TITLE PAGE

Protocol

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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Investigational Product: Antroquinonol (Hocena®)

Protocol Reference Number: GHCovid-2-001
Investigational New Drug: 149841

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SPONSOR APPROVAL

Title: **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**

Protocol Reference Number: **GHCovid-2-001**

I agree to the content of the Clinical Study Protocol as presented.

Sponsor Signature:

12 Jul 2021

Howard Cheng, PhD
VP, Clinical Medicine Research Department
Golden Biotechnology Corporation

Date

INVESTIGATOR AGREEMENT

Title: **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**

Protocol Reference Number: **GHCovid-2-001**

I have read the following protocol and agree to conduct the study as described herein.

Name:
Qualification:

Principal Investigator

Date

SYNOPSIS

Title of study:

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

Indication:

Mild to moderate pneumonia due to COronaVIrus Disease 2019 (COVID-19)

Number of investigators and study centers:

Approximately 15 to 20 sites in the United States, and other countries based on the pandemic situation.

Development phase:

Phase 2

Objectives:

The **primary objective** 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 (ie, no need for invasive mechanical ventilation, non-invasive ventilation, high-flow oxygen, or extracorporeal membrane oxygenation [ECMO]) on Day 14

The **secondary objectives** 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 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)

The **exploratory objective** is to further evaluate efficacy via supportive analyses of:

- 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.

Methodology/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. If the discharge, ET, or Early Withdrawal visit falls within the window of a schedule Day visit, the assessments for the visits can be combined as one visit. 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.

Number of patients:

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.

Diagnosis and criteria for inclusion and exclusion:

Patients must satisfy all of the following **inclusion** criteria at the Screening visit unless otherwise stated:

1. Willing and able to provide informed consent.
2. Male or female patients between 18 and 80 years of age.
3. Oxygen Saturation <94% in room air at screening.
4. Hospitalized with mild COVID-19 disease (not requiring oxygen therapy [WHO COVID-19 Clinical Improvement Ordinal Scale, score of 3] or requiring oxygen therapy by mask or nasal prong [WHO

COVID-19 Clinical Improvement Ordinal Scale, score of 4]). Requirement of oxygen therapy by mask with reservoir to treat severe COVID-19 pneumonia is not allowed for enrollment.

Note: Hospitalized patients can also include patients admitted to centers conditioned as hospitals to treat COVID-19 patients.

5. Chest x- ray or computerized tomography (CT) scan consistent with pneumonia.
6. Onset of COVID-19 symptoms within 2 weeks prior to randomization.
7. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection confirmed by a polymerase chain reaction (PCR) test, antigen, or any authorized commercial or public health assay (nasopharyngeal, oropharyngeal, or respiratory samples, not serology testing).
8. Male patients and female patients of childbearing potential must agree to use protocol-specified methods of contraception.
9. Female patients of childbearing potential must have a negative pregnancy test at Screening or pretreatment on Day 1.
10. Male patients must agree not to donate sperm from the first dose through 90 days after the last dose of study treatment; female patients of childbearing potential should refrain from donation of ova from Day 1 until 90 days after the last dose of study treatment.
11. Patient is, in the opinion of the investigator, willing and able to comply with the study treatment regimen and all other study requirements.

Patients will be excluded from the study if they satisfy any of the following **exclusion** criteria at the Screening visit unless otherwise stated:

1. Female patient is pregnant or breastfeeding.
2. Any patient's concomitant life-threatening condition, including but not limited to: requiring mechanical ventilation, acute respiratory distress syndrome, shock, or cardiac failure.
3. Evidence of multi-lobar consolidation pneumonia or cavities on chest x-ray or CT scan.
4. Severe COVID-19 disease as defined by the WHO COVID-19 Clinical Improvement Ordinal Scale, scores of 5 (non-invasive ventilation or high-flow oxygen), 6 (intubation and mechanical ventilation), or 7 (ventilation + additional organ support-pressors, renal replacement therapy, ECMO).
5. Medical history significant for the following pulmonary diseases: lung cancer, cystic fibrosis, empyema.
6. Respiratory rate >30 respirations per minute.
7. History of abuse of drugs or alcohol that could interfere with adherence to study requirements, as judged by the investigator.
8. Treatment 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.
9. Use of *Antrodia camphorata* -containing products within 2 weeks prior to the first administration of study drug.
10. Use of other investigational drugs within 30 days of dosing, or plans to enroll in another clinical trial of an investigational agent while participating in the present study. Note: authorized COVID-19 vaccines are not considered investigational and are not exclusionary.
11. Clinically significant abnormal electrocardiogram (ECG) at Screening, as determined by the investigator.
12. Patient requires frequent or prolonged use of systemic corticosteroids (≥20 mg of prednisone/day or equivalent for >4 weeks) or other immunosuppressive drugs (eg, for organ transplantation or autoimmune conditions).
13. Abnormal laboratory values at Screening:
    a. Estimated glomerular filtration rate <50 mL/min.
    b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × upper limit of normal (ULN), or ALT/AST >3 × ULN plus total bilirubin >2 × ULN.

c. Total bilirubin >1.5 × ULN, unless the patient has known Gilbert's syndrome.
d. Hemoglobin <9 g/dL for females or <11 g/dL for males.
e. Absolute neutrophil count <1,500/mm^3.
f. Thrombocytopenia (platelets count <100 × 10^9/L).

14. Treatment with any antiviral drugs (except remdesivir or other authorized treatments for COVID-19), or with any drugs known to be strong inducers or inhibitors of cytochrome P450 isoform (CYP) 2C19, CYP3A4, CYP2C8, and CYP2E1 within 14 days or 5 half-lives prior to the start of study treatment. Drugs with a narrow therapeutic index that are substrates of 1A2, 2B6, 2C8, 2C9, 2C19, 3A, and 2D6 are also prohibited.
15. Inability to swallow oral medications or a gastrointestinal disorder with diarrhea (eg, Crohn's disease), malabsorption, or diarrhea of any etiology at baseline.
16. Any other clinically significant medical condition or laboratory abnormality that, in the opinion of the investigator, would jeopardize the safety of the patient or potentially impact patient compliance or the safety/efficacy observations in the study.

Test product, dose, and mode of administration:

Antroquinonol in a dose of 100 mg (1 capsule) administered BID orally, for 14 days.

Reference therapy, dose, and mode of administration:

Placebo (1 capsule) administered BID orally, for 14 days.

Duration of patient participation in study:

Total duration of patient participation is planned to be a maximum of 33 days.

The screening period is planned to be up to 3 days. The planned study treatment duration is 14 days. Follow-up/EOS assessments will be performed on Day 28 (±2 days).

Study populations:

Intention-to-treat (ITT): All randomized patients. Patients will be analyzed according to the treatment to which they were randomized.

modified ITT (mITT): All randomized patients who received at least 1 dose of study drug.

Per Protocol Set (PPS): All patients from the ITT set who have no important protocol deviations during the study. Patients with any important protocol deviations shall be excluded from the PPS prior to database lock.

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.

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.

The ITT set will be the primary analysis population for efficacy and the mITT and PPS will be the supportive analysis populations for efficacy analysis. Safety endpoints will be analyzed using the SS. The PKS will be used for PK assessment.

Endpoints:

The **primary efficacy endpoint** is:

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

The **secondary efficacy endpoints** are:

- 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 Days 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.

The **exploratory efficacy endpoints** include:

- 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

The **safety endpoints** include the following 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

The **PK parameters** to be assessed from plasma samples (sentinel cohort only) are:

- 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). On Day 14, if patients are still hospitalized, a predose and a 2-hours postdose sample will also be collected.

Statistical methods:

General Principles:

Continuous variables will be summarized by the standard descriptive statistics: number of patients (n), mean, standard deviation, median, minimum, and maximum. Frequency of patients or events and percentages will be summarized in categorical variables.

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.

Efficacy Analysis:

Primary Efficacy Analysis

The proportion of patients from each treatment group who are alive and free of respiratory failure on Day 14 will be compared using logistic regression. The p-value will be based on the Wald test. The primary model will be

stratified by remdesivir or other authorized treatments for COVID-19 use at baseline and by age at baseline (≤65 years vs >65 years).

Secondary Efficacy Analysis

- Clinical improvement measured as a score on the WHO COVID-19 Clinical Improvement Ordinal Scale will be analyzed at each timepoint, adjusted for the clinical improvement score at baseline, age at baseline, and remdesivir or other authorized treatments for COVID-19 use at baseline, using an ordinal logistic regression on Days 7, 14, and 28. In addition, descriptive statistics will be provided for average score, and the proportion of patients at or below each score, at each timepoint. 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 time to event outcomes will be estimated by the Cox proportional hazard model, with patients censored at the time they are provided any antiviral therapy not prescribed at baseline, or on Day 28 if they have not yet recovered. Patients who die at any time will be considered not yet recovered by Day 28. 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. The p-value for comparison between groups will be obtained based on proportional hazards modeling stratified by the same covariates as the primary model.
- Duration of hospitalization and ICU stay up to Day 28 will be analyzed using normal regression, using the same covariates as for the primary endpoint. Patients who have died will be considered as continuing to require hospitalization or ICU up to Day 28 for the purposes of this analysis.
- 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. All patients who have died will be considered as not having cleared the virus by Day 28.
- Rate of change in viral load will be summarized descriptively and estimated using a Mixed Model for Repeated Measurements model. The model will include the treatment group, age, remdesivir or other authorized treatments for COVID-19 use at baseline, visit, and the interaction between visit and the treatment group as fixed factors, and will include the baseline value as a covariate.
- Proportion of patients with vital status of death in both groups on Days 7, 14, and 28 will be analyzed using logistic regression stratified by the same covariates as the primary model.
- Proportion of patients alive and free of respiratory failure on Days 7 and 28 will be compared using the same analysis as the primary endpoint.
- COVID-19 symptoms at screening and on Days 7, 14, and 28 will be summarized, and compared using logistic regression following the same method as the primary endpoint.

Exploratory Analyses

Subgroup analyses will be provided for the parameters of age, sex, and remdesivir or other authorized treatments for COVID-19 use at baseline. Investigation of the interaction between these parameters and the treatment effect 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.

Safety Analysis:

Adverse events will be coded according to Medical Dictionary for Regulatory Activities version 23.0 dated 19 April 2020 (exclusively meant for COVID-19), or later.

The number and percentage of patients with treatment-emergent AEs (TEAEs), serious AEs (SAEs), TEAEs related to study treatment, SAEs related to study treatment, TEAEs leading to treatment discontinuation, and TEAEs leading to death will be summarized by system organ class (SOC), preferred term (PT), and treatment group. In addition, the severity of TEAEs and relationship to study treatment will be summarized by SOC, PT, and treatment group.

Test values and change from baseline will be summarized descriptively for specific laboratory test results, vital signs, and complete physical examination, ECG, and chest imaging (x-ray or CT scan) findings. Where applicable, shift tabulations by treatment group will be presented.

Pharmacokinetic Analysis:

Descriptive statistics will be provided for antroquinonol plasma concentrations at prespecified timepoints and derived PK parameters.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
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
BID	twice daily
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
CSA	clinical study agreement
CT	computerized tomography
C_{trough}	trough (predose) plasma concentration
CYP	cytochrome P450 isoform
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EC	Ethics Committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study
EOT	End of Treatment
ET	Early Termination
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
GCP	Good Clinical Practice
HBV	hepatitis B virus
HEENT	head, eyes, ear/nose/throat, and neck
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IMP	investigational medicinal product
IND	investigational new drug
IRB	Institutional Review Board
ITT	intention-to-treat
IWRS	Interactive Web Response System
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homolog
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat

Abbreviation	Definition
NOAEL	no-observed-adverse-effect-level
NSCLC	nonsmall cell lung cancer
PaO_2	partial pressure of oxygen
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
PKS	Pharmacokinetic Set
PPS	Per Protocol Set
PSS	Patient Safety Services
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SoC	standard of care
SOC	system organ class
SpO_2	peripheral capillary oxygen saturation; oxygen saturation
SS	Safety Set
$T_{1/2}$	half-maximum concentration $C_{1/2}$
TEAE	treatment-emergent adverse event
TID	3 times daily
t_{max}	time to C_{max}
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

In 2019, an outbreak of respiratory disease caused by a novel coronavirus was first detected in Wuhan City, Hubei Province, China.[1] The virus has been named Severe Acute Respiratory Syndrome COronaVirus 2 (SARS-CoV-2), and the disease it causes has been named COronaVIrus Disease 2019 (COVID-19). This virus has now been detected in many locations internationally, and COVID-19 was characterized as a pandemic by the World Health Organization (WHO) on 11 March 2020.[2]

1.1. Study Rationale

This is a Phase 2 clinical trial to evaluate the safety and efficacy of antroquinonol in patients hospitalized with mild to moderate pneumonia due to COVID-19.

Currently, there is no approved treatment for COVID-19. An effective therapeutic is urgently needed.

COVID-19 infection is characterized by the presence of systemic symptoms followed by a cytokine storm with elevated IL-6 leading to lung injury and requirement of mechanic ventilation, multi organ failure, and death.[3] Antroquinonol modulates systemic immune responses by suppression of T-cell proliferation / activation and suppression of serum inflammatory cytokines expression including IL-6, MCP-1, IL-12, IFN-γ, TNF-α, and IL-10 without affecting B cell activation.[4] Examination of the antiviral activity of antroquinonol against hepatitis B virus (HBV) replication showed significantly suppressed HBV protein expression, including surface antigen and e antigen at 1 to 5 μM in HepG2.2.15 cells (human hepatoblastoma cell line HepG2 and characterized by having stable HBV expression) and suppressed expression of HBV DNA as shown by significantly suppressed HBV replicative intermediates (relaxed-circular, linear, and single-stranded DNA) at 5 μM in Qs5 cells (HBV-producing rat hepatoma cell line) (sponsor data).

