NYU Langone Health

BARCONA

a clinical study for bardoxolone methyl in COVID-19

BARCONA Trial: A phase II/III, randomized, double-blind, placebo-controlled, multi-center study of the effects of bardoxolone methyl in participants with SARS-Corona Virus-2 (COVID-19)

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NYULMC Study Number:	S20-00591
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IND Number:	150943
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Study Product:	Bardoxolone methyl
Study Product Provider:	Reata Pharmaceuticals, Inc.
ClinicalTrials.gov Number	NCT04494646

Protocol Version: 1.1
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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Protocol Signature Page

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Version Date: September 9, 2020

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Signature of Principal Investigator Date

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Printed Name of Principal Investigator

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Name of Facility

_____

Location of Facility (City, Country)

Table of Contents

List of Abbreviations

Abbreviation or Specialist Term	Explanation
ADPKD	Autosomal dominant polycystic kidney disease
AE	Adverse event
AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BNP	B-type natriuretic peptide
BUN	Blood urea nitrogen
CCC	Clinical Coordination Center
CFR	Code of Federal Regulations (US)
CGI-I	Clinical Global Impression - Improvement
CK	Creatine kinase
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Coronavirus disease 2019
CrCl	Creatinine clearance
CRO	Clinical research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
DCC	Data Coordinating Center
EC	Ethics Committee
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ERA	Endothelin receptor antagonist
FDA	Food and Drug Administration (US)

Abbreviation or Specialist Term	Explanation
FSGS	Focal segmental glomerular sclerosis
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
hCG-Qual	Human chorionic gonadotropin-qualitative
HDPE	High-density polyethylene
HO-1	Heme oxygenase-1
ICH	International Conference on Harmonization
IgAN	IgA nephropathy
INR	International normalized ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
Keap1	Kelch-like ECH associated protein-1
LAR	Legally Authorized Representative
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B-cells
Nrf2	Nuclear factor (erythroid-derived 2)-related factor 2
PBO	Placebo
PH	Pulmonary hypertension
RRT	Renal replacement therapy
SAE	Serious adverse event
SAP	Statistical analysis plan
T2D	Type 2 diabetes
TBL	Total bilirubin
ULN	Upper limit of normal
UP	Unanticipated Problem
US	United States
WHO	World Health Organization
WOCBP	Women of child bearing potential

Protocol Summary

Title	BARCONA Trial: A phase II/III, randomized, double-blind, placebo-controlled, multi-center study of the effects of bardoxolone methyl in participants with SARS-Corona Virus-2 (COVID-19)
Short Title	BARCONA Trial: A Randomized Trial of Bardoxolone Methyl in Patients Infected with SARS-Corona Virus-2 (COVID-19)
Brief Summary	This multi-center, double-blind, placebo-controlled, randomized Phase 2/3 trial will study the safety, tolerability, and efficacy of bardoxolone methyl in approximately 400-440 patients hospitalized with confirmed COVID-19. The Phase 2 portion of the trial will include approximately 40 patients and is designed to provide an early interim analysis of safety. The Phase 3 portion of the trial will include approximately 360-400 additional patients, and is designed to determine whether bardoxolone methyl increases the probability of recovery at Day 29 when compared with matching placebo. Patients will be randomized using permuted block randomization in a 1:1 fashion to either once-daily administration of bardoxolone methyl (20 mg) or matching placebo and treatment will be administered for the duration of hospitalization (until recovery), with a maximum treatment duration of 29 days.
Phase	Phases 2/3
Objectives	**Phase 2** **Primary**: To provide an initial assessment of the safety of bardoxolone methyl in COVID-19 patients when compared with matching placebo **Phase 3** **Primary:** To determine whether bardoxolone methyl in COVID-19 patients increases the probability of recovery at Day 29 when compared with matching placebo. To assess the safety of bardoxolone methyl in COVID-19 patients when compared with matching placebo **Secondary and Exploratory:** To assess the effect of bardoxolone methyl on other endpoints including renal function when compared with matching placebo.

