Statistical Analysis Plan

A Phase 2 Randomized, Double-blind, Placebo-controlled, Proof of Concept Study to Evaluate the Safety and Efficacy of Antroquinonol in Hospitalized Patients with Mild to Moderate Pneumonia due to COVID-19

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Glossary of Abbreviations

Abbreviation	Term
AE	Adverse Event
ANOVA	Analysis of variance
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-last}}$	area under the plasma concentration versus time curve from time zero to the time of last quantifiable concentration
AUC_{tau}	area under the plasma concentration versus time curve within a dosing interval
BMI	Body Mass Index
BID	twice daily
BLQ	below the level of quantification
BOR	Best Overall Response
CI	Confidence Interval
CT	computerized tomography
CV	Coefficient of Variance
C_{max}	maximum plasma concentration
COVID-19	Coronavirus Disease 2019
C_{trough}	trough (predose) plasma concentration
DCR	Disease Control Rate
DOR	Duration of Response
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECMO	extracorporeal membrane oxygenation
EOS	End of Study
ET	Early Termination
eCRF	Electronic Case report form
ICF	Informed Consent Form
ICU	intensive care unit
ITT	intention-to-treat
LDL-C	Low Density Lipoprotein-Cholesterol
LLOQ	the lower limit of quantification
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
NC	not calculated
mITT	modified intention-to-treat
PK	Pharmacokinetics
PKS	Pharmacokinetic Set
PPS	Per Protocol Set
PT	Preferred Term
QTcB	Bazett corrected QT interval
QTcF	Fridericia corrected QT interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SoC	Standard of Care
SS	Safety Set
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures and Listings

t_{max}	Time to C_{max}
WHO	World Health Organization

1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	07 July 2021	4.0
eCRF	06 September 2021	3.06

2. Protocol Details

2.1 Study Objectives

The primary objectives of this study is:

- To evaluate the efficacy of antroquinonol treatment of mild to moderate pneumonia due to COVID-19, as measured by the proportion of patients alive and free of respiratory failure (i.e., no need for invasive mechanical ventilation, non-invasive ventilation, high-flow oxygen, or extracorporeal membrane oxygenation [ECMO]) on Day 14

Secondary objectives of this study are:

- To further evaluate the efficacy of antroquinonol compared with placebo in this patient population as measured by:
    - World Health Organization (WHO) COVID-19 Clinical Improvement Ordinal Scale score on Days 7, 14, and 28
    - Duration of hospitalization up to Day 28
    - Virological clearance on Days 5, 14, and 28
    - Vital status (death) on Days 7, 14, and 28
    - Duration of intensive care unit (ICU) stay up to Day 28
    - Proportion of patients alive and free of respiratory failure on Days 7 and 28
    - COVID-19 symptoms on Days 7, 14, and Day 28
- To evaluate the safety of antroquinonol treatment in patients with mild to moderate pneumonia due to COVID-19.
- To assess the pharmacokinetics (PK) of antroquinonol in a subset of 20 patients (first 10 patients randomized to antroquinonol and first 10 patients to placebo)

Exploratory objective of this study is:

- To further evaluate efficacy via supportive analyses of:
    - Subgroup analyses of selected covariates
    - Impact on efficacy of any new authorized treatments recommended as standard of care (SoC) for COVID-19 during the course of the study.

2.2 Overall Study Design

This is a randomized, double blind, placebo-controlled, Phase 2, proof of concept study in hospitalized patients with mild to moderate pneumonia due to COVID-19. Written informed consent must be obtained from all patients during screening (Days -2 to 0). Following completion of all screening assessments and meeting of eligibility criteria, patients will either receive antroquinonol or placebo for 14 days in combination with SoC therapy per local SoC policies.

A total of 174 patients are planned to be randomized in a 1:1 ratio to antroquinonol or placebo.

The study will consist of a sentinel cohort of 20 patients (10 patients randomized to antroquinonol and 10 patients to placebo), and an expansion cohort of 154 patients (77 patients in each treatment group). Enrollment will pause after the 20th patient in the sentinel cohort has been enrolled and started treatment, until the results of the interim analysis 1 are known. Once the 20th patient in the sentinel cohort has completed 14 days of treatment, an unblinded Data Monitoring Committee (DMC) will assess the safety, tolerability, efficacy, and PK of 100 mg twice daily (BID) antroquinonol in COVID-19 patients in the sentinel cohort (interim analysis 1). The DMC will issue a recommendation to enroll patients for the expansion cohort, or to stop the study depending on the safety and futility assessment. Once the 80th patient has been enrolled, and completed 14 days of treatment, the DMC will review the safety, tolerability, and efficacy data (interim analysis 2). Enrollment may be restricted at the 100th patient until the DMC has completed the assessment to prevent excessive enrollment. The DMC will continue to review safety and assess the risk/benefit profile on an ongoing basis. A DMC Charter, which includes detailed processes, will be prepared.

Patients will undergo assessment during hospitalization or could be discharged after start of study treatment any time after Day 2 if judged to be ready for discharge. If discharged, patients will then be requested to take study treatment at home (as prescribed) up to Day 14. End of Treatment assessments at Day 14 (+2 days) (at home or site visit) will be performed. A Day 5 (+/- 1 day) visit (at home or site visit) will be performed if the patient is discharged prior to Day 5. If the patient is discharged after completion of treatment and before the follow-up visit, he/she will be followed up on Day 28 (±2 days) for study assessments (a telephone or telemedicine visit). Post discharge, assessments will be done by telephone or telemedicine, except for Day 5, Day 14, and Early Termination (ET) of Study Treatment. On days of laboratory assessments, discharged patients will have a home visit. On days of no laboratory assessments, discharged patients will complete their assessments via telephone, telemedicine, or other means of remote communication. Additionally, patients will receive a diary to capture all doses after a discharge.

2.3 Sample Size

A total of 174 patients are planned to be randomized into the study:

- 20 patients in the sentinel cohort (10 patients in each treatment group)
- 154 patients in the expansion cohort (77 patients in each treatment group).

This enrollment level ensures 80% power to demonstrate proof of concept efficacy with one-sided alpha of 0.2.

The sample size is based on the following assumptions:

- The randomized allocation ratio is 1:1 between the antroquinonol group and the placebo group
- The proportion of patients alive and free of respiratory failure is approximately 78% on placebo vs 89% on antroquinonol

- The following nonbinding rules will be considered by the DMC for futility, and the DMC will not make any recommendations to stop for early efficacy:
    - Interim analysis 1 (sentinel cohort): An odds ratio of 3.5 on the primary endpoint in favor of placebo.
    - Interim analysis 2: An odds ratio of 1.2 on the primary endpoint in favor of placebo. This analysis will be conducted on all data collected up to the 80th randomized patient completing 14 days of treatment. Enrollment may be restricted at the 100th patient until the DMC has completed the assessment to prevent excessive enrolment.

