Outcomes Related to COVID-19 Treated with Hydroxychloroquine among In-patients with Symptomatic Disease (ORCHID)

STATISTICAL ANALYSIS PLAN (SAP)

Acronym: ORCHID

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1. INTRODUCTION

This document is the Statistical Analysis Plan for the ORCHID Trial and accompanies version 4 of the ORCHID protocol (dated June 4, 2020). The main text of this document describes the statistical approaches and methods used for the trial. Appendix A is a list of outcome variables along with their definitions and methods for analysis. Appendix B includes definitions for derived and composite variables and imputation methods. Appendix C contains a list of on-study measurements, their definitions, and methods for analysis.

2. BRIEF TRIAL SUMMARY

Title	Hydroxychloroquine for the Early Treatment of COVID-19 in Hospitalized Adults: A Multicenter Randomized Clinical Trial
Acronym	ORCHID **O**utcomes **R**elated to **C**OVID-19 treated with **H**ydroxychloroquine among **I**n-patients with symptomatic **D**isease
Background	Hydroxychloroquine is an antimicrobial agent with immunomodulatory and antiviral properties that has demonstrated *in vitro* activity against SARS-CoV-2, the virus that causes COVID-19. Preliminary reports suggest potential efficacy in small human studies. Clinical trial data are needed to determine whether hydroxychloroquine is effective in treating COVID-19.
Study Design	Blinded, multicenter, placebo-controlled randomized clinical trial
Intervention group	Hydroxychloroquine 400 mg twice daily for two doses, then 200 mg twice daily for the subsequent eight doses (10 total doses)
Control group	Matched placebo twice daily for 10 total doses
Sample Size	Up to 510 patients
Population	Hospitalized adults with acute respiratory illness from laboratory-confirmed SARS-CoV-2 infection.
Randomization	Eligible participants will be randomized 1:1 to hydroxychloroquine versus placebo. Randomization will be completed in permuted blocks of variable size and stratified by site.
Blinding	Patients, treating clinicians, trial personnel, and outcome assessors will be blinded to group assignment.
Primary Outcome	COVID Ordinal Outcomes Scale on Study Day 15: 1. Death 2. Hospitalized on invasive mechanical ventilation or ECMO 3. Hospitalized on non-invasive ventilation or high flow nasal cannula 4. Hospitalized on supplemental oxygen 5. Hospitalized not on supplemental oxygen 6. Not hospitalized with limitation in activity 7. Not hospitalized without limitation in activity
Analysis	The primary analysis will be an intention-to-treat comparison of the primary outcome between patients randomized to hydroxychloroquine versus placebo using a proportional odds model.

3. TRIAL DESCRIPTION

3.1 Background

Coronavirus Disease 2019 (COVID-19) is an acute respiratory infectious illness caused by *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2).[1,2] Based on mechanism of action and early clinical experiences, several agents currently available in the United States (US) have been proposed as potential therapies to prevent progression of COVID-19.[3–5] Among these potential therapies, hydroxychloroquine has generated substantial interest due to its antiviral and immunomodulatory activity and established safety profile. Many US hospitals have recommended hydroxychloroquine as first-line therapy for hospitalized patients with COVID-19. Thus, data on the safety and effectiveness of hydroxychloroquine for the treatment of COVID-19 are urgently needed to inform practice. The ORCHID trial was designed to evaluate the safety and efficacy of hydroxychloroquine for hospitalized adults with COVID-19.

3.2 Study Aims

3.2.1 Study aim

To compare the effect of hydroxychloroquine versus placebo on clinical status 14 days after randomization (Study Day 15) as assessed with a seven-category ordinal scale, among hospitalized adults with COVID-19.

3.2.2 Study hypothesis

Among adults hospitalized with COVID-19, administration of hydroxychloroquine will improve clinical status 14 days after randomization.

3.3 Study Design

ORCHID is an investigator-initiated, multicenter, blinded, placebo-controlled, randomized clinical trial evaluating hydroxychloroquine for the treatment of hospitalized adults with COVID-19.

4. STUDY POPULATION

4.1 Inclusion Criteria

1. Age ≥18 years
2. Currently hospitalized or in an emergency department with anticipated hospitalization.
3. Symptoms of acute respiratory infection, defined as one or more of the following:
    a. Cough
    b. fever (> 37.5° C / 99.5° F)
    c. shortness of breath (operationalized as any of the following: subjective shortness of breath reported by patient or surrogate; tachypnea with respiratory rate ≥22 /minute; hypoxemia, defined as SpO2 <92% on room air, new receipt of supplemental oxygen to maintain SpO2 ≥92%, or increased supplemental oxygen to maintain SpO2 ≥92% for a patient on chronic oxygen therapy).
    d. sore throat
4. Laboratory-confirmed SARS-CoV-2 infection within the past 10 days prior to randomization

