Clinical Protocol REN-005

The PREVENT Study

A Phase 2, Randomized, Placebo-Controlled Study to Evaluate the Effect of RBT-9 on Progression of COVID-19 Infection in High-Risk Individuals

IND 149226

SPONSOR

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1 STUDY TITLE

A Phase 2, Randomized, Placebo-Controlled Study to Evaluate the Effect of RBT-9 on Progression of COVID-19 Infection in High-Risk Individuals

2 SPONSOR INFORMATION

2.1 Sponsor:

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Medical Monitor
Renibus Therapeutics, Inc.

3 LIST OF ABBREVIATIONS

Abbreviation	Definition
AKI	acute kidney injury
CFR	Code of Federal Regulations
CHF	congestive heart failure
CKD	chronic kidney disease
COVID-19	coronavirus disease 2019
CRO	contract research organization
DSMB	data safety and monitoring board
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture
EOF	end of follow-up
EOS	end of study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HO-1	Heme oxygenase
ICF	informed consent form
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Report
ICU	intensive care unit
IL-10	interleukin-10
IND	investigational new drug
IRB	Institutional Review Board
IWRS	Interactive Web Response System
Nrf2	nuclear factor erythroid 2-related factor 2
NQO1	NAD(P)H dehydrogenase quinone 1
NSP1	nonstructural protein synthesis 1
RRT	renal replacement therapy
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

4 STUDY SYNOPSIS

Renibus Therapeutics, Inc.	**Protocol No. REN-005**
Name of Drug: RBT-9	**Phase of Development:** 2
Name of Active Ingredient: Stannous protoporphyrin (SnPP)	**Date of Study Synopsis:** 15 February 2021
Protocol Title: A Phase 2, Randomized, Placebo-Controlled Study to Evaluate the Effect of RBT-9 on Progression of COVID-19 Infection in High-Risk Individuals	
Investigational Sites: Up to 25 sites in the United States.	
Study Objectives: The overall objective is to evaluate the efficacy, tolerability, and safety of a single dose of RBT-9 versus placebo in coronavirus disease 2019 (COVID-19) infection in non-critically ill adults who are at high risk of progression. **Primary Objective** The primary objective is to evaluate the effect of RBT-9 versus placebo on clinical status as measured using the 8-point World Health Organization (WHO) Ordinal Clinical Scale through Day 28. **Secondary Objectives** The secondary objectives are to evaluate the effect of RBT-9 versus placebo on the following through Day 28: • Time to first occurrence of death from any cause or new/worsened organ dysfunction • All-cause survival • Oxygen saturation (SpO_2)/fraction of inspired oxygen (FiO_2) ratio • Fever incidence • Acute kidney injury (AKI) incidence • New or worsening congestive heart failure (HF) • Hospitalization status • Length of hospital stay • Oxygen-free days • Intensive care unit (ICU) status • Days on ventilator • Time to and duration of vasopressor or inotrope utilization • Ventricular tachycardia or fibrillation lasting at least 30 seconds and/or associated with hemodynamic instability or pulseless electrical activity, or resuscitated cardiac arrest • Dialysis status • Safety parameters **Exploratory Objectives** The exploratory objectives are to evaluate the effect of RBT-9 versus placebo on the following: • Duration of COVID-19 symptoms	
Study Design: This is a Phase 2, randomized, placebo-controlled, multicenter study that will evaluate the efficacy, tolerability, and safety of a single dose of RBT-9 on the progression of COVID-19 infection in non-	

critically ill adults who are at high risk due to age and/or comorbid conditions. Subjects with documented SARS-CoV-2 infection who are at high risk for disease progression, as defined in the inclusion criteria (see Section 9.1), and require observation and/or treatment in a hospital (or controlled facility such as an emergency room, urgent care facility, temporary/modular hospital, infusion center, clinical research unit, etc; hereafter referred to as hospital) will be screened for entry into the study. Eligible subjects will be stratified by time since COVID-19 diagnosis (<48 hours, ≥48 hours) and randomly assigned in a 2:1 ratio to receive a single intravenous infusion of 90 mg RBT-9 or placebo (normal saline). No more than 24 hours can elapse between Screening and RBT-9 Dosing.

All subjects will be assessed through Day 56. All subjects will be assessed on Days 7, 14, 21, and 28, according to the Event Schedule (see Section 5.1). Assessments will include severity of COVID-19 measured by the 8-point WHO Ordinal Clinical Scale, physical examination, vital signs, clinical laboratory evaluations, concomitant medications, and adverse events. For subjects who have been discharged from the hospital, visits on Days 7, 14, and 21 will be conducted virtually (eg, by telephone or video contact). The Day 28 visit should be conducted in person, but may be conducted virtually. Subjects will also be assessed at safety follow-up visits, which will be conducted virtually (eg, by telephone or video contact) on Days 42 and 56.

An independent data and safety monitoring board (DSMB) will actively monitor interim data to make recommendations regarding study conduct/continuation. The DSMB will meet once the first 30 subjects complete the Day 7 assessment to perform the first interim analysis of the safety data. Enrollment of 30 additional subjects will proceed if the safety profile of RBT-9 is deemed acceptable (as determined by the DSMB). Two additional DSMB safety and efficacy (futility) analyses will be performed once 60 and 90 subjects complete the Day 7 evaluation. The last DSMB analysis will assess both safety and efficacy (futility) once 150 subjects complete the Day 28 evaluation; sample size re-estimation will also be performed to allow a sample size increase to 252 subjects based on pre-defined conditional power rules.

Number of Subjects to be Enrolled:

Up to 252 subjects are planned to be enrolled and randomly assigned in a 2:1 ratio to receive RBT-9 or placebo (normal saline).

Inclusion Criteria:

Eligible subjects must meet all of the following criteria:

1. Male or female, ≥18 years of age at Screening.
2. Confirmed infection with SARS-CoV-2.
3. High risk of COVID-19 disease progression, defined as:
   a. 18-69 years of age with lymphopenia AND at least 1 risk factor (described below)
   b. 18-69 years of age without lymphopenia AND at least 2 risk factors (described below)
   c. ≥70 years of age with lymphopenia OR at least 1 risk factor (described below)

   Risk Factors
   - Documented history of coronary artery disease
   - Heart failure (New York Heart Association Class 3 or 4)
   - Chronic lung disease (eg, asthma or chronic obstructive pulmonary disease) requiring treatment
   - Documented history of stroke
   - Diabetes mellitus, requiring at least 1 prescription medicine for management
   - Documented chronic kidney disease with an estimated glomerular filtration rate <30 mL/min, not on dialysis
   - Obesity (Class 2 or 3; body mass index >34.9 kg/m^2)
   - On immunosuppressive therapy
   - Oxygen saturation between 90 and 95% with or without supplemental oxygen
4. Admitted to a hospital for observation and/or treatment.
5. If female, must be postmenopausal, surgically sterile, or if of childbearing potential, must be practicing 2 effective methods of birth control during the study and through 30 days after completion of the study.
6. For females of childbearing potential, a urine pregnancy test must be negative at the Screening Visit.
7. If male, must be surgically sterile or willing to practice 2 effective methods of birth control during the study and through 30 days after completion of the study.

Inclusion Criteria continued:

8. Must be willing and able to give informed consent and comply with all study procedures.

Exclusion Criteria:

Subjects will be ineligible for study participation if they meet any of the following criteria:

1. Anticipated need for ICU care and/or ventilatory support (invasive or non-invasive) within 24 hours.
2. Evidence of acute cardiac injury, as determined by the Investigator at the time of Screening. This may be based upon clinical signs and symptoms, ECG findings, or elevated troponin I levels.
3. Evidence of acute kidney injury not due to pre-renal azotemia or urinary tract obstruction at the time of Screening.
4. Oxygen saturation <90% on supplemental oxygen with a nasal cannula, including high-flow oxygen.
5. Requires non-invasive ventilation at the time of Screening.
6. Requires dialysis at the time of Screening.
7. Has received or is receiving anti-IL-6 therapies (eg, Tocilizumab, Sarilumab, Siltuximab, etc) for the treatment of COVID-19; subjects receiving anti-IL-6 therapies for underlying medical conditions unrelated to COVID-19 are not excluded from eligibility.
8. Pregnant or lactating.
9. History of photosensitivity or active skin disease that, in the opinion of the Investigator, could be worsened by RBT-9.
10. Known hypersensitivity or previous anaphylaxis to RBT-9 (stannous protoporphyrin) or any tin-based product.
11. Treatment with an investigational drug or participation in an interventional trial within 30 days prior to treatment with study drug.
12. Has received COVID-19 vaccination.
13. Has received anti-SARS-CoV-2 antibody therapy.
14. Inability to comply with the requirements of the study protocol.