3. Efficacy and Safety Variables

3.1 Primary Efficacy Endpoint

The proportion of patients who are alive and free of respiratory failure (e.g., no need for invasive mechanical ventilation, non-invasive ventilation, high-flow oxygen, or ECMO) on Day 14.

3.2 Secondary Efficacy Endpoints

- Clinical improvement score as measured by the WHO COVID-19 Clinical Improvement Ordinal Scale, as follows:
    - Time to 2-point improvement from baseline.
    - Supportive analysis, time to score 2 or lower.
    - Supportive analysis, time to score 0.
- Duration of hospitalization (days) up to Day 28
- Virological clearance evaluated using PCR testing from nasopharyngeal or mid-turbinate samples on Day 5, 14, and 28:
    - Time to virological clearance, measured as study days from start of treatment to first negative SARS-CoV-2 PCR test
    - Rate of change in viral load will be evaluated depending on availability of quantitative assays.
- Vital status (death) on Days 7, 14, and 28
- Duration of ICU stay up to Day 28
- Proportion of patients alive and free of respiratory failure on Days 7 and 28
- COVID-19 symptoms on Days 7, 14, and 28. Assessment will evaluate: presence or absence of dry cough, dyspnea (shortness of breath/ difficulty in breathing), or chills/rigors, myalgia (muscle pain), headache, sore throat, and loss of taste or smell; other symptoms that could be related to COVID-19 will also be recorded.

3.3 Exploratory Efficacy Endpoint

To further evaluate the impact of the following parameters on the primary endpoint, the interaction term of treatment and following parameters will be fitted into the primary model one at a time.

- Age, sex, and remdesivir or other authorized treatments for COVID-19 use at baseline.
- Use of any new authorized treatments recommended as SoC for COVID-19 during the course of the study.

3.4 Safety Variables

- Adverse events (AEs)
- Standard safety laboratory tests (hematology, clinical chemistry, and urinalysis)
- Vital signs: respiratory rate, body temperature, blood pressure, pulse rate
- Complete physical examination: general appearance; head, eyes, ear/nose/throat, and neck; and lymphatic, cardiovascular, respiratory, gastrointestinal, musculoskeletal, neurological, and dermatological systems
- 12-lead ECG
- Chest imaging (x-ray or CT scan) findings

4. Pharmacokinetic Variables

- Trough (predose) plasma concentration (C_{trough})
- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- Area under the plasma concentration versus time curve (AUC) from time zero to the time of last quantifiable concentration ($AUC_{0\text{-}last}$)
- AUC within a dosing interval (AUC_{tau}, where tau = 12 hours).

5. Analysis populations

5.1 All Enrolled Set

All patients who signed the informed consent form (ICF) will be included in the all enrolled set.

5.2 Intention-to-treat (ITT) Set

All randomized patients. Patients will be analyzed according to the treatment to which they were randomized.

5.3 Modified ITT (mITT) Set

All randomized patients who received at least one dose of study drug.

5.4 Per Protocol Set (PPS)

All patients from the ITT set who have no important protocol deviations during the study. Patients with important protocol deviations considered to have a major effect on efficacy shall be excluded from the PPS prior to database lock.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations and may significantly impact the correctness, accuracy, and/or reliability of the study data or that may significantly affect a Patient's rights, safety, or well-being. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Section 5.4.1 details the deviations.

5.4.1 Important Protocol Deviations Leading to Exclusion from the PPS Analysis

Only those important protocol deviations considered to have a major effect on efficacy will lead to complete exclusion of the patient from the PPS. For the purposes of this study, the following criteria have been identified as important protocol deviations leading to exclusion from the PPS as it is considered that the occurrences of any of these criteria might have an important influence on the primary efficacy endpoint. Patients will be assessed purely by comparison of their eCRF data with the criteria below.

Type	Important Protocol Deviation Leading to Exclusion from the PPS	Method of Identification
Inclusion Criteria 2	patient aged under 18 or over 80.	**Non-Programmable** check of age collected during screening visit.
Inclusion Criteria 4	patient does not meet the condition of mild COVID-19 disease.	**Non-Programmable** check of the WHO COVID-19 Clinical Improvement Ordinal Scale collected during screening visit.
Inclusion Criteria 5	patient with Chest x-ray or CT scan inconsistent with pheumonia.	**Non-Programmable** check of the chest imaging result during the screening visit.
Inclusion Criteria 6	patient does not meet: onset COVID-19 symptoms within 2 weeks prior to randomization.	**Non-Programmable** check of COVID-19 symptoms assessment during the screening visit.
Inclusion Criteria 7	patient does not have SARS-CoV-2 infection confirmed by a PCR test, antigen, or any authorized commercial or public health assay.	**Non-Programmable** check of SARS-CoV-2 test result during the screening visit.
Exclusion Criteria 2	patient with concomitant life threatening condition, including but not limited to: requiring mechanical ventilation, acute respiratory distress syndrome, shock, or cardiac failure.	**Non-Programmable** check of the medical history.
Exclusion Criteria 3	patient with evidence of multi lobar consolidation pneumonia or cavities on chest x-ray or CT scan.	**Non-programmable** check of the chest imaging form during the screening visit.
Exclusion Criteria 4	patient with score of 5, 6 or 7 in COVID-19 Clinical Improvement Ordinal Scale.	**Non-Programmable** check of the WHO COVID-19 Clinical Improvement Ordinal Scale during the screening visit.
Exclusion Criteria 5	patient with medical history for the following pulmonary diseases: lung cancer, cystic fibrosis, empyema.	**Non-Programmable** check of the medical history.
Exclusion Criteria 6	patient with respiratory rate >30 respirations per minute.	**Non-Programmable** check of the vital signs at the screening visit
Exclusion Criteria 8	patient treated with other drugs thought to possibly have activity against COVID-19 within 7 days prior to enrollment or concurrently. Note: remdesivir or other authorized treatments for COVID-19 is allowed if considered SoC, if started prior to randomization or during the study.	**Non-Programmable** check of the prior medications.

