as an event.

Table 1 Time to Death or Requiring Mechanical Ventilation and Censoring Status

Event	Censor	Date
Patient with death or requiring mechanical ventilation* recordings on or prior to Day 28	No	Earlier of date of death and/or first date requiring mechanical ventilation
Patient without death and not requiring mechanical ventilation recordings on or prior to Day 28;		
If patient with safety follow-up	Yes	Earlier of the date of Day 28 and the date of last available follow-up**
If patient without safety follow-up	Yes	Earlier of the date of Day 28 and the date of last available in-hospital assessment ***

* Mechanical ventilation is defined as mechanical invasive ventilation or ECMO per CRF; ** Follow-up includes (1) safety follow-up per CRF, (2) 7-ordinal scale assessment in hospital, (3) oxygen saturation assessment in hospital; *** In-hospital assessment includes (1) 7-ordinal scale assessment in hospital, (2) oxygen saturation assessment in hospital. For patients without any oxygen saturation or ordinal scale assessment in-hospital assessment, date is set to Day 1.

4.5.2 Controlling for Type I Error

The primary and key secondary efficacy endpoints will be evaluated in a hierarchical manner to control the overall study-wide Type 1 error rate at the 5% significance level. If the primary efficacy endpoint reaches statistical significance at the two-sided 5% significance level, the following list of key secondary efficacy endpoints will be tested at the two-sided 5% significance level in the predefined order below:

1. Time to hospital discharge or “ready for discharge” up to Day 28
2. Time to improvement in ordinal clinical status up to Day 28 relative to baseline based on a 7-category ordinal scale of clinical status

3. Time to clinical failure up to Day 28, defined as the time to death, mechanical ventilation, ICU admission, or withdrawal (whichever occurs first)
4. Mortality rate by Day 28

Testing of the first secondary endpoint will be gated on the success (significance $p<0.05$) of the primary efficacy endpoint, and testing of subsequent secondary endpoints will be gated on the success (significance $p<0.05$) of the previous secondary endpoint. Testing will stop once an endpoint fails to reach statistical significance ($p\geq0.05$).

Other secondary endpoint and exploratory efficacy endpoints will be tested at the nominal two-sided 5% significance level for exploratory purposes without any adjustment for multiplicity.

4.5.3 Secondary Efficacy Endpoints

Time to event secondary endpoints will be compared between the TCZ group and the placebo group using similar analytic methodologies as the primary efficacy endpoint. The Kaplan-Meier approach will be used to estimate and plot survival rates up to Day 28 for each treatment arm. The median time to event with its 95% CI will be summarized by treatment whenever they are estimable.

For the endpoints of time to hospital discharge or "ready for discharge" and time to improvement in clinical status, deaths will be right censored (at Day 28). Consequently, for these endpoints, patients censored on Day 28 could have two different states, death or failure to meet the criterion of improvement outcome. Therefore, it is important to understand the efficacy outcome in the context of the number and timing of deaths by treatment arm. In addition, in order to evaluate the effect of competing risk of death in these endpoints, the cumulative incidence function plots for both death and the event of interest will be produced using the non-parametric Aalen–Johansen estimator.

4.5.3.1 Key Secondary Efficacy Endpoints

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

This key secondary endpoint is defined as time from Day 1 to hospital discharge or "ready for discharge" up to Day 28 based on the 7-category ordinal scale.

Assessment of clinical status using an ordinal scale will be recorded at baseline and once daily while hospitalized.

The ordinal scale categories are as follows:

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

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

The efficacy event and the censoring rules for this endpoint are described in Table 2.

Table 2 Time to Hospital Discharge and Censoring Status

Event	Censor	Date
If patient with discharge or "ready for discharge" recordings on or prior to Day 28	No	Earliest discharge day
Else if before discharge or "ready for discharge", patient died on or prior to Day 28	Yes	Day 28
Else if patient without discharge or "ready for discharge" recordings on or prior to Day 28	Yes	Earlier of the date of Day 28 and the date of last ordinal scale assessment*

* For patients without any ordinal scale assessment in-hospital assessment, date is set to Day 1.