Drug, Dose and Mode of Administration:

Subjects will be randomly assigned in a 2:1 ratio to receive a single dose of RBT-9 (90 mg) or placebo administered intravenously over a 120-minute period on Day 1.

RBT-9 is supplied as a sterile liquid for intravenous injection at a concentration of 9 mg/mL in 5-mL glass vials that are protected from light. Instructions for dose preparation will be specified in the Pharmacy Manual.

Commercially available 0.9% sodium chloride (normal saline) for injection will be used for placebo administration.

Study Duration:

Study duration is approximately 56 days per subject.

Criteria for Evaluation:

Efficacy and safety assessments include the following:

- Severity of COVID-19 measured by the 8-point WHO Ordinal Clinical Scale (1. Ambulatory [not hospitalized], no limitation of activities; 2. Ambulatory [not hospitalized], limitation of activities; 3. Hospitalized, no oxygen therapy; 4. Hospitalized, oxygen by mask or nasal prongs; 5. Hospitalized, non-invasive ventilation or high-flow oxygen; 6. Hospitalized, intubation and mechanical ventilation; 7. Hospitalized, ventilation plus additional organ support – vasopressors [pressors], renal replacement therapy [RRT], extracorporeal membrane oxygenation [ECMO]; 8. Death)
- Vital signs
- Symptom-directed physical examination
- Clinical laboratory evaluations (clinical chemistry, hematology, and urinalysis)

- Duration of COVID-19 symptoms

Criteria for Evaluation continued:

- Adverse event and concomitant medication use reporting

Statistics:

Efficacy Endpoints

Primary Endpoint: Percentage of subjects in each treatment group in categories 4 through 8 of the 8-point WHO Ordinal Clinical Scale through Day 28.

Secondary Endpoints:

- Time to first occurrence of either death from any cause or new/worsened organ dysfunction through Day 28, defined as at least one of the following:
    - Respiratory decompensation
    - New or worsening congestive heart failure
    - Requirement of vasopressor therapy and/or inotropic or mechanical circulatory support
    - Ventricular tachycardia or fibrillation lasting at least 30 seconds and/or associated with hemodynamic instability or pulseless electrical activity, or resuscitated cardiac arrest
    - Initiation of renal replacement therapy.
- Percentage of subjects who are alive at Day 28.
- Among subjects who begin oxygen therapy, mean change from initiation to last day on oxygen or Day 28 (whichever happens first) in SpO_2/FiO_2 ratio.
- Percentage of subjects with fever through Day 28.
- Percentage of subjects who develop AKI, as determined by the Investigator, through Day 28.
- Percentage of subjects with new or worsening congestive HF through Day 28.
- Percentage of subjects with ventricular tachycardia or fibrillation lasting at least 30 seconds and/or associated with hemodynamic instability or pulseless electrical activity, or resuscitated cardiac arrest through Day 28.
- Percentage of subjects who remain hospitalized at Day 28.
- Length of hospitalization through Day 28.
- Number of oxygen-free days through Day 28.
- Percentage of subjects transferred to the ICU through Day 28.
- Number of days on mechanical ventilation through Day 28.
- Time to and duration of vasopressor or inotrope utilization through Day 28.
- Percentage of subjects who begin dialysis through Day 28.

Exploratory Endpoints:

- Duration of COVID-19 symptoms through Day 56

Analysis Populations: The primary efficacy analysis will be conducted in the Intent-to-Treat population (all randomized subjects) and a secondary efficacy analysis will be conducted in the Per Protocol population

(all randomized subjects who had no major protocol deviations). Safety analyses will be conducted in all subjects receiving any amount of study drug.

Statistics continued:

Efficacy Analysis: The primary efficacy endpoint will be analyzed using a 2-sided Fisher Exact test and a logistic regression model to control for the stratification factor (time since COVID-19 diagnosis); the method of Firth will be used to predict outcomes. A 2-sided Wilcoxon rank sum test will be used to compare the distributions of scores on the 8-point WHO Ordinal Clinical Scale for the 2 treatment groups. Continuous endpoints will be evaluated using a mixed model repeated measures analysis using a compound symmetry error structure. Time to event outcomes (e.g., extubation, hospital discharge, death) will be displayed using a Kaplan-Meier life table and treatment distributions compared using a stratified log-rank test and Cox proportional hazards model to control for time since diagnosis and treatment including the interaction term. A Greenwood test will be performed using the Day 28 estimates from the Kaplan-Meier lifetable.

Safety Analysis: Safety measures including adverse events, clinical laboratory tests, vital signs, physical examinations, and concomitant medication usage will be summarized descriptively by treatment group.

When appropriate, summary statistics will be provided (number of non-missing values, mean, median, standard deviation, minimum, and maximum for continuous variables and number and percentage of patients for categorical variables) by treatment group for all measures, including demographic and baseline assessments, safety, and efficacy endpoints. Baseline for all safety and efficacy endpoints is defined as the last observations before administration of study drug. No imputation will be used for missing data.

Interim Analyses: A group sequential design will be conducted with 4 pre-planned interim analyses after 30, 60, and 90 subjects complete the Day 7 evaluation and 150 subjects complete the Day 28 evaluation. At each interim, the DSMB will evaluate an independently conducted analysis in order to assess safety and futility.

The interim analyses will be subject to adaptations according to Cui; 2-sided 0.1% alpha at the second (n=60) interim and 2-sided 0.2% alpha at each of the third (n=90) and fourth (n=150) interim analyses. Enrollment will be stopped for futility if the conditional power is <10% based on the percentage of subjects classified in categories 4 through 8 on the 8-point WHO Ordinal Clinical Scale for RBT-9 versus placebo. Enrollment will be recommended if futility is observed. Efficacy will be declared if the conditional power is >80% at the fourth interim analysis; the DSMB will advise regarding study continuation.

Sample Size Estimate: The following table summarizes the RBT-9 advantages (15-18%) that can be detected with 84-85% power and 252 subjects for a 2-sided hypothesis test with 5% overall Type 1 error with 2-sided 4.5% Type 1 error remaining at the final analysis; this alpha spend accounts for the preplanned interim analyses.

Two group χ^2 test: Null hypothesis is Equal Failure %s (odds ratio = 1)

	84-85% Power			Two-sided p=0.045		
	1	2	3	1	2	3
Test significance level, α	0.045	0.045	0.045	0.045	0.045	0.045
1 or 2-sided test?	2	2	2	2	2	2
Placebo Failure %, π_1	25%	32%	38%	25%	32%	38%
RBT Failure %, π_2	10%	15%	20%	14.6%	20.4%	25.7%
Odds ratio, $\pi_2(1-\pi_1)/[\pi_1(1-\pi_2)]$	0.333	0.375	0.408	0.513	0.545	0.564
Power (%)	84	85	84	NA	NA	NA
Placebo sample size, n1	84	84	84	84	84	84
RBT sample size, n2	168	168	168	168	168	168
Ratio: n2 / n1	2	2	2	2	2	2
N = n1 + n2	252	252	252	252	252	252

5 EVENT SCHEDULE

5.1 Event Schedule – All Subjects

	Hospitalization			Inpatient or Outpatient Visits†				Safety Follow-up Visits	
Phase	**Screening ***	**Dosing ***	**Post-Dosing**						
Procedure / Timepoint	**Day 0 Pre-Dose**	**Day 0/1 Dose**	**Day 1 Post-Dose**	**Day 7 ± 1**	**Day 14 ± 1**	**Day 21 ± 1**	**Day 28 ± 1/ EOS**	**Day 42 ± 4**	**Day 56 ± 4/ EOF**
Informed Consent Form	X								
Eligibility Criteria	X								
Demographic Data	X								
Medical History [1]	X								
COVID-19 Signs and Symptoms	X		X	X	X	X	X	X [2]	X [2]
COVID-19 Complications			X	X	X	X	X		
Prior/Concomitant Medication	X			X	X	X	X		
Physical Examination	X			X [3]	X [3]	X [3]	X [3]		
Body Mass Index	X								
Vital Signs [4]	X		X	X	X	X	X		
Urine Pregnancy Test [5]	X								
Severity of COVID-19 (Ordinal Clinical Scale) [6]	X		X	X	X	X	X	X	X
Clinical Chemistry [7]	X						X [8]		
Serum Troponin I	X								
Hematology [9]	X						X [8]		
Urinalysis [10]	X						X		
Randomization		X							
Study Drug Administration [11]		X							
Adverse Events			X	X	X	X	X	X [12]	X [12]
Safety Follow-up								X [13]	X [13]

Coronavirus disease 2019 = COVID-19; EOF = end of follow-up; EOS = end of study
Note: Hospital can also refer to controlled facility such as an emergency room, urgent care facility, temporary/modular hospital, infusion center, clinical research unit, etc.