Exclusion Criteria 12	patient requires frequent or prolonged use of systemic corticosteroids (⩾20 mg of prednisone/day or equivalent for >4 weeks) or other immunosuppressive drugs (e.g., for organ transplantation or autoimmune conditions).	**Non-Programmable** check of the prior medications.
Treatment Compliance	patient with study treatment compliance <50%	**Non-Programmable** check the study treatment compliance based on drug accountability data.
Prohibited Medication or Therapy	patient has used prohibited medications or therapies documented in the protocol or identified by clinical or medical team	**Non-Programmable** check of the concomitant medication data.

As defined in the table, all important protocol deviations leading to exclusion from the PPS will be determined non-programmatically from the data. Those criteria which require clinical or medical monitoring interpretation will be reviewed prior to database lock.

All important protocol deviations leading to exclusion from the PPS occurring during the study will be reviewed and approved by Golden Biotechnology Corporation prior to database lock and unblinding. Should additional important protocol deviations leading to exclusion from the PPS, not anticipated at the time of preparing this SAP, be identified during the study (and prior to unblinding) they will be documented in a SAP amendment/Per Protocol Set Identification Plan, other document and included in all relevant protocol deviation reviews and approvals.

5.5 Safety Set (SS)

All patients who have received at least 1 dose of the study treatment. Patients will be analyzed according to the study treatment they actually received.

5.6 Pharmacokinetic Set (PKS)

Patients in the sentinel cohort who have received at least 1 dose of the study treatment and have at least 1 evaluable plasma concentration without important protocol deviations or events thought to significantly affect the PK.

6. DATA Handling

6.1 Time points and Visit Windows

Day 1 is defined as the day of first dose of study treatment. Relative days on or after Day 1 are calculated as (target date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (target date – Day 1 date). The day prior to Day 1 is Day -1.

The following visit windows will be used for by-visit analyses.

Visit	Target Day of Visit[a]	Acceptable visit window
Day 3	Day 3	Days 2 to 3
Day 5	Day 5	Days 4 to 6
Day 7	Day 7	Days 7 to 8
Day 14 - EOT	Day 14	Days 14 to 16
Day 28 - Follow up	Day 28	Days 26 to 30

[a] relative to the date of first dose of study treatment.

For all populations, multiple visits within the same window will be dealt with as follows:

- If both scheduled and unscheduled visits fall within the same visit window, the scheduled visit will be used for analysis.
- If multiple scheduled visits occur within a single visit window, then the visit closest to the target day of the visit window will be used in the analysis. If there is a tie, the later visit will be used in the analysis.
- If multiple unscheduled visits occur within a single visit window (with no scheduled visit within the window) then the unscheduled visit closest to the target day of the visit window will be used in the analysis. If there is a tie, the later unscheduled visit will be used in the analysis.

Baseline value is defined as the last scheduled or unscheduled value collected prior to the first dose of study treatment. Assessments carried out on day of first study treatment administration are considered to have taken place before the study treatment administration, if the corresponding times have not been recorded.

6.2 Handling of Dropouts, Missing Data, and Outliers

Unless specified otherwise, no imputation for missing/partial dates will be performed for missing safety, efficacy, PK variables. For time-to-event efficacy variables, the censoring rules for no event data will be included in efficacy analysis section.

For patients with clinical improvement score above 2 or missing at discharge, missing scores on the next day after discharge will be imputed to 2. After above rule implemented, missing scores will be imputed using Last Observation Carried Forward for a maximum of 1 day at Day 7, 2 days at Day 14, and 4 days at Day 28.

Dates in original form will be used in all listings.

No rules for outlier detection are planned.

7. Statistical Methods

7.1 General Principles

All data processing, summarization and analyses will be performed using Covance's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

The following principles will be applied to all TFLs unless otherwise stated:

Principle	Value
Significant tests	Results will be considered statistically significant at one sided alpha of 0.025, and considered to indicate promising trend at one sided alpha of 0.2.

Principle	Value
Treatment group labels and order	Antroquinonol 100 mg BID Placebo
Tables	Data in summary tables presented by treatment group, assessment and visit (where applicable).
Listings	All data collected presented by treatment group, country, site, Patient, assessment and visit (where applicable), unless otherwise specified.
Descriptive summary statistics for continuous variables	Number of patients/observations (n), mean, standard deviation (SD), median, minimum (Min) and maximum (Max).
Descriptive summary statistics for categorical variables	Frequency counts and percentages [n (%)]
Denominator and for percentages	Number of patients in the analysis population, unless stated otherwise in table shell(s).
Precision for percentages	1 decimal place
Include "Missing" as category	Yes, when the number missing is greater than zero for at least one treatment group.
Display to one more decimal place than collected value	For efficacy and safety: Mean Mean Difference Median
Display to two more decimal places than collected value	For efficacy and safety: Standard Error Standard Deviation Confidence Interval
Display to three significant figures	For PK: Mean Standard Deviation Geometric Mean Median Min Max
Limit of precision for displays	4 decimal places
Date Format	DDMMMYYYY

7.2 Patient Disposition and Data Sets Analyzed

Patient disposition will be listed and summarized by treatment group and overall for the all enrolled population and will include the number and percentage of patients that fall into the categories below:

- screened (overall);
- screen failed, including a breakdown of the primary reasons for screen failure;
- eligible but not randomized;
- randomized;
- randomized but not treated;
- treated;

- included in each study population (ITT set, mITT set, PPS, SS, PKS);
- completed/discontinued from the study treatment, including a breakdown of the primary reasons for discontinuation;
- completed/discontinued from the study, including a breakdown of the primary reasons for discontinuation.

Summary of patient disposition by country and site will be provided for each treatment group and overall for the ITT set.

7.3 Protocol Deviations

All protocol deviations will be listed for the ITT set.

All important protocol deviations leading to exclusion from the PPS (see Section 5.4.1) will be listed and summarized by treatment group and overall for the ITT set.

7.4 Baseline Disease Characteristics

Baseline disease characteristics will be listed and summarized by treatment group and overall for the ITT set. Standard descriptive statistics will be presented for the continuous variables of:

- oxygen saturation (SpO2) (%);
- WHO COVID clinical improvement ordinal scale.

The total counts and percentages of patients will be presented for the categorical variables of:

- patient setting;
- chest imaging result (normal, abnormal NCS, abnormal CS);
- SARS-CoV-2 test result (negative, positive);
- WHO COVID clinical improvement ordinal scale (at or below each score);
- COVID-19 symptoms;
- COVID-19 symptoms – maximum severity;
- patients with diarrhea.

7.5 Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be listed and summarized by treatment group and overall for the ITT set. Standard descriptive statistics will be presented for the continuous variables of:

- age (years);
- weight (kg);
- height (cm);
- body mass index (BMI, kg/m^2) [calculated as ($weight/height^2$) where weight is in kg and height is in m].