4.2 Exclusion Criteria

1. Prisoner
2. Pregnancy
3. Breast feeding
4. Unable to randomize within 10 days after onset of acute respiratory infection symptoms
5. Unable to randomize within 48 hours after hospital arrival
6. Seizure disorder
7. Porphyria cutanea tarda
8. QTc >500 ms on electrocardiogram within 72 hours prior to enrollment
9. Diagnosis of Long QT syndrome
10. Known allergy to hydroxychloroquine, chloroquine, or amodiaquine
11. Receipt in the 12 hours prior to enrollment, or planned administration during the 5-day study period that treating clinicians feel cannot be substituted for another medication, of any of the following: amiodarone; cimetidine; dofetilide; phenobarbital; phenytoin; sotalol
12. Receipt of >1 dose of hydroxychloroquine or chloroquine in the 10 days prior to enrollment
13. Inability to receive enteral medications
14. Refusal or inability to be contacted on Day 15 for clinical outcome assessment if discharged prior to Day 15
15. Previous enrollment in this trial
16. The treating clinical team does not believe equipoise exists regarding the use of hydroxychloroquine for the treatment of this patient

4.3 Sample Size and Interim Analyses

The anticipated enrollment for the trial is 510 patients. We calculated the sample size under the assumption that we would have an interim analysis after approximately every 102 patients. The interim analyses employ a Bayesian framework evaluating the primary outcome (Day 15 COVID Ordinal Outcomes Scale, described below). An odds ratio >1.0 indicates more favorable clinical status in the hydroxychloroquine group than the placebo group. The stopping criteria proposed to (and approved by) the data and safety monitoring board include:

- If we determine there is >95% probability of the odds ratio being >1.0, the DSMB should consider stopping the trial for efficacy.
- If we determine there is >90% probability that the odds ratio is <1.1, the DSMB should consider stopping the trial for futility or harm.
- If we determine there is >70% probability that the odds ratio is <0.70, the DSMB should consider stopping the trial for significant harm.

We will use a prior odds ratio of 1.0 (equal chance of harm and benefit; mean log OR of 0.0) and a prior distribution of the standard error for its log set at 0.352 for tests of efficacy and a non-informative prior for tests of futility and harm.

4.4 Randomization and Blinding

Participants confirmed to meet all eligibility criteria who have provided informed consent are randomized 1:1 to hydroxychloroquine versus placebo. A randomization code is provided to the site investigator or

delegate from a centralized, web-based platform. Randomization is completed in permuted blocks of varying size and stratified by site. The participant, treating clinicians, study personnel, and outcome assessors all remain blinded to group assignment until after the database is locked.

5. STUDY INTERVENTIONS

5.1 Hydroxychloroquine Group

Participants assigned to the hydroxychloroquine group receive hydroxychloroquine sulfate 400 mg enterally twice daily for the first two doses and then 200 mg twice daily for the subsequent eight doses. This dosing regimen is a total of 10 doses over 5 days with an 800 mg load in the first 24 hours divided into two doses followed by 400 mg daily divided into two doses over the following 4 days.

5.2 Control Group

Participants randomized to the control group receive matching placebo enterally twice daily matching the dosing regimen described above for hydroxychloroquine.

6. OUTCOMES

6.1 Primary Outcome

COVID Ordinal Outcomes Scale on Study Day 15:

1. Death
2. Hospitalized on invasive mechanical ventilation or ECMO
3. Hospitalized on non-invasive ventilation or high flow nasal cannula
4. Hospitalized on supplemental oxygen
5. Hospitalized not on supplemental oxygen
6. Not hospitalized with limitation in activity
7. Not hospitalized without limitation in activity

6.2 Secondary Outcomes

- Time to recovery, defined as time to reaching level 5, 6, or 7 on the COVID Outcomes Scale, which is the time to the earlier of final liberation from supplemental oxygen or hospital discharge
- All-location, all-cause 14-day mortality (assessed on Study Day 15)
- All-location, all-cause 28-day mortality (assessed on Study Day 29)
- Survival through Day 28
- Hospital discharge through Day 28
- COVID Ordinal Outcomes Scale on Study Day 3
- COVID Ordinal Outcomes Scale on Study Day 8
- COVID Ordinal Outcomes Scale on Study Day 29
- Composite of death or receipt of ECMO through Day 28
- Oxygen-free days through Day 28
- Ventilator-free days through Day 28
- Vasopressor-free days through Day 28

- ICU-free days through Day 28
- Hospital-free days through Day 28

6.3 Safety Outcomes

- Seizure
- Atrial or ventricular arrhythmia
- Cardiac arrest
- Elevation in aspartate aminotransferase or alanine aminotransferase to twice the local upper limit of normal
- Acute pancreatitis
- Acute kidney injury
- Receipt of renal replacement therapy
- Symptomatic hypoglycemia
- Neutropenia, lymphopenia, anemia, or thrombocytopenia
- Severe dermatologic reaction

7. DATA ANALYSIS PLAN

7.1 Trial Population

The primary population for analysis will be all patients enrolled in the trial. The primary approach to analysis will be by intention to treat, in which patients assigned to the hydroxychloroquine group are analyzed in the hydroxychloroquine group and patients assigned to the placebo group are analyzed in the placebo group, regardless of treatments received. All analyses will be intention-to-treat analyses among all enrolled patients unless otherwise specified.