* No more than 24 hours can elapse between screening and dosing with RBT-9.

† Day 7, 14, and 21 will be virtual visits; the Day 28 visit should be in person, but may be conducted virtually.

1 Medical history must include documentation of COVID-19 diagnosis.
2 On Days 42 and 56, COVID-19 symptoms (not signs) will be solicited.
3 Starting on Day 7, physical examination will be symptom-directed visual inspection.
4 Vital signs include assessment of blood pressure, pulse rate, oxygen saturation (SpO_2), fraction of inspired oxygen (FiO_2), and temperature.
5 Pregnancy testing is to be performed in female subjects of childbearing potential.
6 Severity of COVID-19 will be assessed by the 8-point WHO Ordinal Clinical Scale, which includes: 1. Ambulatory (not hospitalized), no limitation of activities; 2. Ambulatory (not hospitalized), limitation of activities; 3. Hospitalized, no oxygen therapy; 4. Hospitalized, oxygen by mask or nasal prongs; 5. Hospitalized, non-invasive ventilation or high-flow oxygen; 6. Hospitalized, intubation and mechanical ventilation; 7. Hospitalized, ventilation plus additional organ support – vasopressors (pressors), renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO); 8. Death. The Ordinal Clinical Scale is the clinical status at the first assessment of a given study day.
7 Parameters include: total protein, albumin, bicarbonate, blood urea nitrogen, serum creatinine, total bilirubin, alkaline phosphatase, glucose, sodium, potassium, phosphorus, calcium, magnesium, gamma-glutamyl transferase, alanine aminotransferase, aspartate aminotransferase, and ferritin.
8 Clinical chemistry and hematology are optional on Day 28.
9 Parameters include: hemoglobin, hematocrit, leukocytes with differential (absolute), and platelets.
10 Parameters include pH, specific gravity, protein, glucose, nitrite, ketones, WBC esterase, and occult blood.
11 Administer study drug after all pre-dose evaluations have been completed.
12 Adverse events that are ongoing on Day 28 will be followed on Day 42; adverse events that are ongoing on Day 42 will be followed on Day 56.
13 Safety follow-up assessment will be conducted virtually by telephone or video contact to determine the following: hospitalization status (hospitalized: yes, no), intubation status (intubated: yes, no), and survival (alive: yes, no).

6 INTRODUCTION

6.1 Background Information

The recently identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the coronavirus disease 2019 (COVID-19) pandemic. SARS-CoV-2 is an enveloped beta coronavirus similar to severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), the coronaviruses responsible for the last 2 epidemics in 2003 and 2012, respectively [Li 2020]. Currently, more than 104 million infections have been reported worldwide and continues to overwhelm health care systems. As of 03 Feb 2021, the United States continues to have more cases of coronavirus (>26.5 million, with >450,000 deaths) than any other country and, as is happening globally, there is a resulting critical shortage of hospital beds, intensive care unit (ICU) beds, and equipment, such as personal protective equipment and ventilators. With continuing spikes in coronavirus cases and mutant strains that are more contagious or cause more severe disease, treatments that can prevent progression of disease severity are paramount.

The median incubation time of COVID-19 is approximately 5 days. Symptoms, including fever, dry cough, dyspnea, myalgia, and fatigue, typically develop within 11.5 days [Lauer 2020]. Within a few days of symptom onset, some patients rapidly progress to respiratory failure requiring mechanical ventilation [Zhou 2020]. Elderly patients and those with medical comorbidities (eg, diabetes, hypertension, underlying cardio-pulmonary disease, immunocompromised state, kidney disease, cancer) are at greater risk of developing severe pneumonia, which can progress to acute respiratory distress syndrome requiring prolonged care in the ICU. These patients also have a higher mortality rate compared to younger patients without comorbid conditions [Zhou 2020].

Patients with COVID-19 may progress to respiratory failure requiring mechanical ventilation. The clinical condition can be further complicated by the development of acute cardiac injury (due to myocarditis or demand ischemia or both), as well as acute kidney injury [Perico 2020]. These data suggest that cardio-renal protective treatments are an important aspect of medical care in patients with COVID-19 and may impact prognosis.

A standardized approach to treating patients with COVID-19 has been proposed based on the 3 grades of severity that correspond with clinical findings, response to therapy, and clinical outcome [Siddiqi 2020]. Stage I is considered to be mild in severity and corresponds to early infection. It is at this stage that viral incubation occurs, with patients experiencing mild, non-specific symptoms, such as fever, malaise, and dry cough. Stage I is the optimal time for treatment with agents that have antiviral activity, enhance viral clearance by the innate immune response, and protect organ function, so that progression of the disease is halted and recovery is undeterred.

Stage II is considered to be moderate in severity and corresponds to pulmonary involvement with or without hypoxia [Siddiqi 2020]. At this stage of severity, patients need to be hospitalized, as viral pneumonia develops and bilateral infiltrates or ground glass opacities are observed in the lungs; increasing lymphopenia is also observed, as

well as transaminitis. Once hypoxia sets in, mechanical ventilation and anti-inflammatory treatment is warranted; antiviral therapy remains a mainstay of treatment.

Stage III is considered to be severe and corresponds to systemic hyperinflammation [Siddiqi 2020]. Cytokine storm is in full effect, and acute respiratory distress syndrome, shock, cardiac failure, and renal failure can manifest. Antiviral therapy should continue, and anti-inflammatory agents should be tailored to prevent multi-organ dysfunction.

6.2 Study Drug

RBT-9 (stannous protoporphyrin) is an agent that preconditions the body to combat insult and injury by eliciting an early stressor response, which subsequently boosts cytoprotective, anti-inflammatory responses that preserve functional and structural organ integrity. In addition to broad organ protection, RBT-9 possesses antiviral activity, which has been demonstrated against several enveloped viruses.

In Phase 1 clinical development conducted by Renibus, Therapeutics, Inc., RBT-9 has been shown to be safe and well tolerated. It was also shown to upregulate the cytoprotective/anti-inflammatory pathways (ie, nuclear factor erythroid 2-related factor 2 [Nrf2], interleukin-10 [IL-10]) that were identified in preclinical studies. RBT-9 is administered as a single dose via intravenous infusion over a 120-minute period. An immediate stressor response is induced, which converts to an antioxidant/anti-inflammatory state within 24 to 48 hours. The antiviral activity of RBT-9, as measured in vitro, has been observed to occur within 24 hours.

The COVID-19 pandemic has now spread to 192 countries and all 50 states in the United States. Treatments that can prevent the progression COVID-19 once a diagnosis has been made (ie, Stage I, early disease) are of critical need. If high-risk patients could be offered early treatment that prevents disease progression and preserves organ function, it would lead to a reduction in ICU admission rates, which may help “flatten the curve” of healthcare utilization.

6.3 Preclinical Experience

Cytoprotective Preconditioning

RBT-9 is a metalloporphyrin, well known for its ability to inhibit the antioxidant enzyme heme oxygenase-1 (HO-1), which protects against oxidative stress, inflammation, and tissue injury. However, RBT-9 is unique among metalloporphyrins in that it is a dual regulator of HO-1. Although RBT-9 initially acts as an HO-1 inhibitor by competitively binding to this enzyme and inhibiting its activity, it also induces HO-1 synthesis [Sardana 1987]. Within 18 hours in mice and 24 to 48 hours in humans, RBT-9 elicits a cytoprotective response that is at least partially mediated by activation of Nrf2, the master transcriptional regulator of the antioxidant response, which controls HO-1 production [Johnson 2017]. The cytoprotective response induced by RBT-9 has been demonstrated in several organs including the kidney, liver, heart, brain, retina, and lung [Johnson 2017; Atef 2017; Dennery 2003; Juncos 2006; Kaizu 2003; Peng 2011; Sutherland 2011; Zager 2015; Zager 2016].