The total counts and percentages of patients will be presented for the categorical variables of:

- age (≤ 65 years, > 65 years);
- sex;
- race;
- ethnicity;
- remdesivir use or other authorized treatments for COVID-19.

Other baseline measurements, such as vital signs and ECG, will be summarized with the post-baseline measurements.

7.5.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) [Version 23.0 dated 19 Apr 2020 or a later version if updated during the study (exclusively meant for COVID-19)]. All medical history will be listed, and the number and percentage of patients with any medical history will be summarized for the ITT set by system organ class (SOC) and preferred term (PT) for each treatment group and overall.

7.5.2 Prior and Concomitant Medications

Medications received prior to or concomitantly with study treatment will be coded using WHODrug Dictionary [Version Global B3 March 2020 (or a later version if updated during the study)].

Prior medications and concomitant medications are defined as follows:

Prior medications are those with a stop date prior to the first dose date of study treatment.

Concomitant medications are those with a start date on or after the first dose date of study treatment, or those with a start date before the first dose date of study treatment and a stop date on or after the first dose date of study treatment or ongoing end of study.

If a medication cannot be classified as "prior" or "concomitant" due to missing/incomplete dates, it will be classified as concomitant.

Prior medications and concomitant medications will be listed together and summarized separately for the ITT set.

The number and percentage of patients using each medication will be displayed together with the number and percentage of patients using at least one medication within each therapeutic class (ATC-Level 2) and generic term.

7.6 Efficacy

Efficacy analyses will be conducted on ITT set, mITT set and PPS, separately, unless otherwise specified. The ITT set will be the primary analysis population for efficacy and the mITT set and PPS will be the supportive analysis populations for efficacy analysis. If it turns out that ITT and mITT populations are identical, then only ITT results will be presented.

7.6.1 Primary Efficacy Analysis

The proportion of patients from each treatment group who are alive and free of respiratory failure on Day 14 will be summarized and compared using logistic regression, with treatment, remdesivir or other authorized treatments for COVID-19 use at baseline (yes vs no) and age at baseline (> 65 years vs $\leqslant$ 65 years) as covariates. The p-value for treatment effect will be provided based on the Wald test. P-value based on Fisher's exact test will also be provided. Odds ratio along with its 95% confidence interval will be provided based on the exact method. In addition, the risk difference for the treatment effect and 95% confidence interval will be calculated based on the proportion of patients alive and respiratory failure free in the control group and the estimates of odds ratio, along with its 95% confidence interval.

7.6.2 Secondary Efficacy Analysis

7.6.2.1 Clinical Improvement Score as Measured by WHO COVID-19 Clinical Improvement Ordinal Scale

Clinical improvement measured as a score on the WHO COVID-19 Clinical Improvement Ordinal Scale will be analyzed using an ordinal logistic regression on Days 7, 14, and 28, with study treatment, clinical improvement score at baseline (as numerical variable), age at baseline (> 65 years vs $\leqslant$ 65 years), and remdesivir or other authorized treatments for COVID-19 use at baseline (yes vs no) as covariates. The p-value for treatment effect will be provided based on the Wald test.

In addition, descriptive statistics will be provided for average score by treatment group, and the proportion of patients at or below each score, at each visit.

Time to 2-point improvement from baseline in WHO COVID-19 Clinical Improvement score, time to score of 2 or lower, and time to score of 0, will also be analyzed. The hazard ratio and its 95% confidence interval for these time-to-event endpoints will be estimated by Cox proportional hazard model, with treatment, remdesivir or other authorized treatments for COVID-19 use at baseline (yes vs no) and age at baseline (> 65 years vs $\leqslant$ 65 years) as covariates. The analysis will be carried out using two different censoring rules: 1) Patients will be censored at the time they are provided any authorized treatment for COVID-19 not prescribed at baseline, or on Day 28 if they have not yet recovered or have died by Day 28; 2) Patients will only be censored on Day 28 if they have not yet recovered or have died by Day 28. The p-value for comparison between treatment groups will be obtained based on the Cox proportional hazards model described above. Median time to 2-point improvement, time to score of 2 or lower, and time to score of 0 will be estimated by Kaplan-Meier (KM) method, and the KM curve will be provided.

7.6.2.2 Duration of Hospitalization and ICU Stay

Duration in days of hospitalization and ICU stay up to Day 28 will be summarized descriptively and analyzed using normal regression, with treatment, remdesivir or other authorized treatments for COVID-19 use at baseline (yes vs no) and age at baseline (> 65 years vs $\leqslant$ 65 years) as covariates. P-values for treatment effect will be provided using the Student's t-test.

Notes: 1) Only hospitalization or ICU stay days on or after the date of first dose of study treatment and up to Day 28 will be used in the calculation of duration of hospitalization or ICU stay, respectively; 2) Patients who have died or with unknown discharge date will be considered as continuing to require hospitalization or ICU stay up to Day 28.

7.6.2.3 SARS-CoV-2 PCR Test

Time to virological clearance, measured as study days from start of treatment to first negative SARS-CoV-2 PCR test, will be evaluated using similar statistical methods as clinical improvement where in this case, the first negative SARS-CoV-2 PCR test is considered as an event. Patients will be censored on Day 28 if they have not yet shown SARS-CoV-2 PCR negative or have died by Day 28.

If quantitative SARS-CoV-2 PCR results are available, the following analyses will be conducted. Note that if a patient has tested negative, they are assumed to be negative until they are tested again and for negative test result, viral load is assumed to be half of the lower limit of detection.

- Rate of change in viral load will be estimated using a Mixed Model for Repeated Measurements model.

  The model will include the treatment group, age at baseline (> 65 years vs $\leqslant$ 65 years), remdesivir or other authorized treatments for COVID-19 use at baseline (yes vs no), log (viral load) at baseline, study day (numerical, 0 for baseline), and the interaction between study day and the treatment group as fixed factors, patient as random factor (random intercept and random slope).

  The model will use natural-log-transformed viral load as the response variable.

  An unstructured covariance structure will be used. In case of a convergence problem with the unstructured covariance matrix, the following structures with robust sandwich estimator for the standard error of the fixed effect estimates will be assessed in a sequential fashion: heterogeneous Toeplitz, heterogeneous first-order autoregressive, Toeplitz and compound symmetry.

  The esitmate of the study day*treatment will be interpreted as the difference between treatment and placebo groups in terms of the rate of change in viral load. The estimate, standard error and p-value of study day*treatment will be reported.