- Time to improvement in clinical status up to Day 28 relative to baseline based on a 7-category ordinal scale of clinical status

This secondary endpoint is defined as time from Day 1 to the time when at least a 2-category improvement in the 7-category ordinal scale is observed on or prior to Day 28. For patients in category 2 at baseline, having a clinical status of category 1 (discharge or "ready for discharge") on or prior to Day 28 will be considered as meeting the threshold.

The event and the censoring rules for this endpoint are described in Table 3 below.

Table 3 Time to Improvement in Ordinal Clinical Status and Censoring Status

Event	Censor	Date
Patient enrolled with scale≥3		
If patient with 2-category improvement in ordinal clinical status on or prior to Day 28 (regardless of whether the patient die after the improvement)	No	First improvement day
Else if patient died prior to improvement in ordinal clinical status	Yes	Day 28
Else if patient without 2-category improvement in ordinal clinical status on or prior to Day 28	Yes	Earlier of the date of Day 28 and the date of last ordinal scale assessment*
Patient enrolled with scale=2		
If patient with 1-category improvement in ordinal clinical status on or prior to Day 28 (regardless of whether the patient die after the improvement)	No	First improvement day
Else if patient died prior to improvement in ordinal clinical status	Yes	Day 28
Else if patient without 1-category improvement in ordinal clinical status on or prior to Day 28	Yes	Earlier of the date of Day 28 and the date of last ordinal scale assessment*

* For patients without any ordinal scale assessment in-hospital assessment, date is set to Day 1.

- Time to clinical failure up to Day 28

This secondary efficacy endpoint is defined as time from Day 1 to first occurrence of death, mechanical ventilation (defined same as in primary endpoint), ICU admission, or withdrawal from study due to any reason on or prior to Day 28. For patients entering the study already in the ICU, time to clinical failure is defined as the first occurrence of, death, mechanical ventilation (defined same as in primary endpoint), two-category worsening in the 7-category ordinal scale from baseline, or withdrawal from study due to any reason on or prior to Day 28.

The event and censoring rules for this endpoint are described in Table 4 below.

Table 4 Time to Clinical Failure and Censoring Status

Event	Censor	Date
No ICU admission prior to first study treatment		
Patient with death, ICU admission, requiring mechanical ventilation* recordings, or withdrawal from study before discharge on or prior to Day 28	No	Earliest of the death date, first ICU admission date, first date requiring mechanical ventilation, and study withdrawal date
Patient without death, ICU admission, requiring mechanical ventilation recordings, and withdrawal from study before discharge on or prior to Day 28		
with safety follow-up	Yes	Earlier of the date of Day 28 and the date of last available follow-up**
without safety follow-up	Yes	Earlier of the date of Day 28 and the date of last available in-hospital assessment ***
For patients whose ICU admission is prior to first study medication administration		
Patient with death, two-category worsening on the ordinal scale, requiring mechanical ventilation* recordings or withdrawal from study before discharge on or prior to Day 28	No	Earliest of the death date, first date with two-category worsening on the ordinal scale, requiring mechanical ventilation* recordings, and study withdrawal date
Patient without death, two-category worsening on the ordinal scale, requiring mechanical ventilation* recordings, and withdrawal from study before discharge on or prior to Day 28		
with safety follow-up	Yes	Earlier of the date of Day 28 and the date of last available follow-up**
without safety follow-up	Yes	Earlier of the date of Day 28 and the date of last available in-hospital assessment ***

* Mechanical ventilation is defined as mechanical invasive ventilation or ECMO per CRF; ** Follow-up includes (1) safety follow-up per CRF, (2) 7-ordinal scale assessment in hospital, (3) oxygen saturation assessment in hospital; *** In-hospital assessment includes (1) 7-ordinal scale assessment in hospital, (2) oxygen saturation assessment in hospital. For patients without any oxygen saturation or ordinal scale assessment in-hospital assessment, date is set to Day 1.

- Mortality rate at Day 28

The difference in proportion of patients who have died by Day 28 will be compared between the treatment arms using the Cochran-Mantel-Haenszel test adjusted for stratification factor age. The adjusted proportion in each treatment arm will be presented along with its 95% CI. Adjusted difference in proportions and its associated 95% CI for the treatment group comparison will also be presented. Any mortality that occurs between Day 1 and Day 28 will be included in the analysis.