In addition to HO-1, other Nrf2-regulated genes that are upregulated in response to RBT-9 are NAD(P)H dehydrogenase quinone 1 (NQO1), thioredoxin, glutathione transferase, and ferritin [Johnson 2017]. Although ferritin is often associated with an

acute inflammatory response in pathogenic conditions, it is also known to be an anti-inflammatory protein. In particular, heavy chain ferritin has ferroxidase activity, which converts iron from the ferrous state to the ferric form, preventing production of hydroxyl radical formation. RBT-9 has been shown to specifically increase heavy chain ferritin [Johnson 2017]. Additionally, IL-10, a key anti-inflammatory cytokine, is also upregulated by RBT-9 [Zager 2015], while the proinflammatory cytokine tumor necrosis factor alpha is downregulated by RBT-9 [Sutherland 2011]. Thus, the overall protein expression profile that results from RBT-9 treatment is consistent with an antioxidant and anti-inflammatory response.

The dual mechanism of inducing an acute stress response followed by a cytoprotective response makes RBT-9 an effective "preconditioning" agent that renders organs resistant to subsequent ischemic, inflammatory, or toxin-mediated attack.

Organ Protection

Preclinical studies with RBT-9 have shown significant protection in the kidney, heart, and liver [Johnson 2017, Zager 2015, Zager 2016]. Preconditioning with RBT-9 was protective against ischemia/reperfusion injury [Johnson 2017]. This protection also inhibited AKI-mediated progression to chronic kidney disease (CKD). Additionally, in the ischemia/reperfusion model of AKI, animals treated with RBT-9 were protected from cardiac injury as demonstrated by inhibition of AKI-mediated increases in troponin I [Zager 2016]. Effects similar to those found in the kidney are also observed in response to RBT-9 in animals that underwent hepatic ischemia. In these animals, RBT-9 was shown to preserve liver function and structural integrity [Zager 2015].

The effects on organ protection were found to be at least partly mediated through activation of Nrf2, as Nrf2-/- animals treated with RBT-9 were not protected from AKI induced by ischemia/reperfusion [Johnson 2018]. Together, these data indicate that the initial stress response associated with HO-1 inhibition is not the prevailing response to RBT-9 treatment. Rather, it is (at least partly) through activation of the well-known cytoprotective Nrf2 pathway that RBT-9 mediates organ protection.

Antiviral Activity

Natural and synthetic porphyrins are known to have antiviral activity in several enveloped viruses, including influenza, human immunodeficiency virus, hepatitis B virus, hepatitis C virus, Dengue, Yellow Fever, Chikungunya, Zika, Mayaro, Sindbis, and Vesicular Stomatitis viruses [Assuncao-Miranda 2016; Chen-Collins 2003; Guo 2011; Hou 2010; Neris 2018; Staudinger 1996; Vzorov 2002; Wen 2009]. A recent study with Dengue virus demonstrated that RBT-9 reduces viral load in HepG2 hepatocytes and THP-1 macrophages, and similar effects were observed with both Dengue and Yellow Fever viruses in BHK-21 hamster kidney cells [Assuncao-Miranda 2016]. These effects were shown to be independent of HO-1 activity, as treatment with cobalt protoporphyrin, a known inducer of HO-1 activity, also reduced viral load. Importantly, these effects were observed without a loss of host cell viability. Further, the porphyrin ring structure played a critical role in antiviral activity, as biliverdin (a noncyclical, non-iron containing metabolite of heme) did not reduce infectivity of Dengue or Yellow Fever viruses [Assuncao-Miranda 2016]. The RBT-9-mediated decrease in viral load was associated with a reduction in viral adsorption and penetration in host cells, as well as a reduction in

the expression of nonstructural protein synthesis 1 (NSP1) and inhibition of viral protein synthesis and viral RNA replication.

In a separate study, RBT-9 was also shown to be effective at inactivating Chikungunya, Zika, Mayaro, Sindbis, and Vesicular Stomatitis viruses, as demonstrated by inhibition of viral plaque formation [Neris 2018]. Inhibition of adsorption, viral entry, and viral fusion to BHK-1 cells was also observed in response to RBT-9 [Neris 2018]. Further, RBT-9 was found to alter the integrity of the viral envelope, causing a loss of symmetry, viral particle aggregation, and reduced viral envelope content. Despite damaging the viral envelope, RBT-9 preserves viral antigenicity [Neris 2018].

Together, the published data indicate that RBT-9 has broad antiviral activity and does so at the early stages of viral infectivity. The effects of RBT-9 on NSP1 are notable as this protein plays a role early in viral infection. NSP1 is one of the first proteins produced by viruses, regulates viral replication, and is critical for blocking the innate immune response that is responsible for clearance of viral infections [Enjuanes 2016; Narayanan 2015]. In human coronavirus, NSP1 is implicated in disease pathogenesis. It has been shown to suppress the antiviral immune response by inhibiting interferon-gamma, increase viral load by facilitating viral replication, and induce cytokine storm by promoting NFkB activity [Enjuanes 2016; Narayanan 2015].

The importance of NSP1 in viral activity is highlighted by the fact that it is a target for vaccine development in SARS coronavirus. Prevention of full infection by SARS coronavirus is observed when the virus is engineered without NSP1. Importantly, the resulting NSP1 mutant virus remains detectable by the immune system, which means that inhibiting NSP1 serves to both induce viral attenuation while preserving antigenicity [Zust 2007].

Similar to the enveloped viruses discussed above, NSP1 forms part of the viral replicase transcriptase complex in SARS-CoV-2 [Li 2020]. Given the published findings on the preconditioning and antiviral activity of RBT-9 treatment, this agent may be beneficial in the early stages of COVID-19, as it has the potential to: 1) provide broad organ protection, 2) reduce viral load, and 3) prevent cytokine storm that leads to multi-organ failure.

6.4 Clinical Experience

Renibus Therapeutics, Inc., has completed a Phase 1 clinical study (Study REN-003) of RBT-9 in 42 subjects (18 healthy volunteers, 12 subjects with Stage 3 CKD, and 12 subjects with Stage 4 CKD). RBT-9 was administered as a single dose at 9, 27, or 90 mg, and safety was assessed through Day 28. RBT-9 was shown to be safe and well tolerated in healthy volunteers and patients with Stage 3/4 CKD.

RBT-9 was observed to increase endogenous antioxidant activity, as demonstrated by increases in plasma HO-1, NQO1, ferritin, and p21. RBT-9 also increased levels of the anti-inflammatory cytokine IL-10.

All of the adverse events were mild in severity, except for 2 adverse events associated with photosensitivity that were considered moderate in severity. The only adverse event considered possibly related to treatment was photosensitivity, which was transient and

resolved without the need for intervention in most cases. No serious adverse events or deaths occurred in this study.

Given its broad protection of various organs through generation of cytoprotective proteins and direct antiviral effect, treatment with RBT-9 may be beneficial in the early stages of COVID-19 infection in patients at high risk of disease progression by virtue of age and/or comorbid conditions.

7 STUDY OBJECTIVES

The overall objective is to evaluate the efficacy, tolerability, and safety of a single dose of RBT-9 versus placebo on the progression of COVID-19 infection in non-critically ill adults who are at high risk due to age and/or comorbid conditions.

7.1 Primary Objectives

The primary objective is to evaluate the effect of RBT-9 versus placebo on clinical status as measured using the 8-point WHO Ordinal Clinical Scale through Day 28.

7.2 Secondary Objective

The secondary objectives are to evaluate the effect of RBT-9 versus placebo on the following through Day 28:

- Time to first occurrence of death from any cause or new/worsened organ dysfunction
- All-cause survival
- SpO_2/FiO_2 ratio
- Fever incidence
- AKI incidence
- New or worsening CHF
- Hospitalization status
- Length of hospital stay
- Oxygen-free days
- ICU status
- Days on ventilator
- Time to and duration of vasopressor or inotrope utilization
- Ventricular tachycardia or fibrillation lasting at least 30 seconds and/or associated with hemodynamic instability or pulseless electrical activity, or resuscitated cardiac arrest
- Dialysis status
- Safety parameters

7.3 Exploratory Objectives

The exploratory objective in this study is to evaluate the effect of RBT-9 versus placebo on the following:

- Duration of COVID-19 symptoms

8 INFORMED CONSENT

The Investigator or designee will be responsible for obtaining a signed, written informed consent form (ICF) and providing a copy to each subject, legally authorized representative, or a person with legal responsibility for the subject's health care decisions prior to the performance of any clinical activities or procedures pursuant to this protocol. Subjects who are vision impaired may have the ICF read to them and their witnessed consent documented. Only the consent form approved by the Institutional Review Board (IRB) will be used. If English is NOT the subject's primary language, the subject will be consented using an IRB-approved ICF in the requisite language. This consent will be conducted by a member of the research team who is fluent in the language and thus able to answer any scientific or procedural questions raised by a non-English speaking subject.