- Natural-log-transformed viral load with change from baseline will be summarized by treatment group and visit using descriptive statistics.
- Arithmetic mean (+SD) of natural-log-transformed viral load vs. time figure for each treatment group will be presented.

7.6.2.4 Vital Status, Patients Alive and Free of Respiratory Failure, and COVID-19 Symptoms

Proportion of patients with vital status of death in both groups on Days 7, 14, and 28 will be summarized compared using the same logistic regression model as the primary model.

Proportion of patients alive and free of respiratory failure on Days 7 and 28 will be summarized and compared using the same analysis as the primary endpoint.

Proportion of patients with each COVID-19 symptoms at baseline and on Days 7, 14, and 28 will be summarized and compared using logistic regression following the same method as the primary endpoint. Shift from baseline in severity table for each COVID-19 symptoms will be provided by treatment group.

7.6.3 Exploratory Efficacy Analysis

Subgroup analyses on primary endpoint will be provided for the parameters of age at baseline (> 65 years vs ≤ 65 years), sex, and remdesivir or other authorized treatments for COVID-19 use at baseline. The interaction between each mentioned parameter and the treatment effect will be added one at a time into the primary logistic model and the corresponding p-value for that interaction term will be provided.

The impact on efficacy of any new authorized treatments recommended as SoC for COVID-19 during the course of the study will also be evaluated using the same method as above.

7.7 Safety

7.7.1 Extent of Exposure and Compliance

Duration of exposure will be defined in days as:

(date of last dose – date of first dose) + 1 – off-drug days.

If date of first dose is missing then date of first dose dispensed will be used. If last dose date is missing then date of the last known dose consumed will be used.

Duration of exposure will be listed and summarized using descriptive statistics for each treatment group for the SS. The number and percentage of patients with treatment exposure by study day will be summarized for the SS.

The total number of capsules taken over the study duration will be summarized descriptively for the SS, where the total number of capsules taken is calculated as total number of capsules dispensed (30) – total number of capsules returned.

Percentage compliance is calculated as 100 * actual number of capsules taken/expected number of capsules taken, where actual number taken is defined as the number dispensed (30) – the number returned and expected number taken is defined as 2*(planned last treatment date – first treatment date + 1). For patients who completed the study treatment, planned last treatment date is the day 14 date; for patients with treatment early termination due to reasons of adverse event, death, physician decision or sponsor decision, planned last treatment date is the end of treatment date; for patients with treatment early termination due to reasons other

than the ones mentioned above, planned last treatment date is either the day 14 date or the end of study date, whichever occurs first.

Percentage compliance will be summarized descriptively by treatment group for the SS. The number and percentage of compliant patients will be presented for the SS, where compliant is defined as percentage compliance between 80.0% and 120.0% inclusive. The following percentage compliance categories will also be presented:

- <50.0%
- ≥50.0% and <80.0%
- ≥80.0% and ≤120.0%
- >120.0%

7.7.2 Adverse Events

All adverse events (AEs) recorded on the eCRF will be coded using the MedDRA dictionary [Version 23.0 dated 19 Apr 2020 or a later version if updated during the study (exclusively meant for COVID-19)] and classified as either pre-treatment AEs or treatment – emergent AEs (TEAEs) as follows:

- Pre-treatment AEs are events that start after the signing the informed consent form and prior to the date of first dose of study treatment.
- TEAEs are events with start date on or after the date of first dose of study treatment and up to 2 weeks after date of last dose of study treatment or events with start date prior to the date of first dose of study treatment whose severity worsens on or after the date of first dose of study treatment.

If an AE can't be classified as pre-treatment AE or TEAE due to missing/partial dates, it will be classified as TEAE.

The number and percentage of patients reporting each pre-treatment AE will be summarized for each treatment group and overall, by System Organ Class (SOC) and Preferred Term (PT) for SS.

All AE data will be listed by treatment group and overall. Treatment-emergence status will be flagged in the listing. In addition, corresponding listings of serious AEs (SAEs), treatment-related AEs, AEs leading to discontinuation of study treatment, AEs leading to discontinuation of study and AEs resulting in death will be produced for the SS.

The severity of all AEs is recorded as mild, moderate, or severe. If severity is missing for a TEAE, it will be considered severe only in the overall category in the summary tables.

The relationship between an AE and treatment is assessed as related, possibly related, unlikely related, or not related. A treatment-related AE is an AE considered by the investigator as related or possibly related to treatment or with missing relationship to treatment.

An overview table will summarize the number and percentage of patients with at least one of the following TEAEs, along with the number of corresponding TEAEs, where

patients with more than one TEAE in a particular category are counted only once in that category:

- any AE;
- any AE by maximum severity (mild, moderate, severe);
- treatment-related AE;
- AE leading to study treatment discontinuation;
- AE leading to study discontinuation;
- AE leading to death;
- SAE;
- treatment-related SAE;
- treatment-related SAE leading to death;
- SAE leading to death;
- SAE leading to treatment discontinuation;
- SAE leading to study discontinuation.

The number and percentage of patients reporting each AE will be summarized by System Organ Class (SOC) and Preferred Term (PT) for the SS. SOC and PT will be sorted by descending frequency in Antroquinonol group. The following summaries will be produced:

- AEs, by SOC and PT;
- AEs by PT;
- AEs related to study treatment, by SOC and PT;
- AEs related to study treatment, by PT;
- AEs by maximum severity, by SOC and PT;
- AEs related to study treatment by maximum severity, by SOC and PT;
- AEs by highest relationship to study treatment, by SOC and PT;
- AEs causing discontinuation from study treatment, by SOC and PT;
- AEs related to study treatment causing discontinuation from study treatment, by SOC and PT;
- AEs causing discontinuation from study, by SOC and PT;
- SAEs, by SOC and PT;
- SAEs related to study treatment, by SOC and PT;
- AEs leading to death, by SOC and PT.

In the above summaries, patients with more than one AE within a particular SOC or PT are counted only once for that SOC or PT. For summaries by maximum severity, patients with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT. AEs with missing severity

will be included as severe in the overall count of patients with AEs, but will not be included in the counts of patients with AEs within a SOC or PT. For summaries by highest severity, patients with multiple AEs within a particular SOC or PT will be counted under the category of their highest relationship to study treatment within that SOC or PT.

No statistical comparisons of AEs between treatment groups will be performed.

7.7.3 Laboratory Evaluations

Data for the following hematology, clinical chemistry, and urinalysis analytes will be listed and summarized by treatment group and overall by visit for the SS. If data for any additional analytes are also received/recorded then these will be listed only.