7.2 Primary Analysis of the Primary Outcome

The primary outcome is patient clinical status 14 days after randomization (on Study Day 15) as assessed with a seven-category ordinal scale (the COVID Ordinal Outcome Scale). The scale consists of the following categories: 1, death; 2, hospitalized, receiving ECMO, invasive mechanical ventilation, or both; 3, hospitalized, receiving noninvasive mechanical ventilation, nasal high-flow oxygen therapy, or both; 4, hospitalized, receiving supplemental oxygen; 5, hospitalized, not receiving supplemental oxygen; 6, not hospitalized, but unable to perform normal activities; 7, not hospitalized, able to perform normal activities.

The primary analysis will be a comparison of the primary outcome between patients randomized to the hydroxychloroquine group versus the placebo group. The comparison will be made using proportional odds regression. The dependent variable will be the primary outcome. Independent variables will include treatment group assignment and the following pre-specified 5 covariates:

- Age at randomization
- Sex
- Clinical status as assessed by the COVID Ordinal Outcome Scale at randomization
- Sequential Organ Failure Assessment (SOFA) score at randomization
- Duration of acute respiratory infection symptoms prior to randomization

The placebo group serves as the referent group for analyses. Because the primary outcome ranges from "death" as the lowest value of 1 to "not hospitalized and without limitations in activities" as the highest value of 7, an odds ratio >1.0 indicates more favorable outcomes with hydroxychloroquine while an odds ratio <1.0 indicates more favorable outcomes with placebo. Results of the primary analysis of the primary outcome will be presented as an adjusted common odds ratio and associated 95% confidence intervals.

7.3 Sensitivity Analyses of the Primary Outcome

We will conduct two sensitivity analyses:

1. **Exclusion of SARS-CoV-2 negative patients**. The primary analysis included all enrolled patients enrolled in the trial. Given delays in SARS-CoV-2 testing early in the pandemic, the trial eligibility criteria initially allowed enrollment of hospitalized patients with suspected or confirmed SARS-CoV-2 infection. As testing capabilities improved, the inclusion criteria were narrowed on April 21, 2020 (after 18 days of enrollment and inclusion of 2 patients without laboratory-confirmed COVID-19) to include only laboratory-confirmed cases. To determine whether the results of the primary analysis of the primary outcome were affected by enrollment of patients who subsequently tested negative for SARS-CoV-2, in this sensitivity analysis the primary analysis will be repeated in the subset of patients with a positive test for SARS-CoV-2 (i.e., excluding patients without laboratory-confirmed SARS-CoV-2).
2. **Modified intention-to-treat**. The primary analysis will be repeated among the subset of patients who received at least one dose of study drug (excluding patients who received no doses of study drug).

7.4 Effect Modification Analyses of the Primary Outcome

We will examine whether pre-specified baseline variables modified the effect of treatment group on the primary outcome using tests of statistical interaction in a proportional odds regression model. Independent variables will include study group assignment, the potential effect modifier of interest, the interaction between the two, and the same pre-specified covariates used in the primary model. Presence of effect modification will be assessed by reference to the P value for the interaction term, with values less than 0.10 considered to suggest a potential interaction and values less than 0.05 considered to confirm an interaction.

We will examine whether the following pre-specified baseline variables modify the effect of study group on the primary outcome:

1. Clinical status at randomization as assessed by the four categories of the seven-category ordinal outcome scale for which patients could qualify at randomization:
    a. Receiving ECMO, invasive mechanical ventilation, or both
    b. Receiving noninvasive mechanical ventilation, nasal high-flow oxygen therapy, or both

    c. Receiving supplemental oxygen
    d. Not receiving supplemental oxygen
2. Located in an intensive care unit at randomization (Yes, No)
3. Sequential Organ Failure Assessment (SOFA) score at randomization
4. Duration of symptoms of acute respiratory infection prior to randomization
5. Age
6. Sex
7. Race and ethnicity

7.5 Analysis of Secondary and Safety Outcomes

Ordinal secondary will be analyzed using a proportional odds model with randomized group assignment as an independent variable and the covariables used in the primary model. Binary secondary outcomes will be analyzed using multivariable logistic regression models with the same pre-specified covariates. Survival and hospital discharge through day 28 will be analyzed using multivariable proportional hazards regression with the same covariates in the primary outcome model. For the hospital discharge model, death will be treated as a competing risk, and the sub-distribution hazard ratio will be reported.[6] Safety outcomes will be analyzed with simple logistic regression without co-variable adjustment.

Detailed data on receipt of invasive mechanical ventilation, vasopressors, intensive care unit admission, and hospitalization were collected during the index hospitalization, but not after discharge from the index hospitalization. Therefore, the main analysis of the associated "-free day" outcomes will use information regarding receipt of the supportive therapy between randomization and hospital discharge or Study Day 29, whichever occurs first ("in-hospital outcome"). Information on death between discharge from the index hospitalization and Study Day 29 is systematically available via follow-up phone calls. Hence, we will use all-cause, all-location death in the calculation of "-free day" outcomes.