9 STUDY POPULATION

9.1 Inclusion Criteria

Eligible subjects must meet all of the following criteria:

1. Male or female, ≥18 years of age at Screening.
2. Confirmed infection with SARS-CoV-2.
3. High risk of COVID-19 disease progression, defined as:
   a. 18-69 years of age with lymphopenia AND at least 1 risk factor (described below)
   b. 18-69 years of age without lymphopenia AND at least 2 risk factors (described below)
   c. ≥70 years of age with lymphopenia OR at least 1 risk factor (described below)

   Risk Factors
   - Documented history of coronary artery disease
   - Heart failure (New York Heart Association Class 3 or 4)
   - Documented history of stroke
   - Chronic lung disease (eg, asthma or chronic obstructive pulmonary disease) requiring treatment
   - Diabetes mellitus, requiring at least 1 prescription medicine for management
   - Documented CKD with an estimated glomerular filtration rate <30 mL/min, not on dialysis
   - Obesity (Class 2 or 3; body mass index >34.9 kg/m^2)
   - On immunosuppressive therapy
   - Oxygen saturation between 90 and 95% with or without supplemental oxygen

4. Admitted to a hospital (or controlled facility such as an emergency room, urgent care facility, temporary/modular hospital, infusion center, clinical research unit, etc; hereafter referred to as hospital) for observation and/or treatment
5. If female, must be postmenopausal, surgically sterile, or if of childbearing potential, must be practicing 2 effective methods of birth control during the study and through 30 days after completion of the study.
6. For females of childbearing potential, a urine pregnancy test must be negative at the Screening Visit.
7. If male, must be surgically sterile or willing to practice 2 effective methods of birth control during the study and through 30 days after completion of the study.
8. Must be willing and able to give informed consent and comply with all study procedures.

9.2 Exclusion Criteria

Subjects will be ineligible for study participation if they meet any of the following criteria:

1. Anticipated need for ICU care and/or ventilatory support (invasive or non-invasive) within 24 hours.
2. Evidence of acute cardiac injury, as determined by the Investigator at the time of Screening. This may be based upon clinical signs and symptoms, ECG findings, or elevated troponin I.
3. Evidence of acute kidney injury not due to pre-renal azotemia or urinary tract obstruction at the time of Screening.
4. Oxygen saturation <90% on supplemental oxygen with a nasal cannula, including high-flow oxygen.
5. Requires non-invasive ventilation at the time of Screening.
6. Requires dialysis at the time of Screening.
7. Has received or is receiving anti-IL-6 therapies (eg, Tocilizumab, Sarilumab, Silituximab, etc) for the treatment of COVID-19; subjects receiving anti-IL-6 therapies for underlying medical conditions that are unrelated to COVID-19 are not excluded from eligibility.
8. Pregnant or lactating.
9. History of photosensitivity or active skin disease that, in the opinion of the Investigator, could be worsened by RBT-9.
10. Known hypersensitivity or previous anaphylaxis to RBT-9 (stannous protoporphyrin) or any tin-based product.
11. Treatment with an investigational drug or participation in an interventional trial within 30 days prior to treatment with study drug.
12. Has received COVID-19 vaccination.

13. Has received anti-SARS-CoV-2 antibody therapy.

14. Inability to comply with the requirements of the study protocol.

9.3 Study Design

This is a Phase 2, randomized, placebo-controlled, multicenter study that will evaluate the efficacy, tolerability, and safety of a single dose of RBT-9 on the progression of COVID-19 infection in non-critically ill adults who are at high risk due to age and/or comorbid conditions. Subjects with documented SARS-CoV-2 infection who are at high risk for disease progression, as defined in the inclusion criteria (see Section 9.1), and require observation and/or treatment in a hospital will be screened for entry into the study. Eligible subjects will be stratified by time since COVID-19 diagnosis (<48 hours, ≥48 hours) and randomly assigned in a 2:1 ratio to receive a single intravenous infusion of 90 mg RBT-9 or placebo (normal saline). No more than 24 hours can elapse between Screening and Dosing of RBT-9.

All subjects will be assessed through Day 56. All subjects, regardless of hospitalization status, will be assessed on Days 7, 14, 21, and 28, according to the Event Schedule (see Section 5.1). Assessments will include severity of COVID-19 measured by the 8-point WHO Ordinal Clinical Scale, physical examination, vital signs, clinical laboratory evaluations, concomitant medications, and adverse events. For subjects who have been discharged from the hospital, visits on Days 7, 14, and 21 will be conducted virtually (eg, by telephone or video contact). The Day 28 visit should be conducted in person, but may be conducted virtually, as well. Subjects will also be assessed at safety follow-up visits, which will be conducted virtually (eg, by telephone or video contact) on Days 42 and 56.

An independent data and safety monitoring board (DSMB) will actively monitor interim data to make recommendations regarding study conduct/continuation. The DSMB will meet once the first 30 subjects complete the Day 7 assessment to perform the first interim analysis of the safety data. Enrollment of 30 additional subjects will proceed if the safety profile of RBT-9 is deemed acceptable (as determined by the DSMB). Two additional DSMB interim analyses will be performed once 60 and 90 subjects complete the Day 7 evaluation. The last DSMB interim analysis will be performed once 150 subjects complete the Day 28 evaluation; sample size re-estimation will also be performed to allow a sample size increase to 252 subjects based on pre-defined conditional power rules.

9.3.1 Stopping Rules

For the second, third, and fourth interim analysis, the primary endpoint will be assessed for futility by the DSMB. Enrollment will be stopped if the conditional power is <10% based on the percentage of subjects classified in categories 4 through 8 on the 8-point WHO Ordinal Clinical Scale for RBT-9 versus placebo.

Efficacy will be declared at the fourth interim analysis if the conditional power is >80% (with all subjects followed through Day 28). If efficacy is declared, the DSMB will advise regarding study continuation.

9.4 Recordkeeping and Monitoring

All subject data will be reported in the electronic data capture (EDC) system. All original source documents should be available for periodic monitoring and/or retrieval by a Sponsor representative designee. The Investigator is responsible for the accuracy of all data entered in the electronic case report forms (eCRFs) and for the timely completion of the eCRFs. The supporting documentation will be maintained at the site for a minimum of either:

1. Two (2) years following the approval of RBT-9 for this indication by the Food and Drug Administration (FDA)

or

2. Two (2) years following notification by Sponsor to the FDA of the termination of the entire investigation.

The Sponsor must be contacted and give written authorization prior to any study records being destroyed at investigative sites.

This study will be conducted in compliance with Good Clinical Practice (GCP), which includes the Sponsor- and IRB-approved protocol and ICF and the FDA and International Conference on Harmonisation (ICH) regulatory guidelines and requirements. No changes will be made without prior approval unless it is imperative for subject safety. Any such departures from the protocol will be reported immediately to the Sponsor and relevant IRB.

All subjects' medical records and study-related documents will be made available to the Sponsor for regular monitoring and audits as well as to the IRB and FDA or other governmental agency with oversight or compliance responsibilities for assuring subject rights and welfare.

9.5 Investigational Supplies

Subjects will be randomly assigned in a 2:1 ratio to receive a single dose of open-label RBT-9 (90 mg) or placebo administered intravenously over a 120-minute period on Day 1.

The proposed dose is based on previous human studies with RBT-9 and preclinical pharmacology and toxicology data. The selected dose was determined to be optimal for safely and maximally increasing biomarkers of cytoprotection within 24 to 48 hours, with effects lasting for at least 7 days.

9.5.1 Study Drug Description

The active investigational product is a mixture of RBT-9 (stannous protoporphyrin) in a solution of sodium chloride.

Commercially available 0.9% sodium chloride for injection will be used for placebo administration at study sites.

9.5.2 Packaging

RBT-9 is supplied as a sterile liquid for intravenous injection at a concentration of 9 mg/mL in 5-mL glass vials that are protected from light. Thus, each vial contains 45 mg of RBT-9.

Following receipt of Form FDA 1572 and IRB approval for a given site, RBT-9 will be sent to the study site.

9.5.3 Investigational Product Dispensing

All investigational products will be dispensed by designated and trained site pharmacy staff.

9.5.4 Dosage Preparation and Administration

Instructions for dose preparation will be specified in the Pharmacy Manual. RBT-9 (90 mg; 2 vials) or placebo will be administered as an intravenous infusion over a 120-minute period under the supervision of the Investigator/study staff.

9.5.5 Storage Requirements

RBT-9 should be stored at controlled room temperature conditions (defined as 20 - 25°C/68 - 77°F with excursions of <24 consecutive hours permitted between 15 - 30°C/59 - 86°F) and protected from light.