Preclinical data shows increased distribution of antroquinonol to the lungs compared to other organs.[5] Antroquinonol has been studied in human trials for the treatment of pancreatic and lung cancer and has been shown to be well tolerated and without revealing safety concerns. This clinical trial represents the first time that antroquinonol will be administered to humans for treatment of mild to moderate pneumonia caused by COVID-19.

Considering the antiviral and anti-inflammatory activity of antroquinonol and known safety profile to date, this study will assess the safety and efficacy of antroquinonol for the treatment of mild to moderate pneumonia due to COVID-19, with the goal to assess suppression of the virus, improvement of symptoms and prevention of disease progression.

1.2. Background

Antroquinonol (Hocena®) is currently being investigated for the treatment of patients with pancreatic cancer, and nonsmall cell lung cancer (NSCLC), under investigational new drug (IND) 133158 and IND 105226, respectively. Preclinical pharmacology and toxicology studies indicated that antroquinonol has a relatively low-toxicity profile, and has shown acceptable tolerability in the clinical trial setting, with no fatal serious adverse drug reactions (ADRs)

reported thus far. Cumulatively, 161 study subjects have been exposed to antroquinonol. Previous research has found antroquinonol to have a high concentration in the lung and have an anti-inflammatory effect. Therefore, Golden Biotechnology Corporation plans to investigate the use of antroquinonol for the treatment of mild to moderate pneumonia due to COVID-19.

1.2.1. Investigational product

Antroquinonol, a novel cyclohexenone compound, is a purified compound from extract of *Antrodia camphorata*. *A. camphorata* is an endemic species in Taiwan, and has been traditionally used for food and drug intoxication, and the treatment of diarrhea, abdominal pain, hypertension, itching of the skin, and liver cancer.[6] Other research has shown *A. camphorata* to have detoxification,[7, 8] anti-inflammatory,[9, 10] immuno-modulatory,[11] liver protection,[12] and anticancer effects.[13, 14, 15, 16, 17, 18]

The mycelium of *A. camphorata* has been marketed as a food supplement by Golden Biotechnology Corporation since 2005. The supplement "*Antrodia camphorata*" has been tested to be safe and approved by Department of Health, Taiwan. The extract of *A. camphorata* has been approved to be marketed by Golden Biotechnology Corporation as health supplement for promoting liver health since 2008. No fatal or severe/serious ADR has been reported by the marketed product of *A. camphorata*.

1.2.2. Nonclinical and preclinical data

For nonclinical data, refer to the investigator's brochure (IB).[5]

1.2.3. Clinical data

Antroquinonol is currently being investigated for the treatment of patients with pancreatic cancer, and nonsmall cell lung cancer (NSCLC), under investigational new drug (IND) 133158 and IND 105226, respectively. Additional investigations for the indications of acute myeloid leukemia, hyperlipidemia, chronic hepatitis B, and atopic dermatitis are underway.

Phase 1 study (Study GOLANTA20090911)

A first-in-human Phase 1 study was performed to determine the maximum tolerated dose and to evaluate pharmacokinetics (PK), safety and tolerability, and efficacy profiles of antroquinonol in NSCLC patients who are refractory to conventional treatment modalities. This open-label, nonrandomized, dose-escalation study enrolled a total of 13 patients, all of whom were Asian. A total of 5 patients were enrolled in an accelerated titration phase (1 patient each in the 50-, 100-, 200-, 300-, and 450-mg dose groups), and 8 patients were enrolled in a standard titration phase (3 patients in the 450-mg dose group and 5 patients in the 600-mg dose group). No dose-limiting toxicities were reported in any patient for any of the doses in the intention-to-treat (ITT) population. Safety results indicated that antroquinonol doses up to 600 mg were generally safe and well tolerated when given daily for 4 weeks.

Under single dose conditions, the maximum antroquinonol concentration was generally observed between 1.00 and 3.70 hours, with the exception of the 200-mg dose group where a median time

to maximum plasma concentration (t_{max}) of 10.00 hours was observed. Under multiple dose conditions, the results were similar, with the median t_{max} ranging from 1.92 to 4.05 hours.

Antroquinonol was rapidly eliminated following single and multiple administrations of antroquinonol with the mean half-life (time between maximum plasma concentration [C_{max}] to half-maximum concentration $C_{1/2}$ [$T_{1/2}$]) ranging from 1.30 to 4.33 hours, independent of the treatment dose. The rate and extent of absorption of antroquinonol increased in a dose-proportional manner over the dosing range of 50 to 600 mg after multiple administrations of antroquinonol. However, under single-dose conditions, the rate and extent of antroquinonol absorption increased in a nondose proportional and a dose-proportional manner, respectively, over the dosing range of 50 to 600 mg. No clear trend was observed when comparing the PK parameters under single dose conditions to those under multiple dose conditions.

Phase 2 study (GHNSCLC-2-001) in NSCLC

A single-arm, open-label, Phase 2 study was conducted to determine the efficacy, safety, and PK of antroquinonol in patients with stage IV (including pleural effusion) NSCLC who had failed 2 lines of anticancer therapy. Thirty-one patients with NSCLC received antroquinonol at 200 mg 3 times daily (TID) (at 8-hour intervals) for 12 weeks with option for extension. A total of 15 patients were Kirsten rat sarcoma viral oncogene homolog (KRAS)-positive and 16 patients were KRAS-negative. After the first 12-week treatment cycle, 5 patients who were progression free received further (12-week) treatment cycles with 200 mg TID antroquinonol (extension phase).

Of the 52 patients screened, 31 patients were enrolled and treated during the Treatment Phase. Overall, 30 (96.8%) patients experienced 268 treatment-emergent adverse events (TEAEs); 28 (90.3%) patients experienced 111 treatment-related TEAEs; 12 (38.7%) patients experienced at least one serious adverse event (SAE).

Average concentrations of antroquinonol in plasma with 200 mg TID antroquinonol treatment were uniformly higher on Day 28 than on Day 1. The mean C_{max} was 276.87 and 393.55 ng/mL for Days 1 and 28, respectively, and the mean area under the plasma concentration versus time curve (AUC) within a dosing interval (AUC_{tau}) was 790.9 and 1224.3 h*ng/mL. The average oral clearance for antroquinonol was higher on Day 1 (254.31 L/h) than on Day 28 (197.82 L/h). The mean values of $T_{1/2}$ on Day 1 and $T_{1/2,eff}$ on Day 28 were 1.617 and 7.643 h, respectively. The mean antroquinonol trough plasma concentration (C_{trough}) were 44.99 and 74.71 ng/mL on Days 1 and 28, respectively. Accumulation of antroquinonol following 28 days of 200 mg TID dosing was estimated to be 1.892-fold.

Phase 2 study (GHLIP-2-001) Hyperlipidemia

A total of 180 subjects were screened and 120 of them were eligible. Of the 120 enrolled subjects, 30 each were randomly assigned to the placebo, antroquinonol 50 mg, antroquinonol 100 mg, and antroquinonol 150 mg groups. One hundred subjects completed the 12-week study treatment period. The main reason of discontinuation was the occurrence of adverse events (AEs) (15 out of 20, 75.0%).

Antroquinonol was generally well tolerated when administered at 50 mg, 100 mg, and 150 mg once daily for 12 weeks. During the study, 55.6% in the antroquinonol group and 46.7% in the placebo group reported at least 1 AE. All AEs, except one, were mild or moderate in severity. The most common AE occurring in the antroquinonol group and placebo group by system organ class (SOC) were gastrointestinal disorders, in which, diarrhoea was the most frequent AE reported in both antroquinonol and placebo groups. The AEs most frequently associated with antroquinonol treatment by preferred terms (PTs) were diarrhoea (32.2%), nausea (6.7%), and vomiting (4.4%). There was an increasing trend in the incidence of diarrhoea as the dose of antroquinonol increased.

Two SAEs were reported in one subject receiving antroquinonol. The SAEs were not related to antroquinonol and did not cause study discontinuation.

There were no clinically meaningful findings in vital signs, physical examination, electrocardiogram (ECG), and laboratory assessments.

Overall, the results of this study showed a positive benefit-risk profile in favor of antroquinonol 100 mg in terms of lipid profile and arterial stiffness. The dosages of antroquinonol were generally well tolerated.

1.3. Benefit-risk Assessment

There remains a significant unmet medical need for treatment options for patients with mild to moderate pneumonia due to COVID-19. Antroquinonol has been observed as a drug with a relatively low-toxicity profile in preclinical pharmacology and toxicology studies and clinical studies. To date, no fatal or severe/serious ADRs have occurred in the clinical studies of antroquinonol. Based on previous studies, antroquinonol has no hepatotoxicity and no cardiac toxicities. Safety of antroquinonol has not been assessed in a patient population hospitalized with mild to moderate pneumonia due to COVID-19. More detailed information about the known and expected benefits and risks and reasonably expected AEs of antroquinonol in other patient populations may be found in the current IB.[5]

The results of PK studies, including absolute bioavailability determination, organ distribution, metabolism related to cytochrome P450 isoform (CYP450), main metabolites in rat urine, and cross-species metabolite comparisons indicated fast absorption, substantial organ distribution (especially in lung, heart, and kidney), and CYP450-involved metabolism profiles of antroquinonol.

No other proven therapeutic options exist for the patient population hospitalized with mild to moderate pneumonia due to COVID-19. If proved effective, use of antroquinonol in mild to moderate pneumonia due to COVID-19 would fulfil an urgent unmet medical need in the context of a global pandemic and a novel coronavirus.

As the design of this study is considered conservative and acceptable, and the study subjects targeted are patients with limited treatment options, the overall benefit/risk assessment supports further investigation of antroquinonol in hospitalized patients with mild to moderate pneumonia due to COVID-19 in a Phase 2 setting.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The **primary objective** 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 (ie, no need for invasive mechanical ventilation, non-invasive ventilation, high-flow oxygen, or extracorporeal membrane oxygenation [ECMO]) on Day 14

The **secondary objectives** are:

- To further evaluate the efficacy of antroquinonol compared with placebo in this patient population as measured by:
- 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 28
- To evaluate the safety of antroquinonol treatment in patients with mild to moderate pneumonia due to COVID-19
- To assess the PK of antroquinonol in a subset of 20 patients (first 10 patients randomized to antroquinonol and first 10 patients to placebo).

The **exploratory objective** 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. Endpoints

The **primary efficacy endpoint** is:

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

The **secondary efficacy endpoints** are:

- Clinical improvement score as measured by the WHO COVID-19 Clinical Improvement Ordinal Scale (Appendix 7), 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 polymerase chain reaction (PCR) testing from nasopharyngeal or mid-turbinate samples on Days 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.

The **exploratory efficacy endpoints** include:

- 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.

The **safety endpoints** include the following variables:

- 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; HEENT (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 computerized tomography [CT] scan) findings

The **PK parameters** to be assessed from plasma samples (sentinel cohort only) are:

- Trough (predose) plasma concentration (C_{trough})
- Maximum plasma concentration (C_{max})
- Time to C_{max} (t_{max})
- 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).

On Day 14, if patients are still hospitalized, a predose and 2-hours postdose sample will be collected.

3. INVESTIGATION PLAN

3.1. Overall study design and plan description

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. As antroquinonol has shown antiviral and anti-inflammatory activity in preclinical studies, it is being planned to use for treatment in patients with COVID-19 infection.

Approximately 15 to 20 sites in the United States, and other countries based on the pandemic situation, are planned to enroll patients.

The main characteristics of hospitalized patients to be included in this study are: adult patients with onset of COVID-19 symptoms within 2 weeks prior to randomization.

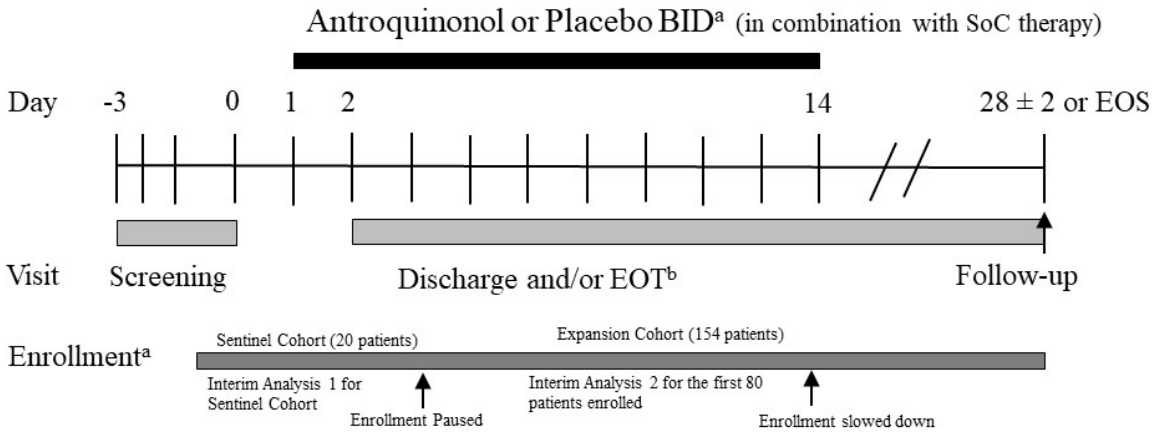
The planned treatment duration is 14 days of administration of antroquinonol or placebo in combination with SoC therapy per local SoC policies. The total study duration is planned to be a maximum of 33 days (screening period up to 3 days, planned study treatment duration up to 14 days, follow-up/End of Study (EOS) assessments up to 28±2 days after start of treatment).

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 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 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 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.

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 (EOT) assessments will be performed at Day 14 (+2 days) (at home or site visit). 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. If the discharge, ET, or Early Withdrawal visit falls within the window of a schedule Day visit, the assessments for the visits can be combined as one visit. The study design is summarized in Figure 1.