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin MCH MCHC MCV Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential (% and absolute values): • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils	Albumin ALP ALT AST BUN Calcium Chloride Cholesterol Creatinine GGT Glucose eGFR LDH Phosphorus Potassium Sodium Total Bilirubin Total CO_2 (measured as bicarbonate) Total Protein Triglycerides Uric acid	Color and appearance pH and specific gravity Bilirubin Glucose Ketones Leukocytes Nitrite Occult blood Protein Microscopic (including RBCs and WBCs)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CO2 = carbon dioxide; eGFR = estimated glomerular filtration rate; GGT = gamma glutamyl transferase; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; WBC = white blood cell.

All laboratory data will be reported in International System of Units (SI). Out-of-reference-range values will be flagged as high (H) or low (L) in the listings.

For analysis purposes, values preceded by a "<" or a ">"sign (i.e. those below or above the limits of quantification) will be multiplied by 0.5 and 1.5 respectively.

Results and changes from baseline (if applicable) of all laboratory parameters will be listed and summarized by treatment group and overall, for each scheduled visit using standard descriptive statistics for the SS.

For hematology, clinical chemistry and numerical urinalysis analytes, shift tables presenting movement in and out of reference range from baseline to each scheduled post-baseline visit will be provided for each treatment group and overall for the SS.

7.7.4 Vital Signs

The following vital sign parameters will be listed and summarized by treatment group and overall and visit.

- systolic and diastolic blood pressure (mmHg);
- pulse rate (bpm);
- respiration rate (breaths/min);
- body temperature (°C).

Vital signs data and changes from baseline in vital signs will be listed and summarized by treatment group and overall, for each scheduled visit using standard descriptive statistics for the SS.

7.7.5 Electrocardiograms

The following quantitative ECG measurements will be taken during the study:

- heart rate (bpm);
- RR interval (msec);
- PR interval (msec);
- QRS interval (msec);
- QT interval (msec);
- Bazett corrected QT (QTcB) interval (msec);
- Fridericia corrected QT (QTcF) interval (msec).

An overall Investigator assessment of ECG will be provided (categories "normal", "abnormal, not clinically significant" and "abnormal, clinically significant").

The ECG measurements and changes from baseline in ECG will be listed and summarized by treatment group and overall for each scheduled visit using standard descriptive statistics for the SS.

The Investigator assessment will be listed and the number and percentage of patients within each assessment category will be tabulated by treatment group and overall for each scheduled visit for the SS. Shifts from baseline in overall investigator assessment at each post-baseline visit will be presented.

QTcB and QTcF intervals and change from baseline will be analyzed. The analysis will include all scheduled and unscheduled values.

The maximum baseline and post-baseline values will be summarized separately, by treatment group and overall according to the following categories:

- ≤450 ms
- >450 and ≤480 ms

- >480 and ≤500 ms
- >500 ms

The maximum increases from baseline will be summarized by treatment group and overall according to the following categories:

- ≤30 ms
- >30 and ≤60 ms
- >60 ms

7.7.6 Physical Examination

Physical examination results (categories "normal", "abnormal, not clinically significant" and "abnormal, clinically significant") and details of abnormalities will be listed for each patient.

For each physical examination body system, shifts from baseline in examination results at each post-baseline visit will be presented by treatment group and overall for the SS.

7.7.7 Chest Imaging

Chest imaging (X-Ray or CT scan) results (categories "normal", "abnormal, not clinically significant" and "abnormal, clinically significant") and other details will be listed for each patient. Shift from baseline in results at each post-baseline visit will be presented by treatment group and overall for the SS.

7.7.8 Oxygenation

Oxygenation parameters (i.e., FiO2, SpO2, PaO2, SpO2/FiO2 and PaO2/FiO2, if available) and other details will be listed for each patient. Change from baseline of SpO2, SpO2/FiO2 and PaO2/FiO2, at each post-baseline visit will be presented by treatment group and overall for the SS, if available.

7.7.9 Other Safety Variables

Other safety variables and corresponding data, if collected, will be listed only.

7.8 Pharmacokinetics

7.8.1 General

The PK parameters of antroquinonol will be calculated based on the actual sampling time using non-compartmental analysis (NCA) methods within Phoenix WinNonlin Version 8.1 or higher (Certara USA, Inc.). If the actual sampling time is missing, the scheduled timepoint will be used in the PK parameter calculation with sponsor approval.

The units of concentration and resulting PK parameters, will be presented as they are received from the analytical laboratory.

The following PK parameters for antroquinonol will be determined where possible from the plasma concentration data collected on Day 3:

Parameter	Definition
$AUC_{0\text{-last}}$	area under the plasma concentration versus time curve (AUC) from time zero to the time of last quantifiable concentration
AUC_{tau}	AUC within a dosing interval, where tau = 12 hours.
C_{max}	maximum plasma concentration
t_{max}	time to C_{max}
C_{trough}	trough (predose) plasma concentration

Additional PK parameters may be determined where appropriate.

AUC parameters will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations.

C_{max}, C_{trough} and t_{max} will be obtained directly from the plasma concentration-time profiles.

The predose and 2 hours post dose samples collected on Day 14 from patients who remained hospitalized will be listed and summarized.

7.8.2 Criteria for Handling Concentrations Below the Limit of Quantification in Pharmacokinetic Analysis

Concentration values that are below the level of quantification (BLQ) will be set to zero, with defined exceptions as follows;

- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK parameter calculations.
- If the predose sample is missing on Day 3, the predose concentration may be set as equivalent to the concentration at the end of the dosing interval (12 hours post dose) if available.
- If the 12 hours post dose sample is missing or not collected on Day 3, the 12 hours concentration may be set as equivalent to the concentration at predose if available.

7.8.3 Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.
- For any partial AUC determination (i.e. AUC within a dosing interval), nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used at the discretion of the Pharmacokineticist.

7.8.4 Anomalous Values

If a value is considered to be anomalous due to being inconsistent with the expected pharmacokinetic profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and study report.

Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

7.8.5 Pharmacokinetic Statistical Methodology

All the PK data will be presented based on the PKS.

Antroquinonol plasma concentration data will be listed and summarized by study day at every scheduled timepoints. The following figures will be plotted:

- The arithmetic mean (+ standard deviation [SD]) plasma concentration-time plot (linear and semi-log) by study day according to the scheduled sampling timepoints;
- Individual plasma concentration-time plot (linear and semi-log) according to the actual sampling time on Day 3 and 14 for every patient.