9.5.6 Investigational Product Accountability

The Investigator or designee is responsible for maintaining accurate records accounting for the receipt, dispensing, and final disposition of all investigational products using the appropriate investigational product logs provided by the Sponsor.

9.5.7 Retrieval and Destruction

Periodically throughout the study, the site will perform investigational product reconciliation on a per-subject basis. The Sponsor's site monitor will review the log and once any discrepancies have been resolved, authorize destruction/disposition of the supplies associated with a given subject by signing the reconciliation log and will witness the destruction/disposition.

9.6 Randomization and Blinding

Each subject will be assigned an identification number by the site after the subject provides written informed consent.

The identification number will consist of a 7-digit number:

- The first 4 digits will designate the site number as assigned by the Sponsor.
- The last 3 digits will designate the order of the subject at that site.

The first subject who signs the ICF at the site is assigned the identification number 001, the second subject who signs the ICF is assigned 002, the third is assigned 003, etc. The subject will maintain the same identification number throughout the entire study. If a subject signs the ICF but does not meet the inclusion/exclusion criteria, the subject will

be marked as a screen fail on the Screening and Enrollment Log provided by the Sponsor and will be entered in the EDC system as a screen failure.

If the subject qualifies for study entry after Screening, the site staff will access the Interactive Response Technology (IRT) system and enter responses regarding the subject's time since COVID-19 diagnosis (<48 hours, ≥48 hours). The system will then provide the subject's open-label treatment assignment (RBT-9 or placebo) according to the randomization code.

9.7 Study Phase

9.7.1 Screening (Within 24 Hours Prior to Dosing)

Study candidates will be evaluated for study entry according to the stated inclusion and exclusion criteria (Sections 9.1 and 9.2, respectively). The following procedures will be performed during Screening to establish each candidate's eligibility for enrollment into the study:

- Obtain signed, written informed consent. The informed consent must be signed before any procedures are performed.
- Record demographic information. The subject should also provide phone/email information for themselves and their closest relative so they can be contacted for virtual visits.
- Record medical history, including documentation of COVID-19 infection.
- Record COVID-19 signs and symptoms.
- Record concomitant medications, including previous treatment with anti-IL-6 therapies or Remdesivir.
- Perform physical examination, including calculation of body mass index.
- Record vital signs (blood pressure, pulse rate, SpO_2, FiO_2, and temperature).
- Obtain urine sample for pregnancy testing for female subjects of childbearing potential.
- Obtain blood samples for clinical chemistry, hematology, and troponin I testing.
- Obtain urine sample for urinalysis.
- Assess the severity of COVID-19 using the 8-point WHO Ordinal Clinical Scale (see Section 9.10.5).

The Investigator will evaluate the results of all examinations, including clinical laboratory tests, and determine each candidate's suitability for the study according to the eligibility criteria.

9.7.2 Day 0/1 (Within 24 Hours of Screening)

Once a candidate is determined to be eligible for the study, the following procedure will be performed.

- Access the IRT system to obtain the subject's randomized treatment assignment (see Section 9.6).

No more than 24 hours can elapse between screening and dosing with RBT-9.

After the subject's randomized treatment is obtained through the IRT system, study drug administration will be performed as follows:

- Study drug will be administered as an infusion over a 120-minute period under the supervision of the Investigator/study staff. The date, rate of infusion, total infusion volume, and start and stop times of dosing will be recorded.

9.7.3 Day 1 (Post-Dose)

- Record COVID-19 signs and symptoms.
- Record COVID-19 complications.
- Record vital signs.
- Record severity of COVID-19.
- Solicit any adverse events.

9.7.4 Visit Days (±1) 7, 14, 21, and 28/EOS

All subjects will be assessed for the procedures listed below. For subjects who have been discharged from the hospital, visits will be conducted virtually (eg, by phone or video contact) on Days (±1) 7, 14, and 21. The visit on Day 28 should be conducted in person, but may be conducted virtually.

- Record COVID-19 signs and symptoms.
- Record COVID-19 complications.
- Record changes in concomitant medication.
- Perform physical examination, which will be symptom-directed visual inspection.
- Record vital signs.
- Assess the severity of COVID-19 using the 8-point WHO Ordinal Clinical Scale (see Section 9.10.5)
- Obtain blood samples for clinical chemistry and hematology testing (Day 28 only).
- Obtain urine sample for urinalysis (Day 28 only).
- Solicit any adverse events.

9.8 Safety Follow-up Visits

9.8.1 Days (±4) 42 and 56/EOF

Subjects will be followed-up by virtual visits (eg, telephone or video contact) on Days (±4) 42 and 56 to determine the following safety parameters:

- Hospitalization status (yes, no)

- Intubation status (yes, no)
- Survival (yes, no)

Responses can be provided by caregivers.

Subjects will also be assessed for COVID-19 symptoms, as well as any adverse events that were ongoing at the previous visit (ie, adverse events ongoing on Day 28 will be followed up on Day 42; adverse events ongoing on Day 42 will be followed up on Day 56).

9.9 Clinical Laboratory Evaluations

All laboratory parameters will be processed at a local laboratory. Each of the laboratory parameters to be evaluated during the study (including clinical chemistry, hematology, and urinalysis) and the corresponding collection times are detailed in the Event Schedule (see Section 5.1). Detailed instructions regarding sample collection and processing are provided in the laboratory manual.

9.10 Clinical Procedures and Observations

Investigators/study staff will regularly monitor subjects throughout study participation.

9.10.1 Medical History

A complete medical history, including documentation of COVID-19 diagnosis, will be obtained at Screening.

9.10.2 Concomitant Medications

All medications being taken concomitantly by the subject at Screening will be recorded. All concomitant medications taken by the subject from Day 1 through Day 28 will be recorded, including the use of antipyretics and vasopressors or inotropes.

9.10.3 Physical Examination

Physical examinations will be performed by the Investigator or designee whose license permits the performing of physical examinations at the timepoints defined in the Event Schedule (see Section 5.1). A physical examination, including calculation of body mass index, should be performed at Screening. Starting on Day 7, physical examination will be symptom-directed visual inspection; the physical exam will be a virtual exam on Days 7, 14, and 21. The physical exam should be conducted in person on Day 28, but may be conducted virtually.

9.10.4 Vital Signs

Vital signs (blood pressure, pulse rate, SpO_2, FiO_2, and body temperature) will be collected throughout the study at the timepoints defined in the Event Schedule (see Section 5.1).

9.10.5 COVID-19 Signs and Symptoms

Signs and symptoms of COVID-19, including any laboratory abnormalities, will be documented at Screening and on Days 7, 14, 21, and 28. Symptoms of COVID-19 will

also be assessed on Days 42 and 56. Any new or worsening of signs/symptoms of COVID-19, including any laboratory abnormalities, should be attributed to COVID-19 and should not be reported as adverse events or serious adverse events.

9.10.6 COVID-19 Complications

Complications of COVID-19, including any laboratory abnormalities, will be documented on Days 7, 14, 21, and 28. Any new or worsening of complications of COVID-19, including associated laboratory abnormalities, should be attributed to COVID-19 and should not be reported as adverse events or serious adverse events.

9.10.7 Severity of COVID-19 (8-Point WHO Ordinal Clinical Scale)

The severity of COVID-19 will be assessed using the following 8-point WHO Ordinal Clinical Scale at the timepoints defined in Section 5.1. The scale measures the clinical status of a subject at the first assessment of a given day.

1) Ambulatory (not hospitalized), no limitation of activities;
2) Ambulatory (not hospitalized), limitation of activities;
3) Hospitalized, no oxygen therapy;
4) Hospitalized, oxygen by mask or nasal prongs;
5) Hospitalized, non-invasive ventilation or high-flow oxygen;
6) Hospitalized, intubation and mechanical ventilation;
7) Hospitalized, ventilation plus additional organ support – vasopressors (pressors), renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO);
8) Death.

10 ADVERSE EVENT REPORTING

All adverse events will be recorded on the designated study eCRF for each subject beginning with the first administration of investigational product and ending with the date of the end of study visit (Day 28). Any unresolved adverse events will be followed by the Investigator until event resolution, the subject is lost to follow-up, or the adverse event is otherwise explained or not considered clinically significant by the Investigator. If the adverse event is ongoing on Day 28, it will be followed until Day 42 (±4). If the adverse event is ongoing on Day 42, it will be followed until Day 56 (±4), at which point it will be considered ongoing if not resolved.