7.6 Presentation of Adverse Events

The frequency and description of adverse events will be reported for all enrolled patients and by randomized group (hydroxychloroquine vs placebo).

7.7 Analysis of On-study Variables

Variables that are measured systematically at intermittent time points during the study will be presented at each time they are measured, stratified by randomized group. These analyses will include:

- QTc measurement on Study Day 2 (24-48-hour time window)
- COVID Ordinal Outcomes Scale on Study Days 2, 3, 4, and 5
- SOFA score on Day 3
- S/F ratio / Respiratory SOFA score on Day 3

7.8 Handling of Missing Data.

Primary Outcome. Primary outcome data will be complete for all patients hospitalized through Day 15 because all data needed to classify the primary outcome are available in the medical record. For patients discharge prior to Day 15, data for the primary outcome are collected via a telephone follow-up call. If primary outcome data are missing for patients who left the acute care PETAL hospital prior to Day 15, the following procedures will be used:

- Patients who left the hospital prior to Day 15 and did not have a COVID Ordinal Outcomes Scale collected via phone follow-up at Day 8 (either because they remained in the hospital from the index hospitalization on Day 8 or, if discharge prior to Day 8, were not reached by phone on Day 8), the primary outcome will be coded as a level 6 (not hospitalized with limitation in activity) on COVID Ordinal Outcomes Scale.
- Patients who completed a COVID Ordinal Outcomes Scale by phone follow-up on Day 8 will have the level from the Day 8 assessment carried forward to the Day 15 primary outcome assessment.

Covariates. We expect missing data for the pre-specified covariates in the proportional odds and logistic regression models to be rare. If missing data do exist for these covariates, values will be imputed using simple imputation of the median value from the trial population with non-missing data.

Secondary Outcomes. Data will not be imputed for secondary outcomes. The frequency of missing data will be reported.

13. REFERENCES

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Appendix A. Outcome variables by ORCHID Use, Type, and Analysis Method.

Variable	ORCHID Use	Type	Analysis Method
Clinical status 14 days after randomization as assessed with a seven-category ordinal scale (COVID Ordinal Outcomes Scale on Study Day 15)	Primary Outcome	Ordinal	Proportional odds model accounting for pre-specified baseline covariates
Time to recovery	Secondary Outcome	Continuous	Proportional odds model accounting for pre-specified baseline covariates
All-location, all-cause 14-day mortality (Study Day 15)	Secondary Outcome	Binary	Logistic regression model accounting for pre-specified baseline covariates
All-location, all-cause 28-day mortality (Study Day 29)	Secondary Outcome	Binary	Logistic regression model accounting for pre-specified baseline covariates
Survival through 28 days (Study Day 29)	Secondary Outcome	Time to event	Proportional hazards regression model accounting for pre-specified baseline covariates
Hospital discharge through 28 days (Study Day 29)	Secondary Outcome	Time to event	Proportional hazards regression model accounting for pre-specified baseline covariates; death treated as a competing risk
COVID Ordinal Outcomes Scale on Study Day 3	Secondary Outcome	Ordinal	Proportional odds model accounting for pre-specified baseline covariates

COVID Ordinal Outcomes Scale on Study Day 8	Secondary Outcome	Ordinal	Proportional odds model accounting for pre-specified baseline covariates
COVID Ordinal Outcomes Scale on Study Day 29	Secondary Outcome	Ordinal	Proportional odds model accounting for pre-specified baseline covariates
Composite of death or receipt of ECMO through Day 28	Secondary Outcome	Binary	Logistic regression model accounting for pre-specified baseline covariates
Oxygen-free days through Day 28	Secondary Outcome	Ordinal	Proportional odds model accounting for pre-specified baseline covariates
Ventilator-free days through Day 28	Secondary Outcome	Ordinal	Proportional odds model accounting for pre-specified baseline covariates
Vasopressor-free days through Day 28	Secondary Outcome	Ordinal	Proportional odds model accounting for pre-specified baseline covariates
ICU-free days through Day 28	Secondary Outcome	Ordinal	Proportional odds model accounting for pre-specified baseline covariates
Hospital-free days through Day 28	Secondary Outcome	Ordinal	Proportional odds model accounting for pre-specified baseline covariates
Seizure	Safety Outcome	Binary	Simple logistic regression
Atrial arrhythmia	Safety Outcome	Binary	Simple logistic regression

Ventricular arrhythmia	Safety Outcome	Binary	Simple logistic regression
Cardiac arrest	Safety Outcome	Binary	Simple logistic regression
Elevation in aspartate aminotransferase or alanine aminotransferase above 2x upper limit of normal	Safety Outcome	Binary	Simple logistic regression
Acute pancreatitis	Safety Outcome	Binary	Simple logistic regression
Acute kidney injury	Safety Outcome	Binary	Simple logistic regression
Receipt of renal replacement therapy	Safety Outcome	Binary	Simple logistic regression
Symptomatic hypoglycemia	Safety Outcome	Binary	Simple logistic regression
Neutropenia	Safety Outcome	Binary	Simple logistic regression
Lymphopenia	Safety Outcome	Binary	Simple logistic regression
Anemia	Safety Outcome	Binary	Simple logistic regression
Thrombocytopenia	Safety Outcome	Binary	Simple logistic regression
Severe dermatologic reaction	Safety Outcome	Binary	Simple logistic regression