Methodology	This multi-center, double-blind, placebo-controlled, randomized Phase 2/3 trial will study the safety, tolerability, and efficacy of bardoxolone methyl in approximately 400-440 patients hospitalized with confirmed COVID-19. Phase 2 has safety as the primary endpoint and approximately 40 patients will be enrolled. A pause in enrollment will occur until the DSMB performs an initial safety assessment of Phase 2. Phase 3 is designed to determine whether bardoxolone methyl increases the probability of recovery at Day 29 compared with matching placebo. In phase 3, approximately additional 360-400 patients will be enrolled. Patients will be randomized using permuted block randomization in a 1:1 fashion to either once-daily administration of bardoxolone methyl (20 mg) or matching placebo. Patients will be stratified by study center and invasive mechanical ventilation (i.e., mechanical ventilation with endotracheal intubation) use at baseline (yes or no). Enrollment of patients ≥70 years of age may be limited (e.g., comprise no more than 10% of all randomized patients), pending safety review by the DSMB and executive committee. Treatment will be administered for the duration of hospitalization (until recovery), with an expected duration of 10 days. For patients who are hospitalized for more than 10 days, treatment can be continued for a maximum treatment duration of 29 days. Dose de-escalation (down to 10 mg) is permitted during the study if indicated clinically, and subsequent dose re-escalation is also permitted. Patients in the Phase 2 and Phase 3 portions of the study will follow the same schedule of dosing and study assessments. Following randomization on Day 1, patients will be assessed while hospitalized on Days 3, 5, 8, 11, 15, 22, and 29. Assessments will include clinical status assessments, vital sign measurements, clinical chemistry collection, and adverse event collection. Patients that recover prior to Day 29 will complete an end-of-treatment visit. Patients will have an in-person follow-up on Day 29, regardless of treatment adherence and recovery status prior to Day 29, and a safety follow-up 60 days after randomization for clinical status assessments, vital sign measurements, clinical chemistry collection, and adverse event collection. Follow-up in-person visits are preferred but recognizing quarantine and other factors may limit the subject's ability to return to the site for the visit. In this case, the visit may be performed by phone. An independent Data and Safety Monitoring Board will advise the study leadership on safety aspects and overall progress of the study.

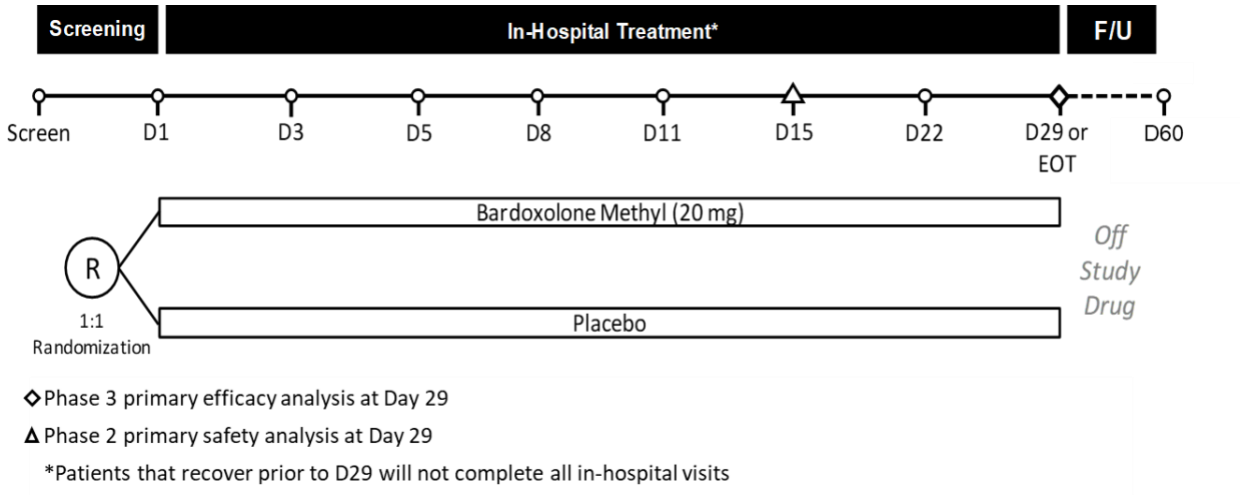
Endpoints	**Phase 2** **Primary:** • Safety (e.g., frequency, intensity, and relationship to study drug of serious adverse events [including unexpected deaths], change from baseline in vital sign and laboratory assessments) at Day 29 **Phase 3** **Primary:** • Proportion of subjects recovered (defined as alive, free of respiratory failure [e.g., need for non-invasive or invasive mechanical ventilation, high flow oxygen, or ECMO], and free of renal replacement therapy [RRT]) at Day 29 **Secondary (assessed at Day 29 unless stated otherwise):** • Number of renal replacement therapy (RRT)-free days • Number of mechanical ventilation-free days • All-cause mortality • Proportion of subjects experiencing a deterioration from baseline (as defined by a 1-point worsening) to end of treatment or Day 29 (whichever comes first) in clinical status using an 11-category ordinal scale: o 0 – Uninfected; no viral RNA detected o 1 – Asymptomatic; viral RNA detected o 2 – Symptomatic; Independent o 3 – Symptomatic; assistance needed o 4 – Hospitalized; no oxygen therapy o 5 – Hospitalized; oxygen by mask or nasal prongs o 6 – Hospitalized; oxygen by NIV or High flow o 7 – Intubation & Mechanical ventilation; pO2/FIO2 >/= 150 or SpO2/FIO2 >/=200 o 8 – Mechanical ventilation SpO2/FIO2 < 150 (SpO2/FIO2 <200) or vasopressors o 9 – Mechanical ventilation pO2/FIO2 < 150 and vasopressors, dialysis or ECMO o 10 – Death **Exploratory (assessed at Day 29 unless stated otherwise):** • Change from baseline in eGFR • Time to recovery • Recovery at Day 60 • Change from baseline in PaO_2/ FiO_2 (while hospitalized on Day 5, 8, 15, and end of treatment)