10.1 Investigator Reporting Requirements

The Investigator must immediately report (within 24 hours by telephone and followed by a written report sent by fax or e-mail) all serious adverse events to the Sponsor, regardless of whether the Investigator believes that they are drug related, including those

events listed in the protocol as anticipated to occur in the study population independent of drug exposure (see Section 10.2).

These serious adverse events must be reported to:

Bhupinder Singh, MD, FASN, FNKF, FCRS
Medical Monitor

Renibus Therapeutics, Inc.
181 Grand Ave, Suite 225
Southlake, TX 76092

Phone: (682) 285-1732
Fax: (817) 549-1254
E-mail: SAE@renibus.com

Because the Investigator is knowledgeable about the human subject (eg, medical history, concomitant medications), administers the investigational drug, monitors the subject's response to the drug, is aware of the subject's clinical state and thus may be sensitive to distinctions between events due to an underlying disease process versus events that may be drug-related, and may have observed the event, the Investigator must include an assessment of causality (ie, whether there is a reasonable possibility that the drug caused the event) in the report to the Sponsor. Copies of each report to the Sponsor will be kept in the Investigator's study file.

The Investigator is responsible for complying with their IRB's requirements for reporting serious adverse events. Any expedited safety report (ie, serious unexpected suspected adverse reaction) received from the Sponsor should be submitted to the IRB. Copies of each report and documentation of IRB notification will be kept in the investigator's study file.

The Investigator must record non-serious adverse events in the eCRF and report them to Sponsor according to the timetable for reporting (eg, end of study).

10.2 Adverse Event Definitions

Adverse Event: Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

Adverse Reaction: Adverse reaction means any adverse event definitely caused by the drug.

Suspected Adverse Reaction: Suspected adverse reaction means any adverse event for which there is a "reasonable possibility" (ie, evidence indefinite but suggests a causal relationship between the drug and the adverse event) that the drug caused the adverse event. By definition, a suspected adverse reaction is identical to the definition of adverse drug reaction per ICH E2A.

Examples that would suggest a causal relationship:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (eg, tendon rupture)
- An aggregate analysis of specific events observed in a clinical trial (eg, known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Unexpected Adverse Event or Unexpected Adverse Reaction: An adverse event or adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed.

Adverse events or adverse reactions that are mentioned as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug will be considered "unexpected" if they are not specifically mentioned as occurring with the particular drug under investigation.

Until the Investigator's Brochure is updated to include a new serious suspected adverse reaction, subsequent occurrences of similar serious suspected adverse reactions must be submitted expeditiously to FDA in Investigational New Drug (IND) Safety Reports and to other appropriate regulatory authorities in countries other than the United States in an Individual Case Safety Report (ICRS) or using a Council for International Organizations of Medical Sciences I form, as appropriate.

Serious Adverse Event or Serious Adverse Reaction: An adverse event or adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

If either the Investigator or Sponsor believes that the event is serious, it must be evaluated by the Sponsor for expedited reporting to regulatory authorities.

Life-Threatening Adverse Event or Life-Threatening Adverse Reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or the Sponsor, its occurrence places the subject at immediate risk of death.

Serious Unexpected Suspected Adverse Reaction: An adverse event for which there is a reasonable possibility that the drug caused the adverse event, and it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed, and it results in any of the serious outcomes listed above. This criterion is consistent with the concepts of FDA 21 Code of Federal Regulation (CFR) 312 and the ICH E2A Guideline for expedited safety reports.

The Sponsor must notify the appropriate regulatory authority(ies) and all participating Investigators in an expedited safety report (eg, IND Safety Report or ICRS) of potentially serious risks from clinical trials or any other source (ie, a serious unexpected suspected adverse reaction), as soon as possible, but no later than 15 calendar days after the Sponsor receives the safety information and determines that the information qualifies for reporting.

During the course of drug development, the Sponsor may become aware of new safety information from a variety of sources and will decide if an individual case of a serious and unexpected adverse event meets the criteria for reporting to regulatory authorities.

If the adverse event does not meet all criteria (ie, reasonable possibility of causality, serious and unexpected), it should not be submitted as an expedited safety report.

Any unexpected fatal or life-threatening suspected adverse reaction must be reported to regulatory authorities no later than 7 calendar days after the Sponsor receives the safety information.

10.3 Assessment of Relationship to Study Drug

The following criteria must be used to by the Investigator to characterize the relationship or association of study drug in causing or contributing to the adverse event:

Unrelated: Relationship suggests no association of the event to study drug; the event is related to other etiologies, such as the subject's clinical state or concomitant medications

Unlikely: Relationship suggests an unlikely association of the event to study drug given the subject's current disease state

Possible: Relationship suggests treatment with study drug caused or contributed to the event; the event follows a reasonable temporal sequence from administration of study drug and/or follows a known response pattern to the study drug; the event might have been produced by other factors (eg, the subject's clinical state or other modes of therapy administered to the subject)

Related: Relationship suggests a definite causal relationship to study drug; the event follows a known response pattern to the study drug and cannot be reasonably explained

by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject

10.4 Assessment of Severity

The following criteria must be used by the Investigator to rate the intensity of the adverse event:

Mild: Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities; symptoms do not require therapy or a medical evaluation; signs and symptoms are transient

Moderate: Events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning

Severe: Events interrupt the subject's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

10.5 Breaking the Blind

Not applicable as this is an open-label study.

11 STATISTICAL CONSIDERATIONS

This section outlines the nature and rationale for the statistical methods to be used for the study design and analysis. A separate Statistical Analysis Plan will describe data handling and statistical techniques in full detail.

11.1 Endpoints

The following efficacy endpoints are defined for the study.

Primary Endpoint: Percentage of subjects in each treatment group in categories 4 through 8 of the 8-point WHO Ordinal Clinical Scale through Day 28.

Secondary Endpoints:

- Time to first occurrence of either death from any cause or new/worsened organ dysfunction through Day 28, defined as at least one of the following:
    - Respiratory decompensation
    - New or worsening congestive heart failure
    - Requirement of vasopressor therapy and/or inotropic or mechanical circulatory support
    - Ventricular tachycardia or fibrillation lasting at least 30 seconds and/or associated with hemodynamic instability or pulseless electrical activity, or resuscitated cardiac arrest

  - Initiation of renal replacement therapy.

- Percentage of subjects who are alive at Day 28.
- Among subjects who begin oxygen therapy, mean change from initiation to last day on oxygen or Day 28 (whichever happens first) in SpO_2/FiO_2 ratio.
- Percentage of subjects with fever through Day 28.
- Percentage of subjects who develop AKI, as determined by the Investigator, through Day 28.
- Percentage of subjects with new or worsening congestive HF through Day 28.
- Percentage of subjects with ventricular tachycardia or fibrillation lasting at least 30 seconds and/or associated with hemodynamic instability or pulseless electrical activity, or resuscitated cardiac arrest through Day 28.
- Percentage of subjects who remain hospitalized at Day 28.
- Length of hospitalization through Day 28.
- Number of oxygen-free days through Day 28.
- Percentage of subjects transferred to the ICU through Day 28.
- Number of days on mechanical ventilation through Day 28.
- Time to and duration of vasopressor or inotrope utilization through Day 28.
- Percentage of subjects who begin dialysis through Day 28.

Exploratory Endpoints:

- Duration of COVID-19 symptoms through Day 56

11.2 Study Populations

The primary efficacy analysis will be conducted in the Intent-to-Treat population (all randomized subjects), and a secondary efficacy analysis will be conducted in the Per Protocol population (all randomized subjects who had no major protocol deviations). Safety analyses will be conducted in all subjects receiving any study drug.

11.3 Data Analysis

The primary efficacy endpoint will be mapped to a binary endpoint (% categories 4-8) and then will be analyzed using a two-sided Fisher Exact test and using a logistic regression model to control for the stratification factors; the method of Firth will be used to predict outcomes. A two-sided Wilcoxon rank sum test will be used to compare the primary efficacy endpoint distributions for the two treatment groups. Continuous endpoints will be evaluated using a mixed model repeated measures (MMRM) analysis using a compound symmetry (CS) error structure. Time to event outcomes (eg, extubation, WHO progression, death) will be displayed using a Kaplan-Meier (KM) lifetable and treatment distributions compared using a stratified log-rank test and Cox proportional hazards model to control for time since COVID-19 diagnosis.

When appropriate, summary statistics will be provided (number of non-missing values, mean, median, standard deviation, minimum, and maximum for continuous variables and number and percentage of patients for categorical variables) by treatment group for all measures, including demographic and baseline assessments, safety, and efficacy endpoints. Baseline for all safety and efficacy endpoints is defined as the last observations before administration of study drug. No imputation will be used for missing data.