Appendix B: Outcome Definitions and Description of Derived Outcome Variables

Terminology for Outcome Intervals, Timing of Assessment, and Location of Assessment

The date and time of randomization represents "time zero" for all study assessments. The calendar day on which randomization occurred is referred to as "Study Day 1." While patients are hospitalized during the index hospitalization, data are collected by in-person assessments and review of the medical record. Data are collected after hospital discharge via telephone calls at Day 8, Day 15, and Day 29. Long-term outcomes will be assessed in an ancillary study called ORCHID-Brain Outcomes and Psychological Disability (ORCHID-BUD). ORCHID BUD results will be reported separately and are not considered in this document.

The primary outcome, some secondary outcomes, and all safety outcomes were assessed until 28 days after randomization (Study Day 29) regardless of the patient's location – referred to as "all-location outcomes." Select secondary outcomes related to organ support (e.g., ventilator-free days) were only assessed until the patient's discharge from the index hospitalization or 28 days after randomization (Study Day 29), whichever occurred first – referred to as "in-hospital outcomes." All data collection ended on Study Day 29.

Definition of the Primary Outcome and SOFA score calculation

Primary Outcome

The primary outcome was patients' clinical status 14 days after randomization (measured on Study Day 15) as assessed with the seven-category COVID Ordinal Outcome Scale:

1. Death
2. Hospitalized on invasive mechanical ventilation or extracorporeal membrane oxygenation
3. Hospitalized on non-invasive ventilation or high-flow nasal cannula
4. Hospitalized on supplemental oxygen
5. Hospitalized not on supplemental oxygen
6. Not hospitalized with limitation in activity
7. Not hospitalized without limitation in activity

If patients remained in the hospital, outcome assessment was performed by review of the electronic health records. For patients who were discharged prior to 14 days after randomization, study staff called patients or their surrogates to obtain patients' clinical status ("all-location outcome"). To distinguish between category 6 (not hospitalized, but unable to perform normal activities) and category 7 (not hospitalized, able to perform normal activities), study personnel assessed the patient's performance of "usual activities" with questions consistent with validated health status measures. An answer of "no problems doing my usual activities" resulted in assignment to category 7.

SOFA Score Calculation

The SOFA score at baseline (pre-randomization) was used as a co-variable in the regression models for the primary and secondary outcomes. The SOFA score was calculated using the definitions based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).[7] The SOFA score was calculated using data available in the 24 hours prior to randomization. We recorded the following data for SOFA score calculation: lowest PaO_2 and FIO_2 at the time of the lowest PaO_2 measurement; lowest SpO_2 and FIO_2 at the time of the lowest SpO_2 measurement; lowest platelet count; highest total bilirubin concentration; lowest Glasgow Coma Score; lowest mean arterial pressure; receipt and dose of inotropes/vasopressors, including dobutamine, dopamine, epinephrine, norepinephrine, phenylephrine, and vasopressin; highest creatinine; urine output; highest INR.

For calculation of the respiratory component of the SOFA score, if recorded, FiO_2 was used in the calculation of P:F or S:F ratio. If no FIO_2 was recorded, FiO_2 was estimated with the following equation: 0.21 + (supplemental oxygen flow rate in liters/minute) * 0.03. If PaO_2 was recorded, the recorded PaO_2 value was used in the calculation of P:F ratio and respiratory SOFA score. If no PaO_2 value was recorded, respiratory SOFA score was classified by SpO_2 and SpO_2:FiO_2 ratio according to the table below based on the validated technique described by Pandharipande[8]:

Respiratory SOFA Score assignment based on SpO_2 and FIO_2 values when no PaO2 is recorded	
Values	**Respiratory SOFA Score Assignment**
SpO_2 ≥95% and FiO_2=0.21 (room air)	0
If SpO_2 <95% or FiO_2 >0.21, calculate the SpO_2:FiO_2 ratio and assign respiratory SOFA score based on the thresholds below:	
SpO_2: FiO_2 ≥357	1
SpO_2: FiO_2 ≥214 and <357	2
SpO_2: FiO_2 ≥89 and <214	3
SpO_2: FiO_2 <89	4

When no P:F or S:F ratio is available, the respiratory SOFA score was imputed as the median observed value in the patients in the trial with non-missing values, consistent with the approach to missingness for other variables.

Definition of Secondary Outcomes

Time to Recovery

Recovery was defined as reaching category 5, 6, or 7 on the seven-category COVID Ordinal Outcome Scale. A patient could reach category 5, 6, or 7 on the seven-category COVID Ordinal Outcome Scale either by (a) being discharged from the hospital or by (b) being liberated from supplemental oxygen for the final time during the index hospitalization. Time to recovery was defined as the time between randomization and the first of either hospital discharge or liberation from supplemental

oxygen for the final time during the index hospitalization. Time to recovery was an "in-hospital outcome" and did not reflect information on receipt of supplemental oxygen, rehospitalization, or death after discharge from the index hospitalization.