4.5.3.2 Other Secondary Efficacy Endpoint

- 7-category ordinal scale at Day 28

The patients' clinical status as assessed by the 7-category ordinal scale at Day 28 will be analyzed by comparing the difference in distributions of the ordinal scale between the TCZ and placebo groups. Patients with missing ordinal scale status at Day 28 will have the value imputed by the last post-baseline available assessment. The Van Elteren test will be used, including the stratification factor age for this comparison. The count and proportion of patients with scores at each category of the scale at Day 28 will be summarized along with the p-value from the Van Elteren test.

In addition, the 7-category ordinal scale at Day 28 will be compared between the TCZ and placebo groups using a proportional odds model stratified by age group as a sensitivity analysis. The odds ratio, p-value, and 95% CI on the odds ratio will be presented.

4.5.4 Exploratory Efficacy Endpoints

- Time to first requiring CPAP or BIPAP

Defined as the time from Day 1 to the first documented date of death, requiring CPAP or BIPAP, or requiring mechanical ventilation (as defined in primary endpoint). Table 5 describes the event/censoring rules for the time to requiring CPAP or BIPAP. This endpoint will be analyzed using the same methodologies as the primary efficacy endpoint.

Table 5 Time to Requiring CPAP or BIPAP and Censoring Status

Event	Censor	Date
Patient with death or requiring CPAP or BIPAP, or requiring mechanical ventilation* on or prior to Day 28	No	Earlier of date of death, and/or first date requiring CPAP or BIPAP, and/or mechanical ventilation
Patient without death, requiring CPAP or BIPAP, and requiring mechanical ventilation recordings on or prior to Day 28		
Patient with safety follow-up	Yes	Earlier of the date of Day 28 and the date of last available follow-up**
Patient without safety follow-up	Yes	Earlier of the date of Day 28 and the date of last available in-hospital assessment ***

* Mechanical ventilation is defined as mechanical invasive ventilation or ECMO; ** Follow-up includes (1) safety follow-up, (2) 7-ordinal scale assessment in hospital, (3) oxygen saturation assessment in hospital; *** In-hospital assessment includes (1) 7-ordinal scale assessment in hospital, (2) oxygen saturation assessment in hospital. For patients without any oxygen saturation or ordinal scale assessment in-hospital assessment, date is set to Day 1.

- Change from baseline in inflammatory markers levels (hs-CRP/CRP, D-dimer, and ferritin) over time

CRP and hs-CRP will be summarized separately. Elevated CRP (yes) will be defined as CRP >50 mg/L or hs-CRP >3 mg/L.

The level of inflammatory markers will be summarized descriptively using means, standard deviations, medians, and ranges at baseline and post baseline, together with the change from baseline values. This summary will be provided for patients with observed data, missing data will not be imputed.

4.5.5 Subgroup Analyses

The primary endpoint (cumulative proportion of patients with death or requiring mechanical ventilation by Day 28) and the key secondary endpoint (time to hospital discharge or “ready for discharge”) will be assessed by the same methodologies as in the mITT population for the following subgroups:

- Sex [Male, Female]
- Age [⩽60, >60 years]
- Race/Ethnicity Combined [Hispanic or Latino, American Indian or Alaska Native, Black or African American, White, Other/unknown]
- Smoking history [Never, Current/Former]
- BMI [<30, >=30]

- Country group [US, ex-US]
- Steroid use, prior (within 7 days of Day 1) and concurrent [Yes, No]
- Anti-viral treatment use, prior (within 7 days of Day 1) and concurrent [Yes, No]
- Elevated CRP [Yes, No; see definition in Section 4.5.4]

Summaries of the endpoints listed above will be produced, separately, for each level of the subgroup variables and displayed on Forest plots. Small subgroups (e.g., with number of patients <30) may be combined to enable meaningful analysis as appropriate.

4.6 SAFETY ANALYSES

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

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

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

4.6.1 Exposure of Study Medication

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

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

4.6.2 Adverse Events

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

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

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

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

The following will also be summarized:

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

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

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

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

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

Listings and summary tables for post-treatment acute kidney injury (defined by 50% increase of creatinine from baseline) will be produced.