Figure 1: Study Design



Abbreviations: BID = twice daily; DMC = Data Monitoring Committee; EOS = end of study; EOT = end of treatment; PK = pharmacokinetics; SoC = standard of care.
[a] Sentinel cohort of 20 patients and an expansion cohort of 154 patients. The sentinel cohort will be treated with 100 mg antroquinonol or placebo BID. Enrollment will pause after the 20th patient in the sentinel cohort has started treatment. Once the 20th patient in the sentinel cohort has completed 14 days of treatment, an unblinded DMC will assess the data for safety, tolerability, efficacy, and PK 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, efficacy, and tolerability data (interim analysis 2). Enrollment may be restricted at the 100th patient until the DMC has completed the assessment to prevent excessive enrollment.
[b] Patients could be discharged after start of 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 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, except for Day 5, Day 14, and Early Termination of Study Treatment. If the discharge, Early Termination, or Early Withdrawal visit falls within the window of a schedule Day visit, the assessments for the visits can be combined as one visit.

3.2. Discussion of study design, including the choice of control groups

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 infection. The rationale for this study is outlined in Section 1.1 and described in detail below.

The study is designed to obtain initial safety, efficacy, tolerability, and PK of antroquinonol in patients in a sentinel cohort. Once the DMC assesses safety, efficacy, tolerability, and PK of a sentinel cohort, patient enrollment will resume. The study will assess the efficacy and safety in all of the patients (174 patients).

Antroquinonol has been studied for NSCLC and pancreatic cancer. Preclinical studies showed that antroquinonol appeared to distribute to the lungs more than any other organ, followed by heart, kidneys, and small intestine (Section 5.2.3 of the IB[5]). Hence, the sponsor has planned use to assess the safety and efficacy of antroquinonol in the COVID-19 patient population.

The variability of individual clinical courses in COVID-19 and the incomplete understanding of this newly recognized disease can seriously affect the reliability of any conclusions based on uncontrolled data. Therefore, per the FDA's recommendation, this is a randomized, placebo-controlled study.

There are safety concerns in this patient population, both because of risks associated with the disease and because of the potential for adverse effects from the treatment that might be difficult to recognize.

In addition, altering the immune response during an acute infection could theoretically have either beneficial or harmful consequences that cannot be precisely predicted. For this reason, the DMC will review safety data in 2 interim analyses, and will continuously monitor for safety until completion.

The safety endpoints in this study are standard. Assessment of AEs, vital signs, complete physical examination, 12-lead ECGs, chest imaging, and safety laboratory tests are planned to be conducted and provide a robust approach to assess the safety of this patient population.

Efficacy endpoints have been chosen to assess virological and clinical parameters to evaluate clinical improvement including measures that maximize objectivity such as, requirement of ICU care, and vital status, and also include the WHO COVID-19 Clinical Improvement Ordinal Scale.

The PK of antroquinonol will be assessed from blood samples taken after the first study drug dose of the day on Day 3 and Day 14 (if patients are still hospitalized), in the sentinel cohort. Although PK has been well characterized in earlier studies, this is an acute patient population which may experience third-spacing and may be hemodynamically unstable. For this reason, intensive serial plasma PK samples (7-8 samples per patient) are being collected on Day 3 from hospitalized patients to characterize the PK of antroquinonol in the COVID-19 patient population. Every effort will be made to have PK samples taken close to the times as other blood sampling for serum to reduce the number of contacts between hospital staff and the patient. The PK samples will not be collected for the expansion cohort.

3.3. End of study definition

The end of the study is defined as the date of the last visit of the last patient in the study.

3.4. Selection of doses in the study

Antroquinonol is already in clinical development, albeit in cancer patients, and shown to be well tolerated. Levels have included oral single doses of 50-600 mg and 200 mg BID (BID use has occurred due to a short plasma half-life of 1.30 to 4.33 hours). For the proposed clinical work, a starting dose of 100mg (given BID due to short half-life) is proposed based around anti-inflammatory activity in mouse efficacy work and the rat no-observed-adverse-effect-level (NOAEL) from toxicology testing. In the former, a 15-50 mg/kg/12.3 body surface factor was calculated to correspond to a 1.22-4.07 mg/kg human equivalent dose, or 85-285 mg for a 70 kg person. Therefore, a dose of 100 mg BID is within the animal efficacy range. The proposed dose is also supported by the rat study NOAEL on a mg/m² basis with an approximate 2-fold safety

margin [NOAEL in rat (30 mg/kg) x 6 (to convert dose in mg/kg to dose in mg/m²) = 180 mg/m² vs human 200 mg daily dose = 2.9 mg/kg x 37 (dose in mg/kg to dose in mg/m²) which converts to 108 mg/m² for a 70 kg person].

The safety of antroquinonol in patients with mild to moderate pneumonia caused by COVID-19 will be confirmed at 100 mg BID in the sentinel and expansion cohorts, which is within the animal efficacy range.

Treatment duration was selected based on the clinical presentation of the disease. Patients with COVID-19 experience systemic symptoms for approximately 7 to 10 days, and patients with disease progression but without ventilator use are typically hospitalized for 5 to 7 days. In a subset of patients, a cytokine storm can emerge resulting in complications. A treatment duration of 14 days should be adequate to treat the infection and prevent the immune response complications.

4. SELECTION OF STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1. Inclusion Criteria

Patients must satisfy all of the following criteria at the screening visit unless otherwise stated:

1. Willing and able to provide informed consent.
2. Male or female patients between 18 and 80 years of age.
3. Oxygen saturation <94% in room air at screening.
4. Hospitalized with mild COVID-19 disease (not requiring oxygen therapy [WHO COVID-19 Clinical Improvement Ordinal Scale, score of 3] or requiring oxygen therapy by mask or nasal prong [WHO COVID-19 Clinical Improvement Ordinal Scale, score of 4]). Requirement of oxygen therapy by mask with reservoir to treat severe COVID-19 pneumonia is not allowed for enrollment.
   Note: Hospitalized patients can also include patients admitted to centers conditioned as hospitals to treat COVID-19 patients.
5. Chest x-ray or CT scan consistent with pneumonia.
6. Onset of COVID-19 symptoms within 2 weeks prior to randomization.
7. SARS-CoV-2 infection confirmed by a PCR test, antigen, or any authorized commercial or public health assay (nasopharyngeal, oropharyngeal, or respiratory samples, not serology testing).
8. Male patients and female patients of childbearing potential must agree to use protocol-specified methods of contraception (Appendix 4).
9. Female patients of childbearing potential must have a negative pregnancy test at screening or pretreatment on Day 1.
10. Male patients must agree not to donate sperm from the first dose through 90 days after the last dose of study treatment; female patients of childbearing potential should refrain from donation of ova from Day 1 until 90 days after the last dose of study treatment.
11. Patient is, in the opinion of the investigator, willing and able to comply with the study treatment regimen and all other study requirements.

4.2. Exclusion Criteria

Patients will be excluded from the study if they satisfy any of the following criteria at the screening visit unless otherwise stated:

1. Female patient is pregnant or breastfeeding.

2. Any patient's concomitant life-threatening condition, including but not limited to: requiring mechanical ventilation, acute respiratory distress syndrome, shock, or cardiac failure.

3. Evidence of multi-lobar consolidation pneumonia or cavities on chest x-ray or CT scan.

4. Severe COVID-19 disease as defined by the WHO COVID-19 Clinical Improvement Ordinal Scale, scores of 5 (non-invasive ventilation or high-flow oxygen), 6 (intubation and mechanical ventilation), or 7 (ventilation + additional organ support-pressors, renal replacement therapy, ECMO).

5. Medical history significant for the following pulmonary diseases: lung cancer, cystic fibrosis, empyema.

6. Respiratory rate >30 respirations per minute.

7. History of abuse of drugs or alcohol that could interfere with adherence to study requirements as judged by the investigator.

8. Treatment 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.

9. Use of *A. camphorata*-containing products within 2 weeks prior to the first administration of study drug.

10. Use of other investigational drugs within 30 days of dosing, or plans to enroll in another clinical trial of an investigational agent while participating in the present study. Note: authorized COVID-19 vaccines are not considered investigational and are not exclusionary.

11. Clinically significant abnormal ECG at screening, as determined by the investigator.

12. Patient requires frequent or prolonged use of systemic corticosteroids (≥20 mg of prednisone/day or equivalent for >4 weeks) or other immunosuppressive drugs (eg, for organ transplantation or autoimmune conditions).

13. Abnormal laboratory values at screening:
    a. Estimated glomerular filtration rate <50 mL/min.
    b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × upper limit of normal (ULN), or ALT/AST >3 × ULN plus total bilirubin >2 × ULN.
    c. Total bilirubin >1.5 × ULN, unless the patient has known Gilbert's syndrome.
    d. Hemoglobin <9 g/dL for females or <11 g/dL for males.

e. Absolute neutrophil count <1,500/mm^3.

f. Thrombocytopenia (platelets count <100 × 10^9/L).

14. Treatment with any antiviral drugs (except remdesivir or other authorized treatments for COVID-19), or with any drugs known to be strong inducers or inhibitors of CYP2C19, CYP3A4, CYP2C8, and CYP2E1 within 14 days or 5 half-lives prior to the start of study treatment. Drugs with a narrow therapeutic index that are substrates of 1A2, 2B6, 2C8, 2C9, 2C19, 3A, and 2D6 are also prohibited.

15. Inability to swallow oral medications or a gastrointestinal disorder with diarrhea (eg, Crohn's disease), malabsorption, or diarrhea of any etiology at baseline.

16. Any other clinically significant medical condition or laboratory abnormality that, in the opinion of the investigator, would jeopardize the safety of the patient or potentially impact patient compliance or the safety/efficacy observations in the study.

4.3. Disease Diagnostic Criteria

Patients with SARS-CoV-2 infection confirmed by a PCR test, antigen, or any authorized commercial or public health assay (nasopharyngeal, oropharyngeal, or respiratory samples, not serology testing) and any symptoms of mild to moderate COVID-19 as defined by the WHO Clinical Improvement Ordinal Scale are required for enrollment (see Section 4.1).

4.4. Discontinuation Criteria

4.4.1. Screen failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

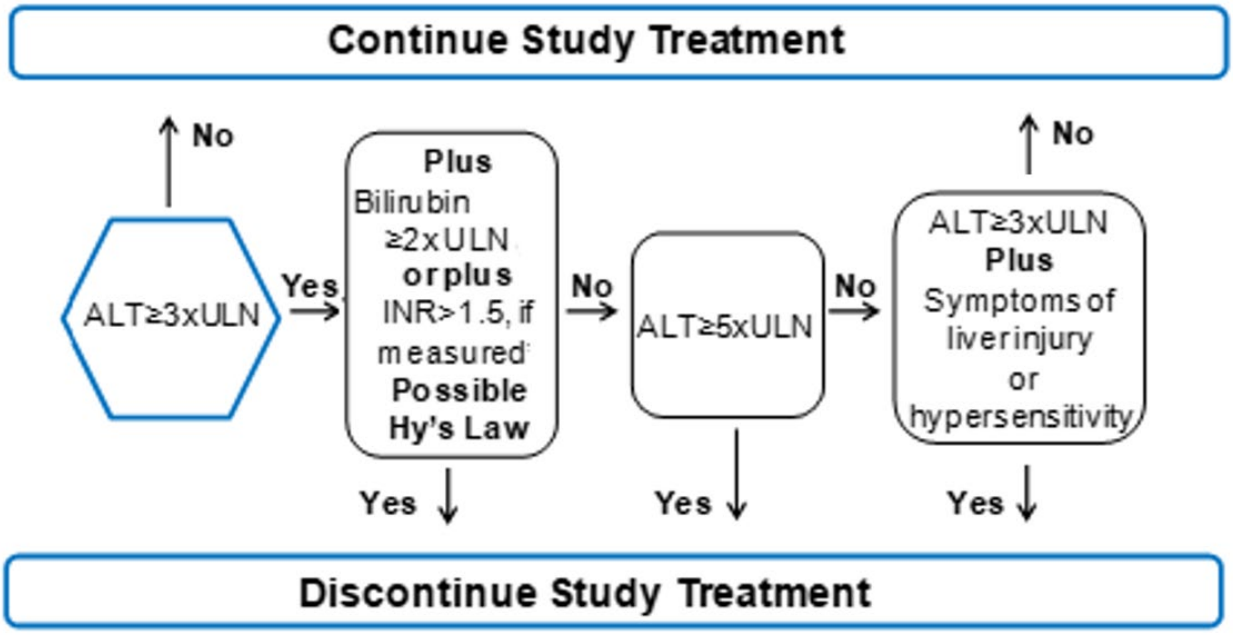
Patients who do not meet the criteria for participation in this study may not be rescreened.

4.4.2. Hepatic injury or renal impairment

4.4.2.1. *Hepatic injury*

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a patient meets one of the conditions outlined in Figure 2 or if the investigator believes that it is in the best interest of the patient.

Figure 2: Stopping Criteria for Liver Injury



Abbreviations: ALT = alanine aminotransferase; INR = international normalized ratio; ULN = upper limit of normal
Note: INR value is not applicable to patients on anticoagulants.

4.4.2.2. *Renal impairment*

If a patient has renal impairment (creatinine clearance <50 mL/min), treatment should be discontinued.

4.4.3. Discontinuation of study treatment

A patient may be discontinued early from study drug treatment (ET of study treatment) for the following reasons:

- Lack of efficacy (e.g. patients who require nonstudy antiviral or anticytokine therapy due to progression of COVID-19), and the investigator's decision. Note: remdesivir or other authorized treatments for COVID-19 is allowed if considered SoC, if started prior to randomization or during the study. Initiation of remdesivir or other authorized treatments for COVID-19 during the study will be considered a treatment failure if started due to progression of disease.
- Adverse event
- Withdrawal by patient (specify reason in the eCRF)
- Lost to follow-up
- Death

- Physician decision (i.e. investigator decision based on protocol deviation, assessment that it is not in the patient's best interest to continue, or other reason [specify reason in the eCRF]).

- Sponsor decision (specify reason in the electronic case report form [eCRF])

No temporary treatment discontinuation is permitted.