11.4 Analysis of Efficacy Endpoints

The primary efficacy endpoint will be analyzed using a 2-sided Fisher Exact test and a logistic regression model to control for the stratification factors; the method of Firth will be used to predict outcomes. A 2-sided Wilcoxon rank sum test will be used to compare the distributions of scores on the 8-point WHO Ordinal Clinical Scale for the 2 treatment groups. Continuous endpoints will be evaluated using a mixed model repeated measures analysis using a compound symmetry error structure. Time to event outcomes (eg, extubation, hospital discharge, death) will be displayed using a Kaplan-Meier life table and treatment distributions compared using a stratified log-rank test and Cox proportional hazards model to control for time since diagnosis and treatment including then interaction term. A Greenwood test will be performed using the Day 28 estimates from the Kaplan-Meier lifetable.

11.5 Analysis of Safety Endpoints

Safety measures including adverse events, clinical laboratory tests, vital signs, and concomitant medication usage will be summarized descriptively by treatment group.

The principle of treatment emergence will be employed for the analysis of adverse event data. A treatment-emergent adverse event is defined to be any event that occurs during the observation period of the study and was not present at baseline, or exacerbation of a condition present at baseline.

Treatment-emergent adverse events will be classified by the Medical Dictionary for Regulatory Activities. The type, incidence, timing (onset, duration), relationship, and severity will be reported for all adverse events. Reasons for withdrawal due to adverse events will also be reported.

11.6 Sample Size Calculations

The following table summarizes the RBT-9 advantages (15-18%) that can be detected with 84-85% power and 252 subjects for a 2-sided hypothesis test with 5% overall Type 1 error with 2-sided 4.5% Type 1 error remaining at the final analysis; this alpha spend accounts for the preplanned interim analyses.

Two group χ^2 test: Null hypothesis is Equal Failure %s (odds ratio = 1)

	84-85% Power			Two-sided p=0.045		
	1	2	3	1	2	3
Test significance level, α	0.045	0.045	0.045	0.045	0.045	0.045
1 or 2-sided test?	2	2	2	2	2	2
Placebo Failure %, π_1	25%	32%	38%	25%	32%	38%
RBT Failure %, π_2	10%	15%	20%	14.6%	20.4%	25.7%
Odds ratio, $\pi_2(1-\pi_1)/[\pi_1(1-\pi_2)]$	0.333	0.375	0.408	0.513	0.545	0.564
Power (%)	84	85	84	NA	NA	NA
Placebo sample size, n1	84	84	84	84	84	84
RBT sample size, n2	168	168	168	168	168	168
Ratio: n2 / n1	2	2	2	2	2	2
N = n1 + n2	252	252	252	252	252	252

11.7 Interim Analysis

A group sequential design will be conducted with 3 pre-planned interim analyses after 30, 60, and 90 subjects complete the Day 7 evaluation and once 150 subjects complete the Day 28 evaluation. At each interim, the DSMB will evaluate an independently conducted analysis in order to assess safety and futility.

The interim analyses will be subject to adaptations according to Cui; 2-sided 0.1% alpha at the second interim and 2-sided 0.2% alpha at each of the third and fourth interim analyses. Enrollment will be stopped if the conditional power is <10% based on the percentage of subjects classified in categories 4 through 8 on the 8-point WHO Ordinal Clinical Scale for RBT-9 versus placebo.

For the second, third, and fourth interim analyses, the conditional power will be assessed. Futility will be declared if the conditional power is <10%, while efficacy will be declared at the fourth interim analysis if the conditional power is >80% (with all subjects followed through Day 28); sample size re-estimation will be performed to increase the sample size to 252 subjects. Enrollment will be recommended if futility is observed. If efficacy is declared, the DSMB will advise regarding study continuation.

12 WITHDRAWAL FROM STUDY

Every reasonable effort should be made to maintain protocol compliance and participation in the study. Should a subject withdraw or be prematurely terminated from the study for any reason, the reason for early study withdrawal will be recorded. If withdrawal is the result of a serious adverse reaction, the subject will be followed until the condition has resolved, as determined by the Investigator.

The Investigator or Sponsor may withdraw any subject at any time for medical reasons or for administrative reasons (ie, subjects unable or unwilling to comply with the protocol). If so, the subject will be censored at time of withdrawal and, if possible, a final evaluation (End of Study procedures) will be made. All treated subjects will be included in the safety analyses.

In the unlikely event the Sponsor or FDA should determine it is appropriate to terminate the study early, every effort will be made for transitioning subjects with minimal disruption to the subject and Investigator. The IRB will be notified of termination, and reason(s) and procedures for follow-up of research subjects will be developed by the study physician in consultation with the Sponsor and IRB.

13 DATA MANAGEMENT

The standard procedures for handling and processing records will be followed as per GCP and data management standard operating procedures. A comprehensive Data Management Plan will be developed and approved by the Sponsor.

13.1 Database Lock

The database will be locked in order to protect write access after the following preconditions are fulfilled:

- All data are entered in the database
- All adverse events are recorded to the satisfaction of the Chief Medical Officer
- All data queries have been resolved to the satisfaction of the Lead Biostatistician
- All decisions have been made regarding all protocol violators and population exclusions
- Written authorizations to lock the database are obtained from Clinical Data Management and the Chief Medical Officer.

14 ETHICAL CONSIDERATIONS

14.1 Ethical Conduct of the Study

The study will be conducted in accordance with United States Title 21 CFR and the ICH E6 (R1) Guidelines of GCP. The Declaration of Helsinki and its most recent updates (Fortaleza, Brazil; 2013) will be observed.

The Investigator will provide the Sponsor/designee with documentation of IRB approval of the protocol and the sample informed consent document before the study may begin at the investigative site. The IRB will review the protocol as required.

The Investigator will supply the following to the IRB:

- The current Investigator's Brochure and updates
- Study protocol and amendments
- Informed consent and assent document and updates
- Relevant curricula vitae
- Safety alerts
- Serious adverse reaction reports

The Investigator must provide the following documentation to the Sponsor or designee:

- The IRB original approval of the protocol and the informed consent, and re-approval of the study (annual or semi-annual, per IRB guidelines)
- The IRB approvals of any revisions to the informed consent document or amendments to the protocol
- All other documents that are required by local regulatory authorities

14.2 Regulatory Considerations

After reading the protocol, each Investigator/sub-Investigator will sign a protocol signature page and return a copy of the signed page to the Sponsor/designee, while maintaining the original at the site.

14.3 Protocol Amendments and Study Termination

The IRB must be informed and give approval for any amendments likely to affect the safety of the subjects or the conduct of the study.

The IRB must be advised in writing of the study's completion or early termination and a copy of the notification must be provided to the Sponsor.

14.4 Safety Monitoring

The Sponsor's Medical Monitor will monitor safety data throughout the course of the study. The Sponsor's Drug Safety Department, or their designee, will expedite to the regulatory authorities only the suspected adverse reactions that are product-related and unexpected in accordance with FDA 21 CFR 312, FDA Guidance on Safety Reporting Requirements for INDs, and the ICH E2A guideline.

14.5 Quality Control and Quality Assurance

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCPs, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

By signing this protocol, the Investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The Investigator also agrees to allow monitoring, audits, IRB review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents. Investigators will be given notice before a quality assurance audit occurs.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with GCP standards and applicable federal, state, and local laws, rules and regulations, and promptly submit to the Sponsor all forms and reports required by this

protocol following completion or termination of the clinical study or as otherwise required due to any agreement with the Sponsor.

15 GENERAL CONSIDERATIONS

15.1 Discontinuation of the Study

The Sponsor reserves the right to discontinue this study or the Investigator's participation in this study for safety or administrative reasons at any time.

16 AGREEMENT WITH PROTOCOL

I have read this protocol and agree to conduct this clinical study as outlined herein. I will ensure that all sub-Investigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Renibus Therapeutics, Inc. and its appointed Clinical Research Organization (CRO) during the study. I will adhere to all Food and Drug Administration (FDA), International Conference on Harmonisation (ICH), revised Declaration of Helsinki (2013) and other applicable regulations and guidelines regarding clinical trials on a study drug during and after study completion.

Principal Investigator:

Printed Name: _____

Signature: _____

Date: _____

Protocol REN-005

A Phase 2, Randomized, Placebo-Controlled Study to Evaluate the Effect of RBT-9 on Progression of COVID-19 Infection in High-Risk Individuals

Protocol Version 4.0: 15 February 2021

17 REFERENCES

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