	• Change from baseline in D-dimer, CRP, LDH, troponin and cytokine levels (while hospitalized on Day 5, 8, 15, and end of treatment)
Study Duration	Approximately 12 months
Participant Duration	Approximately 2 months (including follow-up)
Duration of IP administration	Bardoxolone methyl or placebo will be administered for the duration of hospitalization (until recovery), with an expected duration of 10 days. For patients who are still hospitalized for more than 10 days, treatment can be continued for a maximum treatment duration of 29 days.

Population	**Diagnosis and main criteria for inclusion:** 1. Laboratory-confirmed COVID-19 infection as determined by polymerase chain reaction (PCR) 2. Hospitalized patients who meet one of the following conditions: (i) Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.); OR (ii) At rest, blood oxygen saturation ≤ 94%; OR (iii) Require supplemental oxygen; OR (iv) Requiring non-invasive ventilation; OR (v) Requiring invasive mechanical ventilation for up to 2 days. 3. Age ≥ 18 years. Enrollment of patients ≥70 years of age may be limited (e.g., comprise no more than 10% of all randomized patients), pending safety review by the DSMB and executive committee 4. Participant or legally authorized representative is willing to give informed consent **Exclusion criteria:** 1. Intubated and on invasive mechanical ventilation for three or more days at the time of randomization 2. Known left ventricular ejection fraction (LVEF) <40% or prior hospitalization for heart failure 3. Cardiac arrest 4. Shock 5. Known uncontrolled bacterial, fungal, or non-COVID viral infection 6. eGFR <30 ml/min/1.73 m^2 or requiring dialysis 7. ALT or AST > 5X ULN 8. History of cirrhosis, chronic active hepatitis or severe hepatic disease 9. Pregnant or lactating women 10. Enrolled in other trial of unapproved therapies, unless approved by trial Principal Investigator. In general, co-enrollment will be permitted unless there are safety concerns, mechanistic incompatibility or inability to adjudicate serious adverse events and will be decided on a case by case basis. 11. If in the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
Study Sites	Approximately 20 sites
Number of participants	Approximately 400-440 participants across approximately 20 sites
Description of Study Agent/Procedure	Bardoxolone methyl will be administered orally at 20 mg once daily. Patients unable to receive oral dosing will receive study drug via a nasogastric or orogastric tube.

Reference Therapy	Placebo
Statistical Analysis	A total sample size of approximately 400 participants (Phase 2 combined with Phase 3, or Phase 3 alone) randomized 1:1 using permuted block randomization (~200 bardoxolone methyl; ~200 placebo) is expected to provide approximately 80% power at a two-sided 0.05 significance level using a generalized linear model analysis to detect a risk difference of +14%, assuming the following: • Follow-up for events for 28 days after randomization (through Day 29) • 2% of patients in each group drop-out prior to recovery • Recovery for 50% patients randomized to placebo relative to 64% of patients randomized to bardoxolone methyl. At a designated time during the trial (~40% and ~70% of projected sample size has accrued) interim analysis will be performed for safety, harm, and futility. The analysis will be based on intention to treat using a generalized linear model analysis to compare the probability of recovery at Day 29. The phase 2 analysis for safety will not assess the primary endpoint and will not impact the overall type I error rate of the trial. If the DSMB concludes the trial should continue to the Phase 3 part, then the phase 2 patients will be included in the phase 3 portion of the study (unless Phase 2 is unblinded as discussed in Section 8.6).