Patients who discontinue study treatment prematurely will be asked about the reason(s) for discontinuation and will be asked to continue all assessments up to Day 28. Patients will be educated about the continued scientific importance of their data and encouraged to complete the Day 28 Follow-up/EOS assessments even if they discontinue study treatment prematurely.

4.4.4. Study withdrawal

A patient may be discontinued early from the study for the following reasons:

- Withdrawal by patient (specify reason in the eCRF)

- Lost to follow-up

- Death

- Physician decision (i.e. investigator decision based on protocol deviation, assessment that it is not in the patient's best interest to continue, or other reason [specify reason in the eCRF]).

- Sponsor decision (specify reason in the eCRF)

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. Additionally, patients may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. Refer to the Schedule of Assessments (Appendix 5) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. Patients will be asked to complete Follow-up/EOS evaluations.

4.4.5. Lost to Follow-up

A patient will be considered lost to follow-up if he/she repeatedly is unable to be contacted by the study site after hospital discharge.

The following actions must be taken if a patient repeatedly is unable to be contacted:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule, and ascertain whether or not the patient wishes to and/or should continue in the study.

- In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4.4.6. Replacement procedures

Patients who discontinue from the study will not be replaced.

4.4.7. Follow-up of patients who withdraw from the study

Due to the continued scientific importance of patient data even if study treatment is discontinued early, patients who withdraw from the study will be asked to complete final study procedures (Follow-up/EOS visit), as described in the Schedule of Assessments (Appendix 5). Patients who are no longer hospitalized may complete their assessments by telephone or via telemedicine or other means of remote communication.

All SAEs that are ongoing at the time of discontinuation, or that develop prior to the final Follow-up/EOS visit, will be followed until resolution or stabilization, or up to 30 days following the last dose of study treatment, by Covance Patient Safety Services (PSS) group (Section 7.2.1.2).

Steps will be taken by the sites to ascertain vital status in all randomized patients (eg, with a vital records search) up to Day 28.

4.5. Stopping Rules

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 started treatment. Once the 20th patient in the sentinel cohort has completed 14 days of treatment, the unblinded DMC will assess the safety, efficacy, tolerability, and PK of study medication (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 enrolment. The DMC will continue to review safety and assess the risk/benefit profile on an ongoing basis.

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 or higher on the primary endpoint (proportion of patients who are alive and free of respiratory failure on Day 14) in favor of placebo.

- Interim analysis 2: An odds ratio of 1.2 or higher on the primary endpoint (proportion of patients who are alive and free of respiratory failure on Day 14) in favor of placebo.

Enrollment will pause pending unscheduled DMC review of safety data when any of the following criteria is met:

- ≥ 2 patients experience treatment-related SAE, or

- ≥ 2 patients experience treatment-related severe AEs that are of a similar nature.

Enrollment and dosing may restart following review of relevant safety data by the DMC.

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

4.6. Study Termination

The sponsor reserves the right to close a study site or terminate the study (ET of study) at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed. Reasons for study termination may include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable treatment-emergent safety risk to the patients
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients
- Cancellation of drug development.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of a study site by the sponsor or investigator may include, but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the Institutional Review Board/Ethics Committee or local health authorities, the sponsor's procedures, or Good Clinical Practice guidelines
- Inadequate recruitment of participants by the investigator.

5. STUDY TREATMENTS

5.1. Treatments Administered

Details on the active treatment and placebo provided to patients are summarized in Table 1.

Table 1: Treatment Details

Study Treatment Name:	Antroquinonol (Hocena®)	Placebo
Dosage Formulation:	Antroquinonol in corn oil, encapsulated volume 212 µL, in a gelatin capsule	Corn oil, encapsulated volume 212 µL, in a gelatin capsule
Unit Dose Strength(s)	100 mg	N/A
Dosage Level(s):	One capsule BID (200 mg total daily dose)	One capsule BID
Route of Administration:	Oral	Oral
Dosing Instructions:	To be taken every 12 hours approximately within 15 minutes after a meal or refreshment to reduce gastrointestinal adverse effect	To be taken every 12 hours approximately within 15 minutes after a meal or refreshment for consistency with active treatment
Packaging and Labeling:	Antroquinonol will be provided in a polyethylene bottle. Each bottle will be labeled as required per country regulations.	Placebo will be provided in a polyethylene bottle. Each bottle will be labeled as required per country regulations.
Manufacturer:	Golden Biotechnology Corporation	Golden Biotechnology Corporation

Abbreviations: BID = twice daily.

5.1.1. Antroquinonol

The physicochemical properties and the pharmaceutical specifications of antroquinonol are provided in the IB.[5]

Antroquinonol is supplied by Golden Biotechnology Corporation. Antroquinonol (100 mg in corn oil, encapsulated volume 212 µL) will be filled in #2 gelatin capsules and then packed in a light-protected polyethylene bottle and closed with a piece of polyethylene cap liner fitted in the cap for dispensation at each visit. The study treatment will be labeled in accordance with country-specific requirements.

Beginning on Day 1, patients in the sentinel cohort who are randomized to receive active treatment will receive 1 capsule of study treatment (100 mg antroquinonol) orally BID. Antroquinonol should be taken approximately within 15 minutes after a meal or refreshment to reduce any gastrointestinal adverse effect.

5.1.2. Placebo

Placebo is supplied by Golden Biotechnology Corporation and will be in similar packaging as described for antroquinonol in Section 5.1.1.

Placebo (corn oil, encapsulated volume 212 µL) will be filled in #2 gelatin capsules and then packed in a light-protected polyethylene bottle and closed with a piece of polyethylene cap liner fitted in the cap for dispensation at each visit. The study treatment will be labeled in accordance with country-specific requirements.

Beginning on Day 1, patients who are randomized to receive placebo treatment will receive 1 capsule of placebo orally BID. Placebo capsules should be taken approximately within 15 minutes after a meal or refreshment to reduce any gastrointestinal adverse effect. Dosage of placebo will match dosage of antroquinonol.

5.2. Preparation, storage, handling, and accountability

Antroquinonol and placebo will be supplied by Golden Biotechnology Corporation for final formulation and packaging; along with the batch/lot numbers and Certificates of Analysis. The study treatment will be provided as individual patient kits consisting of 1 bottle with 30 capsules (supply for dosing 1 capsule BID for 14 days, plus 2 extra capsules). The sponsor is responsible for shipping both the treatments to the study site and for implementing strict inventory control for drug accountability. During shipping, antroquinonol will be packaged to maintain a temperature below 27ºC/80.6°F.

The study investigator and/or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment. Drug accountability and inventory (capsule counts) will be recorded in the eCRF and the relevant study log.

All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

Only patients enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in a separate document.

5.3. Method of treatment assignment

All patients will either receive antroquinonol or placebo after randomizing in a 1:1 ratio using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

Randomization will be stratified by remdesivir or other authorized treatments for COVID-19 use at baseline and age at baseline (≤ 65 years vs > 65 years).

Patients confirmed eligible at screening will be assigned a patient identifier prior to the administration of study treatment. The patient identifier will consist of the country number, site number, and patient number. The country number will comprise the first 2 digits, the site number will comprise the next 3 digits, and the patient number will comprise the final 3 digits
eg, 01002003 is Country 1, Site 2, Patient 3.

Study treatment will be dispensed at the Day 1 visit (see Schedule of Assessments, Appendix 5).

5.4. Dose Modification

No modification of study treatment dosage for patient management will be permitted.

5.5. Blinding

This is a double-blind study.

The IWRS will be programmed with blind-breaking instructions. The study blind may be broken if, in the opinion of the investigator, it is in the patient's best interest to know the study treatment assignment. The sponsor and the Contract Research Organization (CRO) must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the patient's condition (eg, antidote is available). In this case, sponsor and the CRO must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

5.6. Treatment Compliance

Records shall be maintained of the delivery of study treatment to the study sites, the inventory at the study sites, the use for each patient, and the return to the sponsor.

These records shall include dates, quantities, batch/lot information, expiry dates, and the unique code numbers assigned to the study treatment and study patients.

The investigator shall be responsible for ensuring that the records adequately document that the patients were provided the doses specified in the protocol and that all study treatment received from the sponsor is reconciled.

Site staff will monitor compliance of patients with their assigned randomized treatment (antroquinonol or placebo) by recording the number of capsules actually used.

Patients will be administered treatment by the site staff during hospitalization. On discharge, all patients are to be reminded of the importance of compliance with the treatment with an emphasis on taking their study treatment on schedule and contacting the study site for an appointment as soon as possible if they think they are experiencing worsening of condition. Compliance

information will be captured via eSource (if a patient version is used) or telemedicine. Patients will return unused supply at the EOT visit.

6. PRIOR AND CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Permitted medications

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment or receives during the study must be recorded in the eCRF along with:

- reason for use
- dates of administration including start and end dates, and
- dosage information including dose and frequency.

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Medications, other than that those listed as prohibited medications and other restrictions, which are considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and must be recorded in the appropriate sections of the eCRF.

6.2. Prohibited medications

Simultaneous participation in other clinical treatment study protocols is not allowed.

Treatment with any antiviral drugs (except remdesivir or other authorized treatments for COVID-19), or with any drugs known to be strong inhibitors or inducers of CYP2C19, 3A4, 2C8, and 2E1 are prohibited within 14 days or 5 half-lives prior to the start of study treatment. Drugs with a narrow therapeutic index that are substrates of 1A2, 2B6, 2C8, 2C9, 2C19, 3A, and 2D6 are also prohibited.

A list of commonly known CYP inducers and inhibitors is given in Appendix 6 for reference use.

Antroquinonol is a purified compound from an extract of *A. camphorata*. For this reason, the use of *A. camphorata*-containing products is prohibited within 2 weeks prior to the first administration of study drug, and the use of *A. camphorata*-containing products other than antroquinonol is prohibited throughout the study.

Patients who begin to receive nonstudy antiviral medication after the start of study treatment will be discontinued from study treatment. Note: remdesivir or other authorized treatments for COVID-19 is allowed if considered SoC, if started prior to randomization or during the study. Initiation of remdesivir or other authorized treatments for COVID-19 during the study will be considered a treatment failure if started due to progression of disease.

Administration of an authorized COVID-19 vaccines is permitted as per the local health authority recommendation.

6.3. Other restrictions and contraindications

Antroquinonol is contraindicated in patients who are hypersensitive to components of this product. Since antroquinonol primarily inhibits CYP3A4, some foods that are known to inhibit, induce, or serve as a substrate of CYP3A4 are potential contraindications to administration and should be avoided. These foods include charbroiled food, star fruit, and grapefruit juice. In addition, cruciferous vegetables should not be consumed within an appropriate time interval of study treatment dosing (at least 30 minutes). Alcohol or drug abuse is prohibited during the study. Social drinking is allowed; however, excessive alcohol use or binge drinking is discouraged during the study. In addition, smoking or vaping use is discouraged at least to Day 14, which is the primary endpoint.

7. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Assessments (Appendix 5). As protocol waivers or exemptions are not allowed, with the exception of immediate safety concerns, deviations should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue the study treatment. Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure (Section 4.4.1), as applicable. Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe defined in the Schedule of Assessments (Appendix 5). Additionally, patients will receive instructions for home administration of study treatment and a diary to capture all doses after a discharge.

Results of the confirmatory COVID-19 test already done as SoC can be used to determine eligibility. The test does not need to be repeated at screening if already confirmed and documented. A confirmatory test may be done at screening if the COVID-19 test is not documented as SoC.

At screening, laboratory tests and ECGs will be performed locally, as applicable, to assess eligibility and do not need to be repeated if already done as SoC (eg, within 24 to 48 hours of screening and patient is clinically stable). Chest x-ray or CT scan will be performed, as applicable, to assess eligibility and does not need to be repeated if done within 48 hours of screening. In addition, baseline central laboratory test samples can be taken after confirming eligibility. Baseline laboratory samples can be obtained at screening or on Day 1 (predose). Postbaseline laboratory samples do not need to be taken predose.

7.1. Efficacy Assessments

Efficacy assessment will be based on the clinical status of the patient during the study.

7.1.1. Primary efficacy endpoint

The primary efficacy endpoint is related to the proportion of patients alive and free of respiratory failure (ie, no need for invasive mechanical ventilation, non-invasive ventilation, high-flow oxygen, or ECMO) on Day 14.

7.1.2. Secondary efficacy endpoints

7.1.2.1. *Clinical improvement*

The WHO COVID-19 Clinical Improvement Ordinal Scale will be used to assess a clinical improvement score on Days 7, 14, and 28. See Appendix 7 for details on the scale.

7.1.2.2. *Duration of hospitalization*

The number of days a patient has been hospitalized prior to study entry will be recorded in the eCRF.

Duration of hospitalization is the total number of days the patient is hospitalized during their participation in the study, up to Day 28.

7.1.2.3. *Virological clearance*

PCR testing for SARS-CoV-2 will be performed at a local or central laboratory at screening. Results of a confirmatory COVID-19 test already done as SoC can be used to determine eligibility. All subsequent tests (Day 1 and later) will be performed by a central laboratory. The PCR testing for SARS-CoV-2 will be collected during hospitalization as noted in the Schedule of Assessments (Appendix 5) and evaluated by the central laboratory.

Virological clearance will be measured by:

- **Time to viral clearance:** This endpoint will measure the time (days) to the first negative test for COVID-19.
- **Rate of change in viral load:** if quantitative PCR results are performed, the level of virus will be measured over time (days).

7.1.2.4. *Vital status*

Patient mortality will be recorded up to Day 28 and summarized in the analysis on Days 7, 14, and 28. Every effort will be made to ascertain vital status in all randomized patients (eg, with a vital records search) up to Day 28.

7.1.2.5. *Duration of ICU stay*

Duration of ICU stay is defined as the total number of days the patient is managed in the ICU during their participation in the study, up to Day 28. The date of the start and stop of the ICU stay must be recorded in the eCRF; no daily assessment is needed.