For a patient who was not receiving supplemental oxygen at the time of randomization, and never received supplemental oxygen during the index hospitalization, the time to recovery was 0.0 days. For a patient who received supplemental oxygen at any time between randomization and discharge from the index hospitalization, but was not receiving supplemental oxygen at the time of discharge from the index hospitalization, the time to recovery was the time from randomization to the time of final receipt of supplemental oxygen during the index hospitalization. For a patient who was receiving supplemental oxygen at the time of discharge from the index hospitalization, the time to recovery was the time from randomization to the time of discharge from the index hospitalization. Patients who remained hospitalized and receiving supplemental oxygen 28 days after randomization were not considered to have experienced recovery. All patients who died prior to discharge from the index hospitalization were not considered to have experienced recovery. Patients who did not experience recovery were awarded a value for the outcome of time to recovery of 28.0 days.

All-location, all-cause 14-day mortality

Death between randomization and 14 days after randomization from any cause and in any location, including after discharge from the index hospitalization. Data on death were collected from the electronic health record during the hospitalization and then from telephone calls to the patient or surrogate after discharge on Study Day 8, 15 and 29.

All-location, all-cause 28-day mortality

Death between randomization and 28 days after randomization from any cause and in any location, including after discharge from the index hospitalization. Data on death were collected from the electronic health record during the hospitalization and then from telephone calls to the patient or surrogate after discharge on Study Day 8, 15 and 29.

Survival through 28 days

Dead versus survived will be recorded between randomization and 28 days following randomization using in-hospital data and follow-up calls post-discharge on Study Day 8, 15, and 29. Using these data, survival curves through 28 days following randomization will be constructed.

Hospital discharge through 28 days

Time of hospital discharge from the index hospitalization for COVID-19 will be recorded. Using these data, time to hospital discharge curves through 28 days following randomization will be constructed. Death will be treated as a competing risk.

COVID Ordinal Outcomes Scale on Study Day 3

Clinical status 2 days after randomization (measured on Study Day 3) as assessed with the seven-category COVID Ordinal Outcome Scale, as described in the section on the *Primary Outcome*. Data on clinical status were collected from the electronic health record during the hospitalization. Patients discharge prior to Study Day 3 will have the Day 3 COVID Ordinal Outcome Scale coded as level 6 (not hospitalized with limitation in activity).

COVID Ordinal Outcomes Scale on Study Day 8

Clinical status 7 days after randomization (measured on Study Day 8) as assessed with the seven-category COVID Ordinal Outcome Scale, as described in the section on the *Primary Outcome*. Data on clinical status were collected from the electronic health record during the hospitalization and then from telephone calls to the patient or surrogate after discharge from the index hospitalization ("all-location outcome").

COVID Ordinal Outcomes Scale on Study Day 29

Clinical status 28 days after randomization (measured on Study Day 29) as assessed with the seven-category COVID Ordinal Outcome Scale, as described in the section on the *Primary Outcome*. Data on clinical status were collected from the electronic health record during the hospitalization and then from telephone calls to the patient or surrogate after discharge from the index hospitalization ("all-location outcome"). Missing data for the COVID Ordinal Outcomes Scale on Day 29 will be handled in the same fashion as describe for the primary outcome.

Composite of death or receipt of ECMO through Day 28

Death or receipt of extra-corporeal membrane oxygenation (ECMO) between randomization and discharge from the index hospitalization or 28 days after randomization, whichever occurs first ("in-hospital outcome"). Patients who were receiving ECMO at the time of randomization could qualify for this outcome by experiencing death, but not by continuing to receive ECMO.

Days Free of Support

For all outcomes related to days alive and free from a supportive therapy, "-free days" were calculated as the number of whole calendar days from 00:00 on the day of randomization (Study Day 1) to 23:59 on Study Day 28. The day of randomization contributed to the count of "-free days". Days between randomization and the first receipt of the supportive therapy and days following the last day of the support therapy both counted toward the total number of "-free days". Days alive and free of the supportive therapy that occurred between periods receiving support did not count toward "-free days".

Information on organ support therapies (oxygen, ventilation, vasopressors, ICU care) were collected during the index hospitalization ("in-hospital data") while death was collected both in-hospital and out-of-hospital to Study Day 29 ("all-location data"). Thus, patients who died at any time before Study Day 29 were coded as having zero-free days.