Schematic of Study Design for Phase II and Phase III



1 Key Roles

Role in Study	Name	Address and Email
Principal Investigator	Sripal Bangalore, MD, MHA	New York University Langone Health, 530 First Avenue, SKI 9R-109 New York, NY 10016 Sripal.Bangalore@nyulangone.org
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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Infection with the recently identified SARS-CoV-2 virus leads to an illness known as COVID-19. Mild cases of COVID-19 generally resolve quickly; however, some patients with moderate-to-severe COVID-19 rapidly develop symptoms that lead to serious complications such as acute respiratory distress syndrome (ARDS),

acute kidney injury (AKI), and multiple organ failure (Sarzi-Puttini, 2020; Huang, 2020; Chen, 2020; Guan,2020). The severity of COVID-19, as well as the development of serious complications, is associated with an imbalance in the response of the immune system to the infection with excessive production of pro-inflammatory cytokines and chemokines (Liu, 2020). The Keap1-Nrf2 system rapidly responds to cellular stress by orchestrating an elaborate genetic program that enhances cellular cytoprotective functions, including detoxification, antioxidant, and anti-inflammatory networks (Dinkova-Kostova, 2015).

The potent anti-inflammatory effects of bardoxolone methyl in cultured cells has translated into broad protective activity in animal models of acute lung injury and inflammation (Nichols, 2009, Chen 2015, Pei, 2019; Reddy, 2009; Zhang, 2019; Nagashima, 2019; Kulkarni, 2013). Bardoxolone methyl and analogs significantly reduce neutrophil and macrophage infiltration and suppress proinflammatory cytokine and chemokine levels in the lungs of mice treated with inflammatory stimuli (Nichols, 2009; Chen 2015, Reddy, 2009). In these models, bardoxolone methyl and analogs also reduced pulmonary edema, decreased lung injury scores, prevented fibrosis, and improved lung function (Chen 2015; Pei, 2019; Kulkarni, 2013). Bardoxolone methyl and analogues also reduce proinflammatory cytokines and chemokines, prevent organ damage (lung, liver, and pancreas), and increase survival in models of systemic inflammation (Thimmulappa, 2006; Auletta, 2010, Osburn, 2008; Keleku-Lukwete, 2015; Robles, 2016).

In addition to their anti-inflammatory and tissue protective activity, bardoxolone methyl and analogs have been shown to inhibit viral replication, suppress viral infection, inhibit transcription of viral genes, and prevent latent viral reactivation *in vitro* (Vázquez, 2005; Shao, 2016; Chandra, 2018; Patra, 2019; Nio, 2019; Wyler, 2019; Rothan, 2019). Consistent with the mechanism of action of these compounds, the Nrf2 target heme oxygenase-1 (HO-1) has been shown to exhibit significant antiviral activity (Espinoza, 2017).

In patients with COVID-19, AKI has been reported to occur in up to 28% of all patients and up to 72% of non-survivors (Fanelli, 2020; Yang, 2020; Zhou, 2020; Naicker, 2020). Bardoxolone methyl and analogues protect kidney tissue, reduce inflammation, prevent fibrosis, and increase kidney function in animal models of chronic kidney disease and AKI (Chin, 2013; Tanaka, 2008; Wu, 2011; Aminzadeh, 2013). Moreover, bardoxolone methyl has been shown to improve kidney function—assessed using a variety of measures including measured inulin clearance, creatinine clearance, and estimated glomerular filtration rate—in patients with diabetes, Alport syndrome, autosomal dominant polycystic kidney disease (ADPKD), IgA nephropathy (IgAN), and focal segmental glomerular sclerosis (FSGS) (Pergola, 2011; de Zeeuw, 2013).

The profile of eGFR increases with bardoxolone methyl reflects its multiple protective and anti-inflammatory effects. Early improvements in eGFR evident within the first 4 weeks of bardoxolone methyl treatment are likely attributed to the reversal of acute, dynamic inflammation-mediated processes such as endothelial dysfunction and mesangial cell contraction resulting in glomerular filtration surface area increases (Aminzadeh, 2013; Chin, 2018; Ding, 2013; Ferguson, 2010).

Taken together, the broad anti-inflammatory, antiviral, and tissue protective activities of bardoxolone methyl suggest that it may reduce the excessive production of cytokines and chemokines and prevent ARDS and AKI in patients with COVID-19.