7.1.2.6. *Respiratory failure free*

The proportion of patients alive and respiratory failure free will be evaluated on Days 7 and 28. Respiratory failure is defined as the 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.

7.1.2.7. *COVID-19 symptoms*

COVID-19 symptoms assessment at the times indicated in the Schedule of Assessments in Appendix 5 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.

7.1.3. Exploratory efficacy endpoints

The exploratory efficacy endpoints include:

- Covariates of 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

The final list of covariates for subgroup analyses are as detailed in the final statistical analysis plan.

New authorized treatments to be analyzed will be identified post hoc and will be collected from the concomitant medications eCRF page.

7.2. Safety Assessments

7.2.1. Adverse events

7.2.1.1. *Definitions*

Adverse event definitions and assignment of severity and causality are detailed in Appendix 1.

Adverse events will be elicited from the patient (or, when appropriate, from a caregiver, surrogate, or the patient's legally authorized representative) by the study site staff using a nonleading question such as "How are you feeling today?" or "Have you had any health concerns since your last visit?"

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the patient to discontinue the study treatment.

Adverse events will be assessed from signing the ICF until 2 weeks after the last dose of study treatment (Day 28 ± 2 days) as noted in the Schedule of Assessments table (Appendix 5). Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 dated 19 April 2020 (exclusively meant for COVID-19) or later.

7.2.1.2. *Reporting serious adverse events*

Serious AE reporting will be carried out as per local/country regulations, and will be described in the Safety Management Plan.

All SAEs occurring after the signing of the ICF until 30 days following last dose of the study treatment and regardless of study treatment relationship, must be reported to Covance within 24 hours of obtaining knowledge of the event. The report should include all available information requested on the SAE form.

Serious AEs - Covance PSS

E-mail: SAEintake@covance.com (standard)

The SAE form will collect data surrounding the event (eg, the nature of the symptom[s], time of onset in relation to initiation of therapy, duration, intensity, and whether or not therapy was discontinued). The investigator's assessment of the probable cause of the event will also be included. In addition, relevant medical history, concomitant medications, laboratory and diagnostic tests reports, and procedures as well as all pertinent medical information related to the event will also be collected.

Covance PSS will forward SAE queries requesting incomplete or missing information directly to the investigator. It is the investigator's responsibility to be diligent in providing this information back to Covance PSS as soon as it is available.

7.2.2. Pregnancy

Female patients of childbearing potential will take a pregnancy test during screening (or pretreatment on Day 1), discharge, ET/EOT, and at the Day 28 Follow-up/EOS visit. Additionally, local/country regulations will be followed as applicable (eg., a pregnancy test one month following the last dose of study treatment in female patients of childbearing potential).

A 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).

Following administration of study treatment, pregnancy cases in any patient who is a female of childbearing potential or female partner of a male patient will be reported if known until the patient completes or withdraws from the study. The pregnancy will be reported immediately by telephone and by faxing a completed pregnancy report to the sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the investigator will follow the patient until completion of the pregnancy and must assess the outcome in the shortest possible time. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

The investigator should notify the sponsor (or designee) of the pregnancy outcome by submitting a follow-up pregnancy report. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (eg, spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the investigator will report the event by telephone and by faxing a completed SAE form to the sponsor (or designee) within 24 hours of knowledge of the event.

7.2.3. Clinical laboratory evaluations

Blood and urine samples will be collected for clinical laboratory evaluations at the times indicated in the Schedule of Assessments in Appendix 5. Clinical laboratory evaluations are listed in Appendix 2. Additional clinical laboratory evaluations will be performed at other times

if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

Serum pregnancy test is to be performed in female patients of child bearing potential at a local (site) laboratory, during screening or Day 1, discharge, and ET/EOT. A 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 (no serum pregnancy test confirmation). Additionally, local/country regulations will be followed as applicable (eg., a pregnancy test one month following the last dose of study treatment in female patients of childbearing potential).

Screening laboratory test will be assessed by a local laboratory, and baseline and postbaseline laboratory tests will be assessed by a central laboratory. If delays in transportation of the samples are encountered, then local safety laboratory samples can be obtained instead for samples that can't be frozen for shipment (e.g. hematology and urine). Baseline laboratory tests can be done once patients eligibility is confirmed The investigator will perform a clinical assessment of all clinical laboratory data.

All screening laboratory results must be available and reviewed before the patient receives the first dose of study treatment on Day 1. After the test results are evaluated, the investigator should judge whether the patient is still eligible to stay in the study. Significant abnormal values occurring during the study will be followed until repeat test results return to normal, stabilize, or are no longer clinically significant.

In this study, clinical laboratory tests will be performed predose on Days 1, 5, and 14 (+2 days).

7.2.4. Vital signs, physical examination, and other safety evaluations

7.2.4.1. *Physical examinations*

Patients will be examined at the times indicated in the Schedule of Assessments in Appendix 5. A complete physical examination including general appearance, HEENT, lymphatic, cardiovascular, respiratory, gastrointestinal, musculoskeletal, neurological, and dermatological systems will be performed at screening.

7.2.4.2. *Vital signs*

Seated blood pressure, seated pulse rate, respiratory rate, and body temperature will be assessed for safety and efficacy endpoints at the times indicated in the Schedule of Assessments in Appendix 5. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range. Patients must be seated for at least 5 minutes before blood pressure and pulse rate measurements. Body temperature will be measured according to site's local practices and may include oral, tympanic, rectal, axillary, or frontal.

Pulse oximetry to measure the peripheral capillary oxygen saturation (SpO_2) will be collected in the eCRF during the study. SpO_2 measurements should be collected at Screening, Day 1, Day 3, Day 5, Day 7, Day 14/EOT or Discharge/ET, and Day 28 visits if patient is in hospital (refer to Appendix 5). For discharged patients, SpO_2 should be collected at Day 5 and Day 14 if visits completed in clinic/hospital. SpO2 may be collected if the visit is conducted at home by a home health service professional, but is not required.

Fraction of inspired oxygen (FiO_2) data will be collected and partial pressure of oxygen (PaO_2) will also be collected if done as standard of care as per Appendix 5.

7.2.4.3. *12-lead Electrocardiogram Parameters*

Single 12-lead ECGs will be recorded after the patient has been supine and at rest for at least 5 minutes at screening and after screening as per Appendix 5. The evaluation items for all ECGs will include heart rate, QRS complex, QT interval, QT interval corrected for heart rate, and RR interval. At screening, the investigator should examine the ECG for signs of cardiac disease that could exclude the patient from the study. An assessment of normal, abnormal and not clinically significant, or abnormal and clinically significant will be performed by the investigator. If the ECG is considered abnormal, the abnormality will be documented on the eCRF.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required.

7.2.4.4. *Chest imaging*

A chest x-ray or CT scan will be performed at the times indicated in the Schedule of Assessments in Appendix 5.

7.3. Pharmacokinetic Assessment

The PK evaluation of antroquinonol in patients in the sentinel cohort includes C_{trough}, C_{max}, t_{max}, $AUC_{0\text{-}1ast}$, and AUC_{tau}.

Blood samples for PK evaluations will be on Day 3 at predose and 1, 2, 3, 4, 6, 8, and 12 hours postdose (after the first study drug dose of the day), for hospitalized patients only. For discharged patients/outpatient visits, the 12-hour sample can be omitted for scheduling purposes.

On Day 14 if patients are still hospitalized, predose and 2 hours postdose samples (after the first study drug dose of the day) will also 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.

The PK samples will not be collected for the expansion cohort.

8. SAMPLE SIZE AND DATA ANALYSES

8.1. Determination of sample size

The decision to include 20 patients in the sentinel cohort was chosen arbitrarily.

The sample size for the expansion group has been determined to provide evidence of proof of concept efficacy should the treatment prove effective. The primary endpoint and futility rules are based on assessments at Day 14 to enable rapid decision making, and the assessment at Day 28 will also be presented as a secondary endpoint.

The detailed assumptions are as follows, and the calculations include the patients from the sentinel cohort that were treated with the same dose used for the expansion cohort:

Alpha	0.2 (one-sided)
Power	80%
Drop-Outs assumed	2%
Endpoint	Odds of patient alive and respiratory failure free by Day 14
Effect Size	78% Placebo 89% Antroquinonol
Futility boundary shape	Manually chosen. Odds Ratio of 3.5 at interim analysis 1 in favor of placebo, and 1.2 at interim analysis 2 in favor of placebo. Equivalent to 4 patients not in respiratory failure on antroquinonol vs 7 on placebo at interim analysis 1, or 26 patients not in respiratory failure on antroquinonol vs 28 on placebo at interim analysis 2. Nonbinding
Efficacy boundary shape	None

In addition, the performance of the study under the following scenarios for the efficacy of antroquinonol were also considered:

Antroquinonol harmful	78% Placebo 67% Antroquinonol
Antroquinonol no effect	78% Placebo 78% Antroquinonol

The nonbinding decision rules of the interim analysis and stopping probabilities under:

			Cumulative Futility Stopping Probability		
Look #	Sample Size	Futility Stopping Boundary Odds Ratio	Drug harmful	No effect	Drug effective
Interim analysis 1	20	3.5	25%	17%	5%
Interim analysis 2	80	1.2	79%	44%	9%
Final	174	0.697			

The decision rules may be modified pending discussion with the DMC, but any modifications will still be considered nonbinding; therefore, no adjustment for the final alpha will be made.

The estimates of the probabilities of response are supported by recently published analysis by Richardson et al [19], which reported 21% mortality of hospitalized patients, and 320 patients requiring ventilation. The authors reported 88.1% mortality for patients requiring ventilation, implying that 282 patients died after receiving ventilation. Since 553 patients died overall, this means that 271 patients died without receiving mechanical ventilation, and therefore 320+271 = 591 patients either died or received mechanical ventilation. This leads to the conclusion that 591/2634 (22.4%) patients, either died or received mechanical ventilation at some point.

It is anticipated that at least 50% of patients will need to benefit from antroquinonol to be considered a clinical breakthrough, hence an improvement from 22% to 11% is considered appropriate for the alternative hypothesis.

8.2. Analysis Populations

The following analysis populations will be included for this study:

Intention-to-treat (ITT): All randomized patients. Patients will be analyzed according to the treatment to which they were randomized.

modified ITT (mITT): All randomized patients who received at least 1 dose of study drug.

Per Protocol Set (PPS): All patients from the ITT set who have no important protocol deviations during the study. Patients with any important protocol deviations shall be excluded from the PPS prior to database lock.

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.

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.

The ITT set will be the primary analysis population for efficacy and the mITT and PPS will be the supportive analysis populations for efficacy analysis. Safety endpoints will be analyzed using the SS. The PKS will be used for PK assessment.

8.3. General Considerations

Continuous variables will be summarized by the standard descriptive statistics: number of patients (n), mean, standard deviation, median, minimum, and maximum. Frequency of patients or events and percentages will be summarized in categorical variables.

Missing values on clinical improvement score 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. For

respiratory failure status, where a patient has died, their status will not be considered missing but will be treated as an observation at each timepoint.

Unless otherwise stated, all regression models will be adjusted for age and remdesivir or other authorized treatments for COVID-19 use at baseline.

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.

Additional information is available in the statistical analysis plan (SAP).

8.4. Efficacy Analysis

The efficacy analysis will be based on the final SAP.

8.4.1. Primary efficacy outcome measures

The proportion of patients from each treatment group who are alive and free of respiratory failure on Day 14 will be compared using logistic regression. The p-value will be based on the Wald test. The primary model will be stratified by remdesivir or other authorized treatments for COVID-19 use at baseline and by age at baseline (> 65 years vs ≤ 65 years).

8.4.2. Secondary efficacy outcome measures

Clinical improvement measured as a score on the WHO COVID-19 Clinical Improvement Ordinal Scale will be analyzed at each timepoint, adjusted for the clinical improvement score at baseline, age at baseline, and remdesivir or other authorized treatments for COVID-19 use at baseline, using an ordinal logistic regression on Days 7, 14, and 28. In addition, descriptive statistics will be provided for average score, and the proportion of patients at or below each score, at each timepoint. 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 time to event outcomes will be estimated by Cox proportional hazard model, with patients censored at the time they are provided any antiviral therapy not prescribed at baseline, or on Day 28 if they have not yet recovered. Patients who die at any time will be considered not yet recovered by Day 28. 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. The p-value for comparison between groups will be obtained based on proportional hazards modeling stratified by the same covariates as the primary model.

Duration of hospitalization and ICU stay up to Day 28 will be analyzed using normal regression, using the same covariates as for the primary endpoint. Patients who die will be considered as continuing to require hospitalization or ICU stay up to Day 28 for the purposes of this analysis.

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. All patients who have died will be considered as not having cleared the virus by Day 28

Rate of change in viral load will be summarized descriptively and estimated using a Mixed Model for Repeated Measurements model. The model will include the treatment group, age, remdesivir or other authorized treatments for COVID-19 use at baseline, visit, and the interaction between visit and the treatment group as fixed factors, and will include the baseline value as a covariate. If a patient has tested negative, they are assumed to be negative until they are tested again.

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

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

COVID-19 symptoms at screening and on Days 7, 14, and 28 will be summarized, and compared using logistic regression following the same method as the primary endpoint.

8.4.3. Exploratory outcome measures

Subgroup analyses will be provided for the parameters of age, sex, and remdesivir or other authorized treatments for COVID-19 use at baseline. Investigation of the interaction between these parameters and the treatment effect 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.

8.5. Safety Analysis

Safety variables include incidence of AEs (or TEAEs), laboratory test results, vital signs, and complete physical examination, ECG, and chest imaging (x-ray or CT scan) findings. All safety analyses will be based on the SS. No formal statistical analysis of the safety data will be performed.

Adverse events will be coded according to MedDRA, version 23.0 dated 19 April 2020 (exclusively meant for COVID-19) or later.