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

4.6.3 Laboratory Data

Summary tables will detail the actual values and changes from baseline of the laboratory parameters to post baseline by treatment arm. Arterial blood gases will be summarized separately.

Patients with values outside the reference normal ranges will be listed. A listing of all pregnancies will be presented.

Inflammatory markers hs-CRP, CRP, D-dimer, and ferritin will be analyzed by the methods in Section 4.5.4.

4.6.4 Oxygen Saturation and Vital Signs

Summary statistics on absolute values and their change from baseline for all observed vital signs (diastolic blood pressures, systolic blood pressures, respiratory rate, pulse rate, body temperature and peripheral oxygen saturation) will be presented over time by treatment group. Additionally, a graphical representation of means over time of oxygen saturation and temperature (daily to Day 28) will be presented by treatment group.

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

The level of consciousness will be summarized over time.

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

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

4.7 INTERIM ANALYSES

No interim efficacy analyses have been planned. Safety reviews by the IMC will be performed according to the IMC agreement (See Section 3.2).

5. REFERENCES

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006; 117:391–7.

Xu X, Han M, Li, T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Submitted manuscript. [Resource on the internet]. 2020 [updated 5 March 2020; cited 17 March 2020]. Available from: http://www.chinaxiv.org/abs/202003.00026.

Appendix 1 Protocol Synopsis

PROTOCOL SYNOPSIS

TITLE:	**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF TOCILIZUMAB IN HOSPITALIZED PATIENTS WITH COVID-19 PNEUMONIA**
PROTOCOL NUMBER:	ML42528
VERSION NUMBER:	3
EUDRACT NUMBER:	2020-001154-22
IND NUMBER:	148225
NCT NUMBER:	NCT04372186
TEST PRODUCT:	Tocilizumab (RO4877533)
PHASE:	Phase III
INDICATION:	COVID-19 pneumonia
SPONSOR:	Genentech, Inc.

Objectives and Endpoints

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

Efficacy Objectives

Primary Efficacy Objective

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

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

Secondary Efficacy Objective

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

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

Exploratory Efficacy Objective

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

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

Safety Objective

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

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

STUDY DESIGN

Description of the Study

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

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

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

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

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

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

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

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

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

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

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

Number of Patients

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

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

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

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

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

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

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

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

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

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

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

Exclusion Criteria

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

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

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

End of Study

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

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

Length of Study

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

Investigational Medicinal Products

Test Product (Investigational Drug)

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

Comparator

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

Statistical Methods

Primary Analysis

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

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

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

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

Determination of Sample Size

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

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

Planned Interim Analyses

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

Appendix 2 Schedule of Activities: Days 1 and 2

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

	Screening [a, b]	Baseline		
Study Day	−4 to 0	1		2
Time Post Initial Treatment (Assessment Window)		0 min Pre-dose (approx. −4 hrs)	15 min After end of infusion (approx. +1 hr)	24 hrs (±12 hrs)
Chemistry [d, n]	x			x
hs-CRP/CRP, D-dimer (if available via local laboratory), and ferritin [d]	x			
Study drug administration [o]		x		

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

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

[a] Results from standard-of-care tests or examinations performed prior to obtaining informed consent and within 96 hours before randomization may be used; such tests do not need to be repeated for screening.

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

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

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

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

[f] Screening chest X-ray or CT scans should be performed within 96 hours prior to randomization. If additional chest X-rays/CT scans are taken per local practice during the study, this information should be provided in the eCRF.

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

[h] If arterial blood gases are measured.

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

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

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

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

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

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

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

Appendix 3 Schedule of Activities: Day 3–Study Completion

	Days 3–28 [a]																									Study Completion/ Discontinuation [i]
Study Day	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28 [i]	
Vital signs [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PaO_2/FiO_2 [c]	← Optional →																										(optional)
SpO_2 [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ordinal scoring [d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [e]	←																									→	x
Concomitant medications [f]	←																									→	x
Hematology [g]																										x	x
Chemistry [h]																										x	x
hs-CRP/CRP, D-dimer (if available via local laboratory), and ferritin																										x	x

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

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

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

[c] If arterial blood gases are measured.

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

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

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

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

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

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