2.2 Name and Description of the Investigational Agent

Bardoxolone methyl, an investigational drug, has been shown to activate the Keap1-Nrf2 system, which allows Nrf2 to increase expression of antioxidant and cytoprotective genes and decrease expression of pro-inflammatory NF-κB target genes (Lee, 2009; Dinkova-Kostova, 2005; Rojas-Rivera, 2012; Osburn & Kensler, 2008). Consistent with this activity, bardoxolone methyl and analogues suppress proinflammatory cytokines and chemokines and reduce oxidative stress in many cell types in response to a variety of inflammatory triggers (Chen 2015; Thimmulappa, 2007; Pei, 2019, Nichols, 2009). Approximately 3200 individuals have been exposed to bardoxolone methyl in clinical trials, including studies in patients with cancer, chronic kidney disease (CKD), and pulmonary hypertension (PH).

2.2.1 Preclinical Data

The potent anti-inflammatory effects of bardoxolone methyl in cultured cells has translated into broad protective activity in animal models of acute lung injury and inflammation (Nichols, 2009, Chen 2015, Pei, 2019; Reddy, 2009; Zhang, 2019; Nagashima, 2019; Kulkarni, 2013). Bardoxolone methyl and analogs

significantly reduce neutrophil and macrophage infiltration and suppress proinflammatory cytokine and chemokine levels in the lungs of mice treated with inflammatory stimuli (Nichols, 2009; Chen 2015, Reddy, 2009). In these models, bardoxolone methyl and analogs also reduced pulmonary edema, decreased lung injury scores, prevented fibrosis, and improved lung function (Chen 2015; Pei, 2019; Kulkarni, 2013). Bardoxolone methyl and analogues also reduce proinflammatory cytokines and chemokines, prevent organ damage (lung, liver, and pancreas), and increase survival in models of systemic inflammation (Thimmulappa, 2006; Auletta, 2010, Osburn, 2008; Keleku-Lukwete, 2015; Robles, 2016).

In addition to their anti-inflammatory and tissue protective activity, bardoxolone methyl and analogs have been shown to inhibit viral replication, suppress viral infection, inhibit transcription of viral genes, and prevent latent viral reactivation *in vitro* (Vázquez, 2005; Shao, 2016; Chandra, 2018; Patra, 2019; Nio, 2019; Wyler, 2019; Rothan, 2019). Consistent with the mechanism of action of these compounds, the Nrf2 target heme oxygenase-1 (HO-1) has been shown to exhibit significant antiviral activity (Espinoza, 2017).

Lastly, preclinical studies have demonstrated that bardoxolone methyl and analogues protect kidney tissue, reduce inflammation, prevent fibrosis, and increase kidney function in many different animal models of kidney disease, including: ischemia-reperfusion-induced acute kidney injury (AKI) (Liu, 2014), chemically induced acute kidney injury (AKI) (Tanaka, 2008; Aleksunes, 2010; Wu, 2014), CKD associated with diabetes and/or obesity (Chin, 2013; Tan, 2014; Camer, 2016), CKD caused by nephron loss (Aminzadeh, 2013; Aminzadeh, 2014; Son, 2015), CKD caused by glomerulonephritis (Nagasu, 2019), autoimmune-associated kidney disease (Wu, 2014), and hypertension-associated kidney disease (Hisamichi, 2018).

2.2.2 Clinical Data to Date

Approximately 3200 individuals have been exposed to bardoxolone methyl in clinical trials, including studies in healthy subjects, patients with cancer, pulmonary hypertension (PH), and various forms of chronic kidney disease (CKD). As described in Section **Error! Reference source not found.**, bardoxolone methyl has been shown to improve kidney function—assessed using a variety of measures including measured inulin clearance, creatinine clearance, and estimated glomerular filtration rate—in patients with CKD due to diabetes, Alport syndrome, autosomal dominant polycystic kidney disease (ADPKD), IgA nephropathy (IgAN), and focal segmental glomerular sclerosis (FSGS) (Pergola, 2011; de Zeeuw, 2013).

The profile of eGFR increases with bardoxolone methyl reflects its multiple protective and anti-inflammatory effects. Early improvements in eGFR evident within the first 4 weeks of bardoxolone methyl treatment are likely attributed to the reversal of acute, dynamic inflammation-mediated processes such as endothelial dysfunction and mesangial cell contraction resulting in glomerular filtration surface area increases (Aminzadeh, 2013; Chin, 2018; Ding, 2013; Ferguson, 2010).