The number and percentage of patients with TEAEs, SAEs, TEAEs related to study treatment, SAEs related to study treatment, TEAEs leading to treatment discontinuation, TEAEs leading to study discontinuation, and TEAEs leading to death will be summarized by SOC, PT, and treatment group. In addition, the severity of TEAEs and relationship to study treatment will be summarized by SOC, PT, and treatment group.

The AE summary tables will include counts of patients. Therefore, if a patient experiences more than 1 episode of a particular AE, the patient will be counted only once for that event. If a patient has more than one AE that is coded to the same PT, the patient will be counted only once for that

PT. Similarly, if a patient has more than 1 AE within an SOC, the patient will be counted only once in that SOC.

Test values and change from baseline will be summarized descriptively for specific laboratory test results, vital signs, complete physical examination results, ECG findings, and chest imaging (x-ray or CT scan) findings. Where applicable, shift tabulations by treatment group will be presented.

Pregnancy test results and patients with confirmed positive pregnancy test result will be listed.

8.6. Pharmacokinetic Analysis

Descriptive statistics will be provided for antroquinonol plasma concentrations at prespecified timepoints and derived PK parameters (listed in Section 7.3).

8.7. 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.

9. REFERENCES

1. Food and Drug Administration. Guidance for Industry, Investigators, and Institutional Review Boards: FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency [Internet]. Food and Drug Administration; 2020. Available at: https://www.fda.gov/media/136238/download.

2. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. Available at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed 31 March 2020.

3. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):P1033-1034. https://doi.org/10.1016/S0140-6736(20)30628-0.

4. Tsai PY, Ka SM, Chang JM, et al. Antroquinonol Differentially Modulates T Cell Activity and Reduces Interleukin-18 Production, but Enhances Nrf2 Activation, in Murine Accelerated Severe Lupus Nephritis. *Arthritis & Rheumatism*. Jan 2012;64(1):232-242. doi 10.1002/art.33328.

5. Golden Biotechnology Corporation. Antroquinonol – Investigator's Brochure. (Version 20200401 01). 01 April 2020.

6. Chen CC, Shiao YJ, Lin RD, et al. Neuroprotective diterpenes from the fruiting body of *Antrodia camphorata*. J Nat Prod. 2006;69(4):689-691.

7. Lee TH, Lee CK, Tsou WL, Liu SY, Kuo MT, Wen WC. A new cytotoxic agent from solid-state fermented mycelium of *Antrodia camphorata*. *Planta Med*. 2007;73(13):1412-1415.

8. Hseu YC, Chang WC, Hseu YT, et al. Protection of oxidative damage by aqueous extract from *Antrodia camphorata* mycelia in normal human erythrocytes. Life Sci. 2002;71(4):469-482.

9. Chang JM, Lee YR, Hung LM, et al. An extract of *Antrodia camphorata* mycelia attenuates the progression of nephritis in systemic lupus erythematosus–Prone NZB/W F1 Mice. *Evid Based Complement Alternat Med*. 2011;2011:465894. doi:10.1093/ecam/nen057.

10. Shen YC, Wang YH, Chou YC, et al. Evaluation of the anti-inflammatory activity of Zhankuic acids isolated from the fruiting bodies of *Antrodia camphorata*. *Planta Med*. 2004;70(4):310-314.

11. Chou CJ, Shen YC, Chang TT, Chen CF. Evaluation of the immuno-modulating activity of some active principles isolated from the fruiting bodies of *Antrodia camphorata*. The 12th International Congress of Oriental Medicine 2003.

12. Song TY, Yen GC. Protective effects of fermented filtrate from *Antrodia camphorata* in submerged culture against CC^{l4}-induced hepatic toxicity in rats. *J Agric Food Chem*. 2003;51(6):1571-1577.

13. Chen KC, Peng CC, Peng RY, et al. Unique Formosan mushroom Antrodia camphorate differentially inhibits androgen-responsive LNCaP and –independent PC-3 prostate cancer cells. *Nutr Cancer*. 2007;57(1):111-121.

14. Peng CC, Chen KC, Peng RY, Chyau CC, Su CH, Hsieh-Li HM. *Antrodia camphorata* extract induces replicative senescence in superficial TCC, and inhibits the absolute migration capability in invasive bladder carcinoma cells. *J Ethnopharmacol*. 2007;109(1):93-103.

15. Yang HL, Chen CS, Chang WH, et al. Growth inhibition and induction of apoptosis in MCF-7 breast cancer cells by *Antrodia camphorata*. *Cancer Lett. 2006;231(2):215-227*.

16. Ao ZH, Xu ZH, Lu HY, Xu XY, Zhang XM, Dou WF. Niuchangchih (*Antrodia camphorata*) and its potential in treating liver diseases. *J Ethnopharmacol*. 2009;121(2):194-212.

17. Chen YS, Pan JH, Chiang BH, Lu FJ, Sheen LY. Ethanolic extracts of Antrodia cinnamomea myceliam fermented at varied times and scales have differential effects on hepatoma cells and normal primary hepatocytes. *J Food Sci*. 2008;73(7):H179-85.

18. Ho CM, Huang CC, Huang CJ, et al. Effects of *Antrodia camphorata* on viability, apoptosis, and [Ca2+]i in PC3 human prostate cancer cells. *Chin J Physiol*. 2008;51(2):78-84.

19. Richardson S, Hirsch JS, Narasimhan M, et al., on behalf of the Northwell COVID-19 Research Consortium. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized with COVID-19 in the New York City Area. *JAMA*. 2020; May 26;323(20):2052-2059. doi: 10.1001/jama.2020.6775.

20. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Draft, 2012.

21. World Health Organization. WHO R&D Blueprint. Novel Coronavirus COVID-19 Therapeutic Trial Synopsis. Draft February 18, 2020. Available at: https://www.who.int/blueprint/priority-diseases/key-action/COVID-19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf

10. APPENDICES

Appendix 1. Adverse Event Definitions

Definitions

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. This includes the following:

- Any clinically significant worsening of a pre-existing condition.
- Any recurrence of a pre-existing condition.
- An AE occurring from overdose of a sponsor study drug whether accidental or intentional (ie, a dose higher than that prescribed by a health care professional for clinical reasons).
- An AE occurring from abuse of a sponsor study drug (ie, use for nonclinical reasons).
- An AE that has been associated with the discontinuation of the use of a sponsor study drug.
- Clinically significant laboratory abnormalities (i.e. the laboratory abnormality is associated with symptoms, requires medical intervention, or requires changes to study drug treatment).

Note: A procedure is not an AE, but the reason for a procedure may be an AE.

A pre-existing condition is a clinical condition (including a condition being treated) that is diagnosed before the patient signs the informed consent form and that is documented as part of the patient's medical history.

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is a treatment-emergent AE. An AE is considered to be treatment-emergent if (1) it is not present when the active phase of the study begins and is not a chronic condition that is part of the patient's medical history, or (2) it is present at the start of the active phase of the study or as part of the patient's medical history, but the severity or frequency increases during the active phase. The active phase of the study begins at the time of the first dose of the study drug. The active phase of the study ends at the Day 28 Follow-up/End of Study (EOS) visit.

Disease-specific signs and symptoms that were ongoing prior to study entry will not be considered AEs unless they worsen (eg, increase in frequency or severity) unexpectedly during the course of the trial.

Reporting of Adverse Events

At each visit the investigator, or delegate, will determine whether or not any AEs have occurred. Nonleading questions such as "How are you feeling today?" or "Have you had any health concerns since your last visit?" should be used to elicit the patient to report any possible AEs. If any AEs have occurred, they will be recorded in the AE section of the electronic case report form (eCRF) and in the patient's source documents. If known, the diagnosis should be recorded, in preference to listing the individual signs and symptoms.

Adverse event reporting begins from the time of informed consent and ends 2 weeks after the last dose of study treatment (Day 28 ± 2 days).

Assessment of Severity

The investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
- **Severe**: Interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The investigator will make a determination of the relationship of the AE to the study drug using a 4-category system according to the following guidelines:

- **Not related**: When the AE is definitely caused by the patient's clinical state, or the study procedure/conditions.
- **Unlikely Related**: When the temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- **Possibly Related**: When the AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the patient's clinical state or the study procedures/conditions.
- **Related**: When the AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, and follows a known or hypothesized cause-effect relationship.
- If causality is assessed as Related or Possibly Related, the event will be considered as related for regulatory reporting purposes.

Action Taken for Adverse Events

The investigator or designee will record the action taken for the AE in the eCRF. Actions taken will include:

- **Dose not changed**: The medication schedule was not changed.
- **Drug withdrawn**: The medication schedule was modified through termination of the prescribed regimen of medication.
- Not applicable
- Unknown.

Follow-up of Adverse Events

All (S)AEs that are ongoing at the time of discontinuation, or that develop prior to the final Follow-up/EOS visit, will be followed for up to 30 days following the last dose of study treatment, or until resolution or stabilization.

Adverse Drug Reactions

All noxious and unintended responses to an investigational medicinal product (IMP; ie, where a causal relationship between an IMP and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions (ADRs).

For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function, is to be considered an ADR.

An unexpected ADR is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, investigator's brochure for an unapproved IMP).

Serious Adverse Events

An SAE is any AE occurring at any dose that meets 1 or more of the following criteria:

- Results in death
- Is life-threatening (see below)
- Requires patient hospitalization or prolongation of an existing hospitalization (see below)
- Results in a persistent or significant disability or incapacity (see below)
- Results in a congenital anomaly or birth defect.

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not require hospitalization, or development of drug dependency or drug abuse.

A ***life-threatening adverse event*** is any AE that places the patient at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though drug-induced hepatitis of a more severe nature can be fatal.

Hospitalization or prolongation of a hospitalization is a criterion for considering an AE to be serious. Hospitalization is to be considered only as an overnight admission. In the absence of an AE, the participating investigator should not report hospitalization or prolongation of hospitalization. This is the case in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol (excluding hospitalization required by the index case). Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.
- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study center (eg, stent removal after surgery). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals fall in the same category.

In addition, a hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE (eg, elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the study).

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions (ie, the AE resulted in a significant, persistent, or permanent change, impairment, damage, or disruption in the patient's bodily function/structure, physical activities, or quality of life).

If there is any doubt as to whether a case constitutes an AE or SAE based on the information available, the case should be treated as an SAE.

Pregnancy

The investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor (or designee) within 24 hours of learning of a patient's pregnancy. The patient will be followed to determine the outcome of the pregnancy.

The investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor (or designee) within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy.

Information on the status of the mother and child will be forwarded to the sponsor (or designee). Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the IMP by the investigator will be reported to the sponsor. While the investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

Events not to be reported as adverse events

A lack of drug effect is not an AE in this study because the purpose of the clinical study is to establish treatment effect.

The following study-specific clinical events related to Coronavirus Disease 2019 (COVID-19) are exempt from AE reporting unless the investigator judges the event to be related to study drug:

- Hypoxemia due to COVID-19 requiring non-invasive ventilation or high flow oxygen;
- Respiratory failure due to COVID-19 requiring invasive mechanical ventilation or extracorporeal membrane oxygenation

Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease under study, unless judged by the investigator to be more severe than expected for the participant's condition.

The disease being studied or expected progression, signs, or symptoms of the disease being studied, unless more severe than expected for the participant's condition.

Appendix 2. Clinical Laboratory Evaluations

The following clinical laboratory analytes will be assessed:

Table 2: Clinical Laboratory Evaluations

Clinical Chemistry:	**Hematology (complete blood count):**
Albumin	Hematocrit
ALP	Hemoglobin
ALT	MCH
AST	MCHC
BUN	MCV
Calcium	Platelet count
Chloride	Red blood cell (RBC) count
Cholesterol	White blood cell (WBC) count
Creatinine	WBC differential
GGT	(% and absolute values):
Glucose	Basophils
eGFR	Eosinophils
LDH	Lymphocytes
Phosphorus	Monocytes
Potassium	Neutrophils
Sodium	
Total Bilirubin	
Total CO_2 (measured as bicarbonate)	**For female patients of child bearing potential:**
Total Protein	Pregnancy test (urine, serum)
Triglycerides	
Uric acid	
Complete Urinalysis:	
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; CO_2 = 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.

Appendix 3. Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable local/country laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/ Ethics Committee (EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.
- Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each patient will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Patients will be instructed that they are free to obtain further information from the investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Patients will be given an opportunity to ask questions about the study prior to providing consent for participation.

Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/EC or study center, where applicable. If using a legally authorized representative, informed consent should be obtained from the patient once he/she has regained the cognitive ability to understand the study. The patient or their legally authorized representative will be given a copy of the signed ICF, and the original will be maintained with the patient's records.

Patients must be reconsented to the most current version of the ICF(s) during their participation in the study.

Patient Data Protection

Patients will be assigned a unique identifier and will not be identified by name in electronic case report forms (eCRFs), study-related forms, study reports, or any related publications. Patient and investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual patients or investigators will be redacted according to applicable laws and regulations.

The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient. The patient must also be informed that his/her medical records may be examined by sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the **s**ponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

Data Monitoring Committee (DMC)

The unblinded DMC will assess the safety, efficacy, tolerability, and pharmacokinetics (PK) of study medication. The DMC will assess data in the sentinel cohort (interim analysis 1) and will issue a recommendation to enroll patients for the expansion cohort, or to stop the study depending on the safety 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 enrolment. The DMC will continue to review safety and assess the risk/benefit profile on an ongoing basis.

The DMC members (independent of the sponsor) will be selected on the basis of relevant experience and understanding of clinical research and the issues specific to the therapeutic area, as well as previous DMC experience.

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

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The investigator (or designee) agrees not to disclose such information in any way without prior written permission from the sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All patient data relating to the study will be recorded on eCRFs unless directly transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Predefined, agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator in accordance with 21 CFR 312.62(c) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Investigator Documentation Responsibilities

All individual, patient-specific study data will be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion. All data generated from external sources (eg, central laboratory, pharmacokinetics, pharmacodynamics, electrocardiogram central readers) and transmitted to the sponsor or designee electronically will be integrated with the patient's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each patient who signs an ICF and undergoes any prescreening or screening procedures, according to the eCRF completion instructions. The sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the investigator reviewed and approved the data on the eCRF, the data queries, and the site notifications.