The PK parameters of Day 3 will be listed and summarized.

7.8.6 Presentation of Pharmacokinetic Data

7.8.6.1 Presentation of Pharmacokinetic Plasma Drug Concentration Data

- Descriptive statistics of number of patients (n), number of BLQ values [n (BLQ)], arithmetic mean, SD, geometric mean, geometric coefficient of variance (CV), median, minimum and maximum will be calculated in summaries.
- For the calculation of summary statistics, the BLQ values will be set to zero.
- Where there is no result (NR), these will be set to missing.
- If there are less than three values in the data series, only the min, max and n will be presented. The other summary statistics will be denoted as not calculated (NC).
- If all the values are BLQ, then the arithmetic mean, arithmetic SD, median, min and max will be presented as zero, and the geometric mean and geometric CV% will be denoted as NC.
- If the value of the arithmetic mean or median is below the lower limit of quantification, these values will be presented as zero and the geometric mean and geometric CV% will be denoted as NC.
- Where the actual PK sample collection time deviates outside ± 10% from the planned time point, the concentration may be excluded from the calculation of descriptive statistics. Note: Deviation from Nominal Time = Actual date time [h] of sample collection (relative to last administered dose) - Planned date

time [h] of sample collection (relative to last administered dose); Percent Deviation from Nominal Time (%) = 100 * (Deviation from nominal time [h] / Nominal time point [h]).

7.8.6.2 Presentation of Pharmacokinetic Parameters

- Descriptive statistics of number of patients (n), arithmetic mean, SD, geometric mean, geometric CV, median, minimum and maximum will be calculated in summaries.
- For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.
- The AUC values will be set to NC if they have been calculated using fewer than three concentrations, and/or three concentrations if the last is C_{max}.
- If there are less than three values in the data series, only the min, max and n will be presented. The other summary statistics will be denoted as not calculated (NC).

7.9 Interim Analysis

The following interim analyses will be conducted:

- Interim analysis 1, for safety and futility, will be conducted when the sentinel cohort has completed at least 14 days of treatment. Enrollment will be paused once the 20th patient in the sentinel cohort has been enrolled and started treatment until the results of the interim analysis are known.
- Interim analysis 2, for safety and futility, will be conducted on all data collected up to the 80th randomized patient completing 14 days of treatment. Enrollment may be restricted at the 100th patient until the DMC has completed the assessment to prevent excessive enrollment.

All interim analyses will be reviewed by the unblinded DMC. The DMC will not make recommendations to stop the study early for efficacy. Futility rules provided to the DMC will be nonbinding, and therefore no adjustment of the final analysis will be made. Should either ≥ 2 patients experience treatment related SAEs or severe AEs that are of a similar nature at any time, enrollment will be paused while the DMC reviews safety data.

A DMC Charter, which includes detailed processes, will be prepared.

8. Changes in Planned Analysis

No changes on statistical analysis methods from the protocol.

9. Data Issues

There is no observed data issue while formulating the statistical analysis plan. Should any data issue identified after the SAP is finalized will be documented in regard to the handling of the data issue.”

10. References

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Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary/Reason for Changes
Version 1, Final, 04 October 2020	Not applicable; the first version
Version 2, Final, 23 March 2021	To address FDA's comments, new changes in Protocol 3.0 and additional internal comments.
Version 3, Final, 29 Nov 2021	Protocol updated to version 4.0

Appendix 2: Schedule of Assessments

Study Period	**Screening**	**Treatment**					**Discharge**	**Follow-up**
Visit name	**Screening**	**Baseline**				**EOT [a]**	**Discharge/ ET of Study Treatment/ EOT[a]**	**EOS[a]/ Early Withdrawal/ ET of Study**
Study Day(s)	**-2 to 0**	**1**	**3**	**5 (±1)**	**7 (+1)**	**14 (+2)**	**2-28**	**28 (±2)**
Informed consent	X							
Randomization[b]		X						
Inclusion/exclusion criteria[c]	X	X						
Daily study treatment administration[d]		X						
Demographics	X							
Medical history	X							
Physical examination[e]	X	X				X	X	X
Height, body weight[e]	X							
Vital signs[e]	X	X	X	X	X	X	X	X
Chest x-ray or CT scan[f]	X						X	
Pregnancy test[g]	X	X				X	X	X
Return unused study treatment						X	X	
Efficacy[h]								
[1] Confirm setting (outpatient, in hospital, in ICU)	X		X	X	X	X	X	X
[2] SARS-CoV-2 PCR test	X	X		X		X		X
[3] WHO COVID-19 Clinical Improvement Ordinal Scale	X	X	X	X	X	X	X	X
[4] Vital status		X	X	X	X	X	X	X
[5] Respiratory failure status		X	X	X	X	X	X	X
[6] COVID-19 symptoms assessment	X	X	X	X	X	X	X	X
Safety[i]								
[1] Adverse events	X	X	X	X	X	X	X	X
[2] Laboratory assessments	X	X		X		X	X	
[3] Electrocardiogram	X					X	X	
[4] Prior and concomitant medications	X	X	X	X	X	X	X	X

Study Period	Screening	Treatment					Discharge	Follow-up
Visit name	Screening	Baseline				EOT [a]	Discharge/ ET of Study Treatment/ EOT[a]	EOS[a]/ Early Withdrawal/ ET of Study
Study Day(s)	-2 to 0	1	3	5 (±1)	7 (+1)	14 (+2)	2-28	28 (±2)
Pharmacokinetics[j]								
PK blood collection			X			X		

Abbreviations: AE = adverse event; AUC = area under the plasma concentration versus time siurve;$AUC_{0\text{-last}}$ = AUC from time zero the time of last quantifiable concentration; AUC_{tau} = AUC within a dosing interval, tau = 12 hours; BID = twice daily; C_{max} = maximum plasma concentration; C_{trough} = trough (predose) plasma concentration; COVID-19 = COronaVIrus Disease 2019; CT = computerized tomography; CRF = case report form; DMC = Data Monitoring Committee; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; EOS = End of Study; EOT = End of Treatment; ET = early termination; HEENT = head, eyes, ear, nose and throat; ICF = informed consent form; ICU = intensive care unit; PCR = polymerase chain reaction; PK = pharmacokinetic; SpO_2 = peripheral capillary oxygen saturation; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; t_{max} = time to C_{max}; WHO = World Health Organization.