Please refer to the Investigator's Brochure for a detailed discussion of safety findings for studies in healthy subjects, cancer, CKD, and PH patients with bardoxolone methyl.

2.2.3 Dose Rationale (if applicable)

Several dose-ranging studies which have been conducted with bardoxolone methyl demonstrated that changes in eGFR are dose-dependent. The 20 mg bardoxolone methyl dose used in the present study provides near-optimal pharmacological activity and efficacy while also minimizing potential tolerability issues. Furthermore, most of the available clinical safety and efficacy data for bardoxolone methyl has been collected with the 20 mg dose.

2.3 Rationale

Some patients with moderate-to-severe COVID-19 rapidly develop symptoms that lead to serious complications such as ARDS, AKI, and multiple organ failure. The severity of COVID-19, as well as the development of serious complications, is associated with an imbalance in the response of the immune system to the infection with excessive production of pro-inflammatory cytokines and chemokines.

Bardoxolone methyl and analogues exhibit potent anti-inflammatory activity in vitro. Moreover, bardoxolone and analogues suppress inflammation and tissue damage in animal models of acute lung injury and reduce mortality in models of systemic inflammation. In addition to the anti-inflammatory and tissue protective

effects, bardoxolone methyl and analogues have been shown to possess potent antiviral activity. AKI is a serious complication of COVID-19 and frequently occurs in patients with severe symptoms. Bardoxolone methyl protects the kidney in several animal models of CKD and AKI and improves kidney function in patients with diabetes, Alport syndrome, ADPKD, IgAN, and FSGS. Thus, the collective data suggest bardoxolone methyl may reduce the excessive production of cytokines and chemokines and prevent ARDS and AKI in patients with COVID-19.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

Please refer to the Investigator's Brochure for a detailed discussion of safety findings for studies conducted with bardoxolone methyl in healthy subjects or patients with cancer, CKD, or PH.

2.4.1.1 Fluid Overload

Similar to endothelin receptor antagonists (ERAs) in certain patient populations, including bosentan in advanced congestive heart failure and avosentan in advanced CKD, bardoxolone methyl treatment was found to be associated with an increased risk for fluid overload and heart failure hospitalizations in the BEACON trial, which enrolled patients with Stage 4 CKD (eGFR 15 to 29 mL/min/1.73 m^2) and type 2 diabetes (Chin, 2014). The overall increased risk for fluid overload and heart failure events with bardoxolone methyl appeared to be limited to the first three to four weeks after initiation of treatment. Patients with fluid overload events who were treated with intravenous diuretics generally resolved their symptoms. Elevated BNP and prior hospitalization for heart failure were identified as risk factors that contributed to increased risk for these events. For patients without these baseline characteristics, the risk for heart failure events among bardoxolone methyl- and placebo- treated patients was similar (2%) (Chin, 2014). The increased risk for these events from bardoxolone methyl treatment had also not been observed in six previous CKD studies, which were conducted mostly in patients with Stage 3b CKD (eGFR of 30 to 44 mL/min/1.73 m^2), patients with hepatic dysfunction or cancer, or healthy volunteers.

Subsequent studies, enrolling over 1500 patients, have employed risk mitigation procedures to reduce the potential for bardoxolone methyl-induced fluid overload. These procedures excluded patients with the identified risk factors and ensured close monitoring for fluid retention within the first month of treatment. Since these exclusions have been applied, no increased risk for acute fluid overload AEs with bardoxolone methyl has been observed. As such, BARCONA will exclude patients with known left ventricular ejection fraction (LVEF) <40% or prior hospitalization for heart failure to mitigate this risk.

2.4.1.2 Transaminase and Gamma-glutamyl Transpeptidase (GGT) Elevations

In clinical studies of bardoxolone methyl, almost all patients had increases of transaminase enzymes above baseline upon initiation of treatment, which followed a consistent pattern. These increases were not associated with elevations in bilirubin or other signs of liver toxicity. In BEACON, fewer hepatobiliary SAEs were observed in the bardoxolone methyl arm than in the placebo arm. The elevations begin immediately after initiation of treatment or an increase in dose; they peak approximately two to four weeks later. In most patients, transaminase elevations were mild, but approximately 4% to 11% of patients experienced an elevation greater than 3X the ULN. The elevations resolved to levels less than the ULN in most all patients with elevations, within two weeks after peak values while patients continued taking study drug. Patients who experienced elevations to greater than 3X the ULN sometimes required additional time to resolve. While some patients have had elevations to above 3X the ULN, persistent elevations to above 3X the ULN have not been observed, and the elevations did not recur once resolved, unless caused by other factors.