Publications

If on completion of the study the data warrant publication, the investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement (CSA). Unless otherwise specified in the CSA, the following process shall occur:

The institution and investigator shall not publish or present data from an individual study center until the complete multicenter study has been presented in full or for 2 years after the termination of the multicenter study, whichever occurs first. Subsequent publications must refer to the multicenter findings. Thereafter, if the investigator expects to participate in the publication of data generated from this site, the institution and investigator shall submit reports, abstracts, manuscripts, and/or other presentation materials to the sponsor for review before submission for publication or presentation. The sponsor shall have 60 days to respond with any requested revisions, including (without limitation) the deletion of confidential information. The

investigator shall act in good faith upon requested revisions, except the investigator shall delete any confidential information from such proposed publications. The investigator shall delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

Appendix 4. Contraceptive Guidance

Definitions

Female Patients of Childbearing Potential: Premenopausal female study patients who are anatomically and physiologically capable of becoming pregnant following menarche.

Female Patients of Nonchildbearing Potential:

1. **Surgically sterile:** Female study patients who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the investigator's discretion, prior to screening.
2. **Postmenopausal:** Female study patients at least 45 years of age with amenorrhea for at least 24 months without an alternative medical reason.

Fertile male: A male that is considered fertile after puberty.

Infertile male: Permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Patients

Female patients who are of nonchildbearing potential will not be required to use contraception. Female patients of childbearing potential must be confirmed as not being pregnant at screening or pretreatment on Day 1 and be willing to use an acceptable highly-effective method of birth control from the time of signing the informed consent form (ICF) until 90 days after the last dose of study treatment. 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). Acceptable methods of contraception include:

- hormonal injection (as prescribed)
- combined oral contraceptive pill or progestin/progestogen-only pill (as prescribed)
- combined hormonal patch (as prescribed)
- combined hormonal vaginal ring (as prescribed)
- surgical method performed at least 90 days prior to the screening visit:
    - bilateral tubal ligation
    - Essure® (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- hormonal implant

- hormonal or nonhormonal intrauterine device

- vasectomized male partner (sterilization performed at least 90 days prior to the screening visit) with verbal confirmation of surgical success, and the sole partner for the female patient.

Female patients of childbearing potential should refrain from donation of ova from the first dose through 90 days after the last dose of study treatment.

Male Patients

Male patients (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second highly effective method of acceptable contraception from the first dose through 90 days after the last dose of study treatment. Acceptable methods of contraception for female partners include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring
- surgical method (bilateral tubal ligation or Essure [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or nonhormonal intrauterine device.

An acceptable second method of contraception for male patients is vasectomy that has been performed at least 90 days prior to the screening visit, with verbal confirmation of surgical success.

For male patients (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the first dose until 90 days after the last dose of study treatment. Male patients are required to refrain from donation of sperm from the first dose through 90 days after the last dose of study treatment.

Sexual Abstinence and Same-sex Relationships

Patients who practice true abstinence, because of the patient's lifestyle choice (ie, the patient should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a patient who is abstinent at the time of signing the ICF becomes sexually active, he or she must agree to use contraception as described previously.

For patients who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a patient who is in a same-sex relationship at the time of signing the ICF becomes engaged in a heterosexual relationship, he or she must agree to use contraception as described previously.

Appendix 5. Schedule of Assessments

Table 3: 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 day)**	**7 (+1 day)**	**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
Oxygenation[e]	X	X	X	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

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 day)	7 (+1 day)	14 (+2)	2-28	28 (±2)
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
Pharmacokinetics[j]								
PK parameters[k]			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; FiO_2 = fraction of inspired oxygen; HEENT = head, eyes, ear, nose and throat; ICF = informed consent form; ICU = intensive care unit; PaO_2 = partial pressure of oxygen; 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. Patients will receive instructions for home administration of study treatment and a diary to capture all doses after a discharge.

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 (+/- 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 via telemedicine or other means of remote communication, except for Day 5 (+/- 1 day), Day 14 (+2 days), and Early Termination (ET) of Study Treatment, which would be a home or site visit. If the discharge, ET or Early Withdrawal visit falls within the window of a schedule Day visit, the assessments for the visits can be combined as one 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 will be collected in the eCRF at screening (room air) after screening with vital

signs (Day 1; Day 3, Day 5, Day 7, Day 14/EOT and/or Discharge/ET visits, Day 28 if patient is in hospital). FiO_2 data will be collected the same days as vital signs. PaO_2 will be collected if done as part of the standard of care. Height and body weight will be measured only at screening. After patient is discharged from hospital, SpO_2 should be collected at Day 5 and Day 14 if visits completed in clinic/hospital. Values collected by a home health provider may be utilized, but are not required(refer to Section 7.2.4.2). Body temperature will be measured according to site's local practices and may include oral, tympanic, rectal, axillary, or frontal.

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 screening. 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 (+/-1 day) and Day 14 (+2 days). 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). [4] Patient mortality will be recorded up to Day 28. Every effort will be made to ascertain vital status in all randomized patients (eg, 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 (+/-1 day), then Days 7 (+1 day), 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) and will be performed as applicable at screening, at predose on Day 1, and at Day 5 (+/- 1 day), 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. If delays on transportation of the samples is encountered, then local safety laboratory samples can be obtained instead for samples that can't be frozen for shipment (e.g. hematology and urine). 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 (+/- 1 day), then Days 7 (+1 day), 14 (+2 days), 28 (± 2 days).

j Blood samples 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. Pharmacokinetic parameters include C_{trough}, C_{max}. t_{max}, $AUC_{0\text{-}1ast}$, and $AUC_{tau.}$ 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.

k The PK of antroquinonol will be assessed in the sentinel cohort. The PK samples will not be collected for the expansion cohort.

Appendix 6. Reference List of Known Inducers, Inhibitors, and Substrates of Selected Cytochrome P450 Enzymes

Table 4: Classification of In Vivo Inhibitors of CYP Enzymes

CYP Enzymes	Strong Inhibitors[1] ≥5-fold increase in AUC or >80% decrease in CL	Moderate Inhibitors[2] ≥2-fold but <5-fold increase in AUC or 50% to <80% decrease in CL	Weak Inhibitors[3] ≥1.25-fold but <2-fold increase in AUC or 20% to <50% decrease in CL
CYP1A2	ciprofloxacin enoxacin fluvoxamine	methoxsalen mexiletine oral contraceptives phenylpropanolamine thiabendazole vemurafenib zileuton	acyclovir allopurinol caffeine cimetidine daidzein[4] disulfiram echinacea[4] famotidine norfloxacin propafenone propranolol terbinafine ticlopidine verapamil
CYP2B6	–	–	clopidogrel ticlopidine prasugrel
CYP2C8	gemfibrozil[5]	–	fluvoxamine ketoconazole trimethoprim
CYP2C9	–	amiodarone fluconazole miconazole oxandrolone	capecitabine cotrimoxazole etravirine fluvastatin fluvoxamine metronidazole sulfinpyrazone tigecycline voriconazole zafirlukast
CYP2C19	fluconazole[6] fluvoxamine[7] ticlopidine[8]	esomeprazole fluoxetine moclobemide omeprazole voriconazole	allicin (garlic derivative) armodafinil carbamazepine cimetidine etravirine recombinant human growth hormone (rhGH) felbamate ketoconazole oral contraceptives[9]

CYP Enzymes	Strong Inhibitors[1] ≥5-fold increase in AUC or >80% decrease in CL	Moderate Inhibitors[2] ≥2-fold but <5-fold increase in AUC or 50% to <80% decrease in CL	Weak Inhibitors[3] ≥1.25-fold but <2-fold increase in AUC or 20% to <50% decrease in CL
CYP3A	boceprevir clarithromycin conivaptan grapefruit juice[10] indinavir itraconazole ketoconazole lopinavir/ritonavir mibefradil[11] nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	amprenavir aprepitant atazanavir ciprofloxacin crizotinib darunavir/ritonavir diltiazem erythromycin fluconazole fosamprenavir grapefruit juice[10] imatinib verapamil	alprazolam amiodarone amlodipine atorvastatin bicalutamide cilostazol cimetidine cyclosporine fluoxetine fluvoxamine ginkgo[4] goldenseal[4] isoniazid lapatinib nilotinib oral contraceptives pazopanib ranitidine ranolazine tipranavir/ritonavir ticagrelor zileuton
CYP2D6	bupropion fluoxetine paroxetine quinidine	cinacalcet duloxetine terbinafine	amiodarone celecoxib clobazam cimetidine desvenlafaxine diltiazem diphenhydramine echinacea[4] escitalopram febuxostat gefitinib hydralazine hydroxychloroquine imatinib methadone oral contraceptives pazopanib propafenone ranitidine ritonavir sertraline telithromycin verapamil vemurafenib

CYP Enzymes	Strong Inhibitors[1] ≥5-fold increase in AUC or >80% decrease in CL	Moderate Inhibitors[2] ≥2-fold but <5-fold increase in AUC or 50% to <80% decrease in CL	Weak Inhibitors[3] ≥1.25-fold but <2-fold increase in AUC or 20% to <50% decrease in CL

Abbreviations: AUC = area under the curve; CL = clearance; CYP = cytochrome P450 isoform; OATP1B1 = organic anion transporting polypeptide 1B1; rhGH = recombinant human growth hormone

NOTE: This is not an exhaustive list.

1. A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for that CYP by equal or more than 5-fold.
2. A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.
3. A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 1.25-fold.
4. Herbal product.
5. Gemfibrozil also inhibits OATP1B1.
6. Fluconazole is listed as a strong CYP2C19 inhibitor based on the AUC ratio of omeprazole, which is also metabolized by CYP3A; fluconazole is a moderate CYP3A inhibitor.
7. Fluvoxamine strongly inhibits CYP1A2 and CYP2C19, but also inhibits CYP2C8/2C9 and CYP3A.
8. Ticlopidine strongly inhibits CYP2C19, but also inhibits CYP2B6 and CYP1A2.
9. Effect seems to be due to CYP2C19 inhibition by ethinyl estradiol.
10. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (eg, high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (eg, low dose, single strength).
11. Withdrawn from the United States market.

Source: Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Draft, 2012.

Table 5: Classification of In Vivo Inducers of CYP Enzymes

CYP Enzymes	Strong Inducers ≥80% decrease in AUC	Moderate Inducers 50% to <80% decrease in AUC	Weak Inducers 20% to <50% decrease in AUC
CYP1A2	–	montelukast phenytoin smokers versus nonsmokers[1]	moricizine omeprazole phenobarbital
CYP2B6	–	efavirenz rifampin	nevirapine
CYP2C8	–	rifampin	–
CYP2C9	–	carbamazepine rifampin	aprepitant bosentan phenobarbital St. John's wort[2,3]
CYP2C19	–	rifampin	artemisinin
CYP3A	avasimibe[4] carbamazepine phenytoin rifampin St. John's wort[2,3]	bosentan efavirenz etravirine modafinil nafcillin	amprenavir aprepitant armodafinil clobazamechinacea[3] pioglitazone prednisone rufinamide vemurafenib
CYP2D6	None known	None known	None known

Abbreviations: AUC = area under the curve; CYP = cytochrome P450 isoform.
NOTE: This is not an exhaustive list.

1. For a drug that is a substrate of CYP1A2, the evaluation of the effect of induction of CYP1A2 can be carried out by comparative pharmacokinetic studies in smokers vs. nonsmokers.
2. The effect of St. John's wort varies widely and is preparation-dependent.
3. Herbal product.
4. Not a marketed drug.

Source: Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Draft, 2012.

Table 6: Examples of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range

CYP Enzymes	Sensitive substrates[1]	Substrates with narrow therapeutic range[2]
CYP1A2	alosetrone caffeine duloxetine melatonin ramelteon tacrine tizanidine	theophylline tizanidine
CYP2B6[3]	bupropion efavirenz	–
CYP2C8	repaglinide[4]	paclitaxel
CYP2C9	celecoxib	warfarin phenytoin
CYP2C19	clobazam lansoprazole omeprazole	S-mephenytoin
CYP3A[5]	alfentanil aprepitant budesonide buspirone conivaptan darifenacin darunavir dasatinib dronedarone eletriptan eplerenone everolimus felodipine indinavir fluticasone lopinavir lovastatin lurasidone maraviroc midazolam nisoldipine quetiapine saquinavir sildenafil simvastatin sirolimus tolvaptan tipranavir triazolam	alfentanil astemizole[6] cisapride[6] cyclosporine dihydroergotamine ergotamine fentanyl pimozide quinidine sirolimus tacrolimus terfenadine[6]

CYP Enzymes	Sensitive substrates[1]	Substrates with narrow therapeutic range[2]
	ticagrelor vardenafil	
CYP2D6	atomoxetine desipramine dextromethorphan metoprolol nebivolol perphenazine tolterodine venlafaxine	thioridazine pimozide

Abbreviations: AUC = area under the curve; CYP = cytochrome P450 isoform; OATP1B1 = organic anion transporting polypeptide 1B1; P-gp = P-glycoprotein 1.

NOTE: This is not an exhaustive list.

1. Sensitive CYP substrates refer to drugs with plasma AUC values that have been shown to increase 5-fold or higher when coadministered with a known CYP inhibitor.
2. CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (eg, Torsades de Pointes).
3. The AUC of these substrates were not increased by 5-fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.
4. Repaglinide is also a substrate for OATP1B1, and it is only suitable as a CYP2C8 substrate if the inhibition of OATP1B1 by the investigational drug has been ruled out.
5. Because a number of CYP3A substrates (eg, darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.
6. Withdrawn from the US market.

Source: Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Drug Interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Draft, 2012.

Appendix 7. World Health Organization COVID-19 Clinical Improvement Ordinal Scale

A special World Health Organization committee arrived at an ordinal scale (given in the table below) that measures COVID-19 illness severity over time.