Oxygen-free days through Day 28

For calculation of oxygen-free days, supplemental oxygen was defined as oxygen administered by nasal cannula, face mask, high-flow nasal cannula, non-invasive ventilation, or invasive ventilation. Positive airway pressure (CPAP, BiPAP) provided solely at night as treatment for sleep-disordered breathing (e.g. obstructive sleep apnea) was not considered supplemental oxygen. Oxygen-free days were calculated as the number of whole calendar days alive and not receiving supplemental oxygen between randomization and study day 29. Patients who died before Day 29 received a value of 0. If a patient survived through study day 29 and never received supplemental oxygen, the number of oxygen-free days was 28. If a patient received supplemental oxygen and survived through study day 28, the number of oxygen free-days was calculated as 28 minus the number of calendar days from the first day on which the patient received supplemental oxygen until the last day on which the patient received supplemental oxygen. Days on which the patient did not receive supplemental oxygen that occurred between days on which the patient received supplemental oxygen did not count towards the number of oxygen free days. Data on oxygen use were censored at hospital discharge and the last observed status was carried forward ("in-hospital outcome"). That is, if the patient was receiving supplement oxygen at hospital discharge, the analysis assumed they continued to receive supplemental oxygen through Study Day 29. If the patient was not receiving supplemental oxygen at hospital discharge, the analysis assumed the patient continued not to receive supplemental oxygen through Study Day 29.

Ventilator-free days to Day 28

Ventilator-free days to day 28 was defined as the number of whole calendar days alive and breathing without invasive mechanical ventilation from 00:00 on the day of randomization through Study Day 29. Patients who died before Study Day 29 received a value of 0. If a patient survived to the first of discharge or Study Day 29 and never received invasive mechanical ventilation, the number of VFDs was 28. If a patient received invasive mechanical ventilation and survived to the first of hospital discharge or Study Day 28, the number of VFDs was calculated as 28 minus the number of calendar days from the first day on which the patient received invasive mechanical ventilation until the last day on which the patient received invasive mechanical ventilation. Days on which the patient did not receive invasive mechanical ventilation that occurred between days on which the patient received mechanical ventilation did not count towards the number of VFDs. Data on ventilation were censored at hospital discharge and the last observed status was carried forward ("in-hospital outcome"). That is, if the patient was receiving invasive mechanical ventilation at hospital discharge, the analysis assumed they continued to receive invasive mechanical ventilation through Study Day 29. If the patient was not receiving invasive mechanical ventilation at hospital discharge, the analysis assumed the patient continued not to receive invasive mechanical ventilation through Study Day 29.

Vasopressor-free days to Day 28

For vasopressor-free days, a day on which a patient received of any of the following medications via intravenous drip or push at any dose was be considered a day receiving vasopressors: norepinephrine, epinephrine, vasopressin, phenylephrine, angiotensin II, dobutamine, dopamine, or milrinone. Vasopressor-free days to Day 28 was calculated as the number of whole calendar days alive and not receiving intravenous vasopressors or inotropes from 00:00 on the day of randomization through study day 29. Patients who died before Study Day 29 receive a value of 0. If a patient survived to Study Day 29 and never received intravenous vasopressors or inotropes, the number of vasopressor-free days was 28. If a patient received intravenous vasopressors or inotropes and survived to the first of discharge or Study Day 29, the number of vasopressor-free days was calculated as 28 minus the number of calendar days from the first day on which the patient received vasopressors or inotropes until the last day on which the patient received vasopressors or inotropes. Days on which the patient did not receive vasopressors or inotropes that occurred between days on which the patient received vasopressors or inotropes did not count towards the number of vasopressor-free days. Data on vasopressor use was censored at hospital discharge and the last observed status was carried forward ("in-hospital outcome"). That is, if the patient was known to be receiving vasopressors or inotropes at hospital discharge, the analysis assumed they continued to receive vasopressors or inotropes through Study Day 29. If the patient was not receiving vasopressors or inotropes at hospital discharge, the analysis assumed the patient continued not to receive vasopressors or inotropes through Study Day 29.

ICU-free days to Day 28

Intensive care unit-free days (ICU-free days) to day 28 was defined as the number of whole calendar days alive and not admitted to an intensive care unit from 00:00 on the day of randomization through Study Day 29. Patients who died before Study Day 29 received a value of 0. If a patient survived to the first of discharge or Study Day 29 and was never admitted to an ICU, the number of ICU-free days was 28. If a patient was admitted to an ICU and survived to the first of discharge or Study Day 28, the number of ICU-free days was calculated as 28 minus the number of calendar days from the first ICU admission to final ICU discharge. Days on which the patient was not admitted to an ICU that occurred between days on which the patient was admitted to an ICU did not count towards the number of ICU-free days. Data on ICU use was censored at hospital discharge and the last observed status was carried forward ("in-hospital outcome"). That is, the analysis assumed that a patient who was discharge from the index hospitalization was not readmitted to an ICU between hospital discharge and Study Day 29.

Hospital-free days to Day 28

Hospital-free days to Day 28 was defined as the number of whole calendar days on which the patient was alive and not in the hospital from 00:00 on the day of randomization through Study Day 29. Patients who died before Study Day 29 received a value of 0. If a patient remained in the hospital during the index hospitalization through Study Day 29, the number of hospital-free days was 0. For patients

discharged from the index hospitalization prior to Study Day 28, the number of hospital-free days was calculated as 28 minus the duration of the index hospitalization in calendar days. Information readmissions occurring after discharge from the index hospitalization did not contribute to the calculation of the hospital-free days outcome.