Bardoxolone methyl regulates GGT, a known Nrf2 target gene. In clinical studies, low level GGT elevations during treatment were common, mild, and typically lasted longer than ALT/AST elevations. Bilirubin levels in patients experiencing transaminase or GGT elevations due to treatment with bardoxolone methyl either remained at baseline levels or decreased. The ALT, AST, and GGT elevations were generally self-limiting in patients who continued treatment with study drug.

2.4.1.3 Muscle Spasms

Muscle spasm was the most frequently reported adverse event in clinical trials of bardoxolone methyl in patients with CKD who also had type 2 diabetes. The muscle spasms most often manifested in the first two months of treatment and resolved spontaneously or with empirical treatment. They occurred mostly at night, in the lower extremities, and were generally mild to moderate in severity. Muscle spasms may result from improved insulin sensitivity and glucose uptake in skeletal muscle cells. Increases in glucose uptake, as assessed by the hyperinsulinemic-euglycemic clamp procedure, were observed in response to bardoxolone methyl in a defined subset of patients enrolled in a Phase 2a study. Clinical signs and laboratory findings associated with the reports of muscle spasms have not been consistent with muscle toxicity. Bardoxolone methyl subjects showed no increase in prominent laboratory findings associated with muscle toxicity, such as increased levels of serum markers, including creatinine, creatine kinase, lactate dehydrogenase (LDH), BUN, uric acid, phosphorus, and potassium.

2.4.2 Known Potential Benefits

As seen in Table 1, improvements in kidney function, including eGFR, creatinine clearance, and inulin clearance, have been observed with bardoxolone methyl treatment in multiple clinical studies, including patients with CKD, cancer, and pulmonary hypertension (PH). Bardoxolone methyl was originally considered for development in cancer patients, and in two Phase 1 studies, bardoxolone methyl was observed to reduce serum creatinine levels, corresponding to an increase in eGFR (Hong, 2012). The reductions of serum creatinine concentrations and resultant increases in eGFR were time-dependent and manifested in a majority (82%) of the patients studied. In subsequent studies that enrolled over 2600 patients with type 2 diabetes and CKD, bardoxolone methyl has been shown to consistently produce clinically and statistically significant improvements in eGFR that are durable for at least one year in treated patients (Chin, 2018; Pergola, 2011). The change in serum creatinine was not related to a reduction in creatinine generation (Chertow, 2018); improved kidney function was confirmed in a study of Japanese patients with type 2 diabetes wherein GFR was measured using inulin clearance, as well as estimated, using conventional GFR estimating equations (Nangaku, 2020).

Most recently, bardoxolone methyl was shown to significantly increase eGFR in patients with CKD due to Alport syndrome, ADPKD, IgAN, T1D CKD, or FSGS (Pergola, 2019). The clinical activity of bardoxolone methyl in various forms of CKD with distinct etiologies suggests that the anti-inflammatory and anti-fibrotic effects of bardoxolone methyl target the common final pathway contributing to GFR loss in multiple forms of CKDs.

Table 1: Cross-Study Comparison of Increases in eGFR, Inulin Clearance, and Creatinine Clearance with Bardoxolone Methyl Treatment

Study	Phase/ Country	Study Population	# of Patients	Treatment Duration	ΔeGFR (mL/min/1.73m^2)(1)
CKD Studies					
402-C-0801 (Stratum 1) (open label)	2a/ US	Age ≥ 18, Diabetic nephropathy	60	28 days	6.7 (p<0.001)
402-C-0801 (Stratum 2) (open label)	2b/ US	Age ≥ 18, Diabetic nephropathy	20	56 days	7.2 (p<0.001) CrCl also sig. increased
402-C-0804 (BEAM)	2/ US	Age ≥ 18, T2D and CKD	227	52 weeks	8.6 at WK52 (p<0.001 vs PBO)
402-C-0902	2/ US	Age ≥ 18, T2D and CKD	131	85 days	6.5 (p<0.001)
402-C-0903 (BEACON)	3/ Global	Age ≥ 18, T2D and Stage 4 CKD	2185	Median: 7 months with 522 patients through Week 48	6.4 (p<0.001 vs PBO) CrCl also significantly increased