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

Abbreviations: ECMO = extracorporeal membrane oxygenation; RRT = renal replacement therapy.
Source: World Health Organization. WHO R&D Blueprint. Novel Coronavirus COVID-19 Therapeutic Trial Synopsis. Draft February 18, 2020.

Summary of Amended Protocol Changes

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

Protocol Version 4.0 Date: 09 July 2021, Status: Final
Protocol Version 3.1 Date: 29 March 2021
Protocol Version 3.0 Date: 11 March 2021
Protocol Version 2.0 Date: 02 September 2020 (submitted to FDA)
Protocol Version 1.1 Date: 01 June 2020 (submitted to FDA)
Original Protocol Version 1.0 Date: 14 May 2020 (submitted to FDA)

Investigational Product: Antroquinonol (Hocena®)

Protocol Reference Number: GHCovid-2-001
Investigational New Drug: 149841

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Document History

Protocol Version	Date	Reason for version change
Protocol Version 4.0	08 July 2021	This version was updated to address feedback from Data Monitoring Committee (DMC) and Investigators.
Protocol Version 3.1	29 March 2021	This version was updated to clarify and adapt to changes on management of COVID-19.
Protocol Version 3.0	11 March 2021	This version was updated to clarify and adapt to changes on management of COVID-19.
Protocol Version 2.0	02 September 2020	This version was updated based on the 'study may proceed' letter from the Food and Drug Administration (FDA) on Version 1.1, and addressed feedback from DMC and Investigators.
Protocol Version 1.1	01 June 2020	Submitted to the FDA in response to their questions.
Original Protocol Version 1.0	14 May 2020	Submitted to the FDA in response to their questions.

The primary changes in this amendment, along with the rationale for the/each change as appropriate, are:

1. Section 4.1:
    - New inclusion criterion #3: Inclusion requirement of oxygen saturation <94% at room air at screening was added following the DMC recommendation to ensure the "sicker" of the mild/moderate patients can be enrolled.
    - Current inclusion criterion #4 (previous inclusion criterion #3): Based on DMC and Investigator's feedback, this criterion was modified to exclude patients requiring oxygen therapy by mask with reservoir for treatment of severe Covid-19 pneumonia.
2. Section 7.2.3:
    - Edits made to allow samples to be obtained for local laboratories tests in case of delays in transportation of safety samples to the central laboratory.
3. Section 7.2.4.2:
    - Based on site's local practices, collection of non-oral body temperature (i.e., tympanic, rectal, axillary, and frontal) was also included.
    - Peripheral capillary oxygen saturation (SpO_2) assessment was aligned with vital signs assessments. Data of fraction of inspired oxygen (FiO_2) will be collected along with partial pressure of oxygen (PaO_2) (if PaO_2 is done as standard of care).

4. Section 8.2:
    - To be consistent with the statistical analysis plan (SAP), the Intention-to-Treat (ITT) set will be the primary analysis population for efficacy and the modified ITT (mITT) and Per Protocol Set (PPS) will be the supportive analysis populations for efficacy analysis.
5. Appendix 5:
    - Schedule of assessments table and footnote ‘e’ were updated to include data to be captured for oxygenation and their assessments.
    - SpO2 assessment was aligned with vital signs assessments.
    - Schedule of assessments table and footnote ‘i’ was updated to include edits to allow samples to be obtained for local laboratories tests in case of delays in transportation of safety samples to the central laboratory.

Minor changes not displayed in this summary are:

1. The synopsis was updated according to the changes in the protocol body, as applicable.
2. The version number and date were updated throughout the protocol.
3. Editorial, typographical, and formatting errors that did not change the meaning of the text were corrected, as necessary.
4. Abbreviations were added, as appropriate.
5. Due to Brand Transition, name change from ‘Covance’ to ‘LabCorp Drug Development’ was updated on protocol Title page and in the protocol header. No edits in Sections 4.4.7 and 7.2.1.2 where it will remain as ‘Covance’ Patient Safety Services.

A detailed summary of changes, documenting primary changes only, is presented below. Additions are marked by bold/underlined text and deletions are marked by strike-through text.

Section 4.1. Inclusion Criteria

Inclusion requirement of oxygen saturation <94% at room air at screening was added (new inclusion criterion #3) following the recommendations from the DMC to ensure the "sicker" of the mild/moderate patients can be enrolled. Based on DMC and Investigator's feedback, the criterion (current inclusion criterion #4) was modified to exclude patients requiring of oxygen therapy by mask with reservoir for treatment of severe Covid-19 pneumonia.

Previously read:

1. Willing and able to provide informed consent.

2. Male or female patients between 18 and 80 years of age.

3. Hospitalized with mild COVID-19 disease (not requiring oxygen therapy [WHO COVID-19 Clinical Improvement Ordinal Scale, score of 3] or requiring oxygen therapy by mask or nasal prong [WHO COVID-19 Clinical Improvement Ordinal Scale, score of 4]).
   Note: Hospitalized patients can also include patients admitted to centers conditioned as hospitals to treat COVID-19 patients.

4. Chest x-ray or CT scan consistent with pneumonia.

5. Onset of COVID-19 symptoms within 2 weeks prior to randomization.

6. SARS-CoV-2 infection confirmed by a PCR test, antigen, or any authorized commercial or public health assay (nasopharyngeal, oropharyngeal, or respiratory samples, not serology testing).

7. Male patients and female patients of childbearing potential must agree to use protocol-specified methods of contraception (Appendix 4).

8. Female patients of childbearing potential must have a negative pregnancy test at screening or pretreatment on Day 1.

9. Male patients must agree not to donate sperm from the first dose through 90 days after the last dose of study treatment; female patients of childbearing potential should refrain from donation of ova from Day 1 until 90 days after the last dose of study treatment.

10. Patient is, in the opinion of the investigator, willing and able to comply with the study treatment regimen and all other study requirements.

Now reads:

1. Willing and able to provide informed consent.

2. Male or female patients between 18 and 80 years of age.

3. **Oxygen saturation <94% in room air at screening.**

4. Hospitalized with mild COVID-19 disease (not requiring oxygen therapy [WHO COVID-19 Clinical Improvement Ordinal Scale, score of 3] or requiring oxygen therapy by mask or nasal prong [WHO COVID-19 Clinical Improvement Ordinal Scale, score of 4]). **Requirement of oxygen therapy by mask with reservoir to treat severe COVID-19 pneumonia is not allowed for enrollment.**
   Note: Hospitalized patients can also include patients admitted to centers conditioned as hospitals to treat COVID-19 patients.

5. Chest x-ray or CT scan consistent with pneumonia.

6. Onset of COVID-19 symptoms within 2 weeks prior to randomization.

7. SARS-CoV-2 infection confirmed by a PCR test, antigen, or any authorized commercial or public health assay (nasopharyngeal, oropharyngeal, or respiratory samples, not serology testing).

8. Male patients and female patients of childbearing potential must agree to use protocol-specified methods of contraception (Appendix 4).

9. Female patients of childbearing potential must have a negative pregnancy test at screening or pretreatment on Day 1.

10. Male patients must agree not to donate sperm from the first dose through 90 days after the last dose of study treatment; female patients of childbearing potential should refrain from donation of ova from Day 1 until 90 days after the last dose of study treatment.

11. Patient is, in the opinion of the investigator, willing and able to comply with the study treatment regimen and all other study requirements.

Section 7.2.3. Clinical laboratory evaluations

Edits made to allow samples to be obtained for local laboratories tests in case of delays in transportation of safety samples to the central laboratory.

Previously read:

…

Screening laboratory test 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. The investigator will perform a clinical assessment of all clinical laboratory data.

…

Now reads:

…..

Screening laboratory test will be assessed by a local laboratory, and baseline and postbaseline laboratory tests will be assessed by a central laboratory. **If delays in transportation of the samples are encountered, then local safety laboratory samples can be obtained instead for samples that can't be frozen for shipment (e.g. hematology and urine).** Baseline laboratory tests can be done once patients eligibility is confirmed. The investigator will perform a clinical assessment of all clinical laboratory data.

….

Section 7.2.4.2. Vital signs

Based on site's local practices, collection of non-oral body temperature (i.e., tympanic, rectal, axillary, and frontal) was also included. Peripheral capillary oxygen saturation (SpO_2) assessment was aligned with vital signs assessments. Data of fraction of inspired oxygen (FiO_2) will be collected along with partial pressure of oxygen (PaO_2) (if PaO_2 is done as standard of care).

Previously read:

…

All measurements will be performed singly and repeated once if outside the relevant clinical reference range. Patients must be seated for at least 5 minutes before blood pressure and pulse rate measurements. Body temperature will be measured orally.

Pulse oximetry to measure the peripheral capillary oxygen saturation (SpO_2) (>94% on room air) will be collected in the eCRF during the study if done per standard of care.

Now reads:

…..

All measurements will be performed singly and repeated once if outside the relevant clinical reference range. Patients must be seated for at least 5 minutes before blood pressure and pulse rate measurements. Body temperature will be measured **according to site's local practices and may include** oral~~ly~~**, tympanic, rectal, axillary, or frontal**.

Pulse oximetry to measure the peripheral capillary oxygen saturation (SpO_2) ~~(>94% on room air)~~ will be collected in the eCRF during the study ~~if done per standard of care~~. **SpO_2 measurements should be collected at Screening, Day 1, Day 3, Day 5, Day 7, Day 14/EOT or Discharge/ET, and Day 28 visits if patient is in hospital (refer to Appendix 5). For discharged patients, SpO_2 should be collected at the prior mentioned visits if conducted at a clinic/hospital. SpO2 may be collected if the visit is conducted at home by a home health service professional, but is not required.**

Fraction of inspired oxygen (FiO_2) data will be collected and partial pressure of oxygen (PaO_2) will also be collected if done as standard of care as per Appendix 5.

Section 8.2. Analysis Populations

To be consistent with the SAP, the ITT set will be the primary analysis population for efficacy and the mITT and PPS will be the supportive analysis populations for efficacy analysis.

Previously read:

…

The mITT set will be the primary analysis population for efficacy and the ITT and PPS will be the supportive analysis populations for efficacy analysis. …….

Now reads:

….

The ~~m~~ITT set will be the primary analysis population for efficacy and the **m**ITT and PPS will be the supportive analysis populations for efficacy analysis. ……

Appendix 5. Schedule of Assessments

Schedule of assessments table and footnote 'e' were updated to include data to be captured for oxygenation and their assessments. SpO_2 assessment was aligned with vital signs assessments. Schedule of assessments table and footnote 'i' was updated to include edits to allow samples to be obtained for local laboratories tests in case of delays in transportation of safety samples to the central laboratory.

Previously read:

Table 1: 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 day)**	**7 (+1 day)**	**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	

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 day)**	**7 (+1 day)**	**14 (+2)**	**2-28**	**28 (±2)**
[3] Electrocardiogram	X					X	X	
[4] Prior and concomitant medications	X	X	X	X	X	X	X	X
Pharmacokinetics[j]								
PK parameters[k]			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. Patients will receive instructions for home administration of study treatment and a diary to capture all doses after a discharge.

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 (+/- 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 via telemedicine or other means of remote communication, except for Day 5 (+/- 1 day), Day 14 (+2 days), and Early Termination (ET) of Study Treatment, which would be a home or site visit. If the discharge, ET or Early Withdrawal visit falls within the window of a schedule Day visit, the assessments for the visits can be combined as one 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 screening. 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 (+/-1 day) and Day 14 (+2 days). 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). [4] Patient mortality will be recorded up to Day 28. Every effort will be made to ascertain vital status in all randomized patients (eg, 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 (+/-1 day), then Days 7 (+1 day), 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) and will be performed as applicable at screening, at predose on Day 1, and at Day 5 (+/- 1 day), 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 (+/- 1 day), then Days 7 (+1 day), 14 (+2 days), 28 (± 2 days).

j Blood samples 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. Pharmacokinetic parameters include C_{trough}, C_{max}. t_{max}, $AUC_{0\text{-}1ast}$, and $AUC_{tau.}$ 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.

k The PK of antroquinonol will be assessed in the sentinel cohort. The PK samples will not be collected for the expansion cohort.

Now reads:

Table 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 day)**	**7 (+1 day)**	**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
Oxygenation[e]	**X**	**X**	**X**	**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

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 day)	7 (+1 day)	14 (+2)	2-28	28 (±2)
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
Pharmacokinetics[j]								
PK parameters[k]			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; **FiO_2 = fraction of inspired oxygen;** HEENT = head, eyes, ear, nose and throat; ICF = informed consent form; ICU = intensive care unit; **PaO_2 = partial pressure of oxygen;** 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.

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~~standard of care~~ **at screening (room air) after screening with vital signs (Day 1; Day 3, Day 5, Day 7, Day 14/EOT and/or Discharge/ET visits, Day 28 if patient is in hospital). FiO_2 data will be collected the same days as vital signs. PaO_2 will be collected if done as part of the standard of care.** Height and body weight will be measured only at screening. **After patient is discharged from hospital, SpO_2 should be collected at Day 5 and Day 14 if visits completed in clinic/hospital. Values collected by a home health provider may be utilized, but are not required (refer to Section 7.2.4.2). Body temperature will be measured according to site's local practices and may include oral, tympanic, rectal, axillary, or frontal.**

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 screening. Chest x-ray or CT scan is not required post discharge.

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i Safety parameter assessments: [1] AEs will be assessed from signing the ICF (during hospitalization and post discharge at home) daily to Day 5 (+/-1 day), then Days 7 (+1 day), 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) and will be performed as applicable at screening, at predose on Day 1, and at Day 5 (+/- 1 day), 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. **If delays on transportation of the samples is encountered, then local safety laboratory samples can be obtained instead for samples that can't be frozen for shipment (e.g. hematology and urine).** 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 (+/- 1 day), then Days 7 (+1 day), 14 (+2 days), 28 (± 2 days).

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