Definition of Safety Outcomes ("all-location outcomes")

1. Seizure – Between randomization and Study Day 29, as documented by treating clinicians in the electronic health record or reported by patient or surrogate on follow up telephone call.
2. Atrial arrhythmia - Between randomization and Study Day 29, as documented in the electronic health record or reported by patient or surrogate on follow up telephone call.
3. Ventricular arrhythmia - ventricular tachyarrhythmia (ventricular fibrillation or ventricular tachycardia) treated with a medication or electrical cardioversion or debrillation between randomization and Study Day 29, as documented in the electronic health record or reported by patient or surrogate on follow up telephone call.
4. Cardiac arrest - Between randomization and Study Day 29, as documented in the electronic health record or reported by patient or surrogate on follow up telephone call. Does not include expected cardiac arrests occurring as a part of the dying process for patients on comfort measures.
5. Elevation in aspartate or alanine aminotransferase to twice the upper limit of normal – Between randomization and Study Day 29, as documented in the electronic health record or reported by patient or surrogate on follow up telephone call.
6. Acute Pancreatitis – Clinically-obtained lipase level above the local upper limit of normal between randomization and day 29.
7. Acute Kidney Injury – Stage II or greater acute kidney injury by Kidney Disease Improving Global Outcomes (KDIGO) Criteria between randomization and day 29, defined as any of the following:
    a. Creatinine at least 2.0 times the baseline value
    b. Increase in serum creatinine above 4.0 mg/dl
    c. Urine output less than 0.5 ml/kg/h for at least 12 hours
    d. Initiation of new renal replacement therapy
8. Receipt of renal replacement therapy – Between randomization and Study Day 29, as documented by treating clinicians in the electronic health record or reported by patient or surrogate on follow up telephone call.
9. Symptomatic hypoglycemia – Between randomization and Study Day 29, as documented by treating clinicians in the electronic health record or reported by patient or surrogate on follow up telephone call.
10. Neutropenia – Clinically-obtained absolute neutrophil count < 1000 (cells/mm3) between randomization and Study Day 29
11. Lymphopenia – Clinically obtained absolute lymphocyte count < 1000 (cells/mm3) between randomization and Study Day 29.
12. Anemia – Clinically-obtained hemoglobin < 12.0 g/dL between randomization and Study Day 29.

13. Thrombocytopenia – Clinically-obtained platelet count < 50 (cell/mm3; in thousands) between randomization and Study Day 29.
14. Severe dermatologic reaction – Between randomization and Study Day 29, as documented by treating clinicians in the electronic health record or reported by patient or surrogate on follow up telephone call.

Appendix C: On-study Measurements.

Variable	Category	Variable Type
Proportion of study drug doses received among eligible doses (doses received / doses could have received due to being alive when dose scheduled)	Trial Drug	Proportion
Received ≥ 1 doses of trial drug	Trial Drug	Binary
Doses of trial drug received	Trial Drug	Continuous
Doses of trial drug not received	Trial Drug	Continuous
Reasons dose of trial drug missed	Trial Drug	Categorical
Open-label hydroxychloroquine	Co-interventions	Binary
Chloroquine	Co-interventions	Binary
Remdesivir	Co-interventions	Binary
Lopinavir/ritonavir	Co-interventions	Binary
Other antiviral	Co-interventions	Binary
Corticosteroids	Co-interventions	Binary
Tocilizumab	Co-interventions	Binary
Sarilumab	Co-interventions	Binary
Interferon beta	Co-interventions	Binary
Other immunomodulator	Co-interventions	Binary
Azithromycin	Co-interventions	Binary
Other antibacterial	Co-interventions	Binary
Convalescent plasma	Co-interventions	Binary
High-flow nasal cannula	Co-interventions	Binary
Non-invasive ventilation	Co-interventions	Binary
Invasive mechanical ventilation	Co-interventions	Binary
Extra-corporeal membrane oxygenation	Co-interventions	Binary

Lowest white blood cell count	On-study Lab Values	Continuous
Highest white blood cell count	On-study Lab Values	Continuous
Lowest hemoglobin	On-study Lab Values	Continuous
Lowest platelet count	On-study Lab Values	Continuous
Highest sodium	On-study Lab Values	Continuous
Lowest sodium	On-study Lab Values	Continuous
Highest potassium	On-study Lab Values	Continuous
Lowest potassium	On-study Lab Values	Continuous
Highest chloride	On-study Lab Values	Continuous
Lowest chloride	On-study Lab Values	Continuous
Highest bicarbonate	On-study Lab Values	Continuous
Lowest bicarbonate	On-study Lab Values	Continuous
Highest blood urea nitrogen	On-study Lab Values	Continuous
Highest creatinine	On-study Lab Values	Continuous
Highest troponin	On-study Lab Values	Continuous
Highest AST	On-study Lab Values	Continuous
Highest ALT	On-study Lab Values	Continuous
Lowest albumin	On-study Lab Values	Continuous
Highest PTT	On-study Lab Values	Continuous
SOFA score on Study Day 3	On-study SOFA	Continuous
Readmitted between discharge from index hospitalization and 28 days	Additional Clinical Outcomes	Binary
Emergency department visit between discharge from index hospitalization and 28 days	Additional Clinical Outcomes	Binary