402-C-1102	1/US	Age ≥ 18, T2D and Stage 3b and Stage 4 CKD	24	56 days	9.0 (p<0.05)
RTA402-005 (TSUBAKI)	2/ Japan	Age ≥ 20, T2D and Stage 3 and 4 CKD	108	16 weeks	6.6 (inulin GFR) (p=0.008 vs PBO)
402-C-1603	2/US	Age 12 to 65, Alport Syndrome	30	48 weeks	10.4 (p<0.001)
402-C-1603	3/Global	Age 12 to 70, Alport Syndrome	157	48 weeks	9.5 (p<0.001 vs PBO)
402-C-1702	2/US	Age 18 to 70, ADPKD	31	12 weeks	9.3 (p<0.001)
402-C-1702	2/US	Age 18 to 70, IgA Nephropathy	26	12 weeks	8.0 (p<0.001)
402-C-1702	2/US	Age 18 to 70, T1D CKD	28	12 weeks	5.5 (p=0.02)
Non-CKD Studies					
402-C-0501	1/ US	Age ≥ 18, Advanced Solid Tumors or Lymphoid Malignancies	47	Median: 56 days	18.2 (p<0.0001)
402-C-0702	1/2/ US	Pancreatic Cancer	34	Median: 56 days	32.2 (p=0.001)
402-C-1302 (LARIAT)	2/ US	Age 18 to 75 PH (Baseline eGFR 82 mL/min/1.73 m^2)	54(2)	16 weeks	14.7 (p<0.001 vs PBO)

[a] Unless noted, data are mean eGFR changes from baseline for bardoxolone methyl patients and p-values are calculated from two-sided paired t-tests comparing eGFR change to 0.
[b] Number of patients enrolled in Cohorts 1 and 2.

3 Objectives and Purpose

3.1 Phase 2

3.1.1 Primary Objective

- To provide an initial assessment of the safety of bardoxolone methyl in COVID-19 patients when compared with matching placebo

3.2 Phase 3

3.2.1 *Primary Objectives*

- To determine whether bardoxolone methyl in COVID-19 patients increases the probability of recovery at Day 29 when compared with matching placebo
- To assess the safety of bardoxolone methyl in COVID-19 patients when compared with matching placebo

3.2.2 Secondary and Exploratory Objectives

- To assess the effect of bardoxolone methyl on other endpoints including renal function when compared with matching placebo

3.2.3. Safety Endpoints

The following safety endpoints will be assessed during the study:

- All adverse events that are serious, unexpected, and have a reasonable possibility of having been related to the study drug
- All unexpected deaths

4 Study Design and Endpoints

4.1 Description of Study Design

This multi-center, double-blind, placebo-controlled, randomized Phase 2/3 trial will study the safety, tolerability, and efficacy of bardoxolone methyl in patients hospitalized with confirmed COVID-19. Phase 2 is designed to provide an early interim analysis for safety and will enroll approximately 40 patients. Phase 3 is designed to determine whether bardoxolone methyl increases the probability of recovery at Day 29 compared with matching placebo. In phase 3, approximately 360-400 additional patients will be enrolled.

Patients will be randomized using permuted block randomization in a 1:1 fashion to either once-daily administration of bardoxolone methyl (20 mg) or matching placebo. Randomization will be stratified by study center and invasive mechanical ventilation (i.e., mechanical ventilation with endotracheal intubation) use at baseline (yes or no).

Enrollment of patients ≥70 years of age may be limited (e.g., comprise no more than 10% of all randomized patients), pending safety review by the DSMB and executive committee. Treatment will be administered for the duration of hospitalization (until recovery), with an expected duration of 10 days. For patients who are still hospitalized for more than 10 days, treatment can be continued for a maximum treatment duration of 29 days. Dose de-escalation (down to 10 mg) is permitted during the study if indicated clinically, and subsequent dose re-escalation is also permitted. Once a patient's dose has been reduced, dose re-escalation back to a higher dose is permitted.

Randomization will be performed using an interactive web response system (IWRS). Following randomization on Day 1, patients will be assessed while hospitalized on Days 3, 5, 8, 11, 15, 22, and 29. Assessments will include clinical status assessments, vital sign measurements, clinical chemistry collection, and adverse event collection. Patients that recover prior to Day 29 will complete an end-of-treatment visit. Patients will have an in-person follow-up on Day 29, regardless of treatment adherence and recovery status prior to Day 29, and a safety follow-up 60 days after randomization for clinical status assessments, vital sign measurements, clinical chemistry collection, and adverse event collection. Follow-up in-person visits are preferred but recognizing quarantine and other factors may limit the subject's ability to return to the site for the visit. In this case, the visit may be performed by phone. An independent