Notes:

General note: on days of laboratory assessments, discharged patients will have a home visit. On days of no laboratory assessments, discharged patients will complete all assessments via telephone or telemedicine visits.

a Patients will undergo assessment during hospitalization or could be discharged after start of study treatment any time after Day 2 if judged to be ready for discharge. If discharged, patients will then be requested to take study treatment at home (as prescribed) up to Day 14. End of Treatment assessments at Day 14 (+2 days) (at home or site visit) will be performed. A Day 5 visit (at home or site visit) will be performed if the patient is discharged prior to Day 5. If the patient is discharged after completion of treatment and before the follow up visit, he/she will be followed up on Day 28 (±2 days) for study assessments (a telephone or telemedicine visit). Post discharge, assessments will be done by telephone or via telemedicine or other means of remote communication, except for Day 5, Day 14 (+2 days), and Early Termination of Study Treatment, which would be a home visit.

b Initial sentinel cohort of 20 patients to be enrolled to assess safety, tolerability, efficacy, and PK. Enrollment will pause after the 20th patient in the sentinel cohort has started treatment, until the results of the interim analysis are known. Once the 20th patient in the sentinel cohort has completed 14 days of treatment, an unblinded DMC will assess the safety, tolerability, efficacy, and PK of 100 mg BID antroquinonol in COVID-19 patients in the sentinel cohort (interim analysis 1). The DMC will issue a recommendation to enroll patients for the expansion cohort, or to stop the study depending on the safety and futility assessment. Once the 80th patient has been enrolled and completed 14 days of treatment, the DMC will review the safety, tolerability and efficacy data (interim analysis 2). Enrollment may be restricted at the 100th patient until the DMC has completed the assessment to prevent excessive enrollment.

c Patients must satisfy all of the criteria at the screening visit unless otherwise stated (e.g. some criteria can be evaluated at Day 1 if needed).

d Daily study treatment administration from Day 1 to Day 14.

e A complete physical examination (general appearance, HEENT, lymphatic, cardiovascular, respiratory, gastrointestinal, musculoskeletal, neurological, and dermatological systems) will be performed at screening. Vital signs (respiratory rate, temperature, blood pressure, and pulse rate) to be assessed during hospitalization, on discharge, ET/EOT and Follow-up/EOS visit (for site or in-person visits only). Pulse oximetry to measure SpO_2 (>94% on room air) will be collected in the eCRF during the study if done per standard of care. Height and body weight will be measured only at screening.

f Chest x-ray or CT scan should show findings consistent with pneumonia due to COVID-19 and will be performed at Screening and either at hospital discharge, at ET of Study Treatment, or at ET of Study, whichever comes first (Note: only 1 scan must be done for hospital discharge, ET of Study Treatment, or ET of Study). Chest x-ray or CT scan does not need to be repeated at screening if performed as standard of care and done within 48 hours of diagnosis. Chest x-ray or CT scan is not required post discharge.

g Serum pregnancy test is to be performed in female patients of child-bearing potential at a local (site) laboratory, during screening or pretreatment Day 1, discharge, and ET/EOT. Urine pregnancy test may be performed but must be confirmed with a serum pregnancy test (screening only). The Follow-up/EOS visit test will be a urine pregnancy test only (pregnancy test kit will be provided to the patient when discharged). Additionally, local/country regulations will be followed as applicable (eg., monthly pregnancy test after the last dose of study treatment in female subjects of childbearing potential).

h Efficacy parameter assessments: [1] Confirmation of whether the patient is discharged to home, is in the hospital, or has worsened to require an ICU. The number of days a patient has been hospitalized prior to study entry will be recorded in the eCRF. [2] PCR testing for SARS-CoV-2 will be performed by a local or central laboratory at screening. Results of confirmatory COVID-19 test already done as standard of care can be used to determine eligibility. All subsequent tests will be performed by a central laboratory at baseline/Day 1, Day 5 and Day 14. Also at Follow-up/EOS if patient is hospitalized. Either nasopharyngeal or mid-turbinate samples are allowed for central testing. Only one method should be used throughout the study for the participant. [3] Clinical improvement score will be measured using the WHO COVID-19 Clinical Improvement Ordinal Scale (refer to Appendix 7 of the protocol). [4] Patient mortality will be recorded up to Day 28. Every effort will be made to ascertain vital status in all randomized patients (e.g., with a vital records search) up to Day 28. [5] Respiratory failure is considered as patient need for invasive mechanical ventilation, non-invasive ventilation, high-flow oxygen, or ECMO. The date of the start of the respiratory intervention must be recorded in the eCRF; no daily assessment is needed. [6] COVID-19 symptoms (presence or absence of dry cough, dyspnea (shortness of breath/ difficulty in breathing), or chills/rigors, myalgia (muscle pain), headache, sore throat, and loss of taste or smell; other symptoms that could be related to COVID-19) will also be assessed during hospitalization, on discharge, ET/EOT and Follow-up/EOS visit (at the site, home visit, or via telephone or telemedicine if patient has been discharged).

i Safety parameter assessments: [1] AEs will be assessed from signing the ICF (during hospitalization and post discharge at home) daily to Day 5, then Days 7, 14 (+2 days), 28 (±2 days) until Follow-up/EOS; [2] Standard safety laboratory tests will include all parameters of hematology, clinical chemistry, and urinalysis (refer to Appendix 2 of the protocol) and will be performed as applicable at Screening, at predose on Day 1, Day 5, and Day 14 (+2 days) (a home visit, or a site visit if discharged). Screening laboratory tests will be assessed by a local laboratory, and baseline and postbaseline laboratory tests will be assessed by a central laboratory. Baseline laboratory tests can be done once patients eligibility is confirmed. [3] 12-lead ECGs to be performed at screening while the patient is in supine position and at rest for at least 5 minutes. Additionally, 12-lead ECGs will be performed at Day 14/EOT or early treatment termination while the patient is hospitalized or at the time of discharge if the patient is discharged prior to Day 14. [4] Prior and concomitant medications to be recorded from screening assessments daily to Day 5, then Days 7, 14 (+2 days), 28 (± 2 days).

j Blood samples for determination of antroquinonol plasma concentrations will be collected for patients in the sentinel cohort (first 20 patients) only on Day 3 at predose and 1, 2, 3, 4, 6, 8, and 12-hours postdose for hospitalized patients only. Samples are collected after the first study drug dose of the day. For discharged patients (ie, on Day 2)/outpatient visit, the 12-hour sample can be omitted. On Day 14, if patients are still hospitalized, predose and 2 hours postdose samples (after the first study drug dose of the day) will be collected. Patients who are discharged from the hospital on Day 2 prior to PK sampling will not need to return to the clinic for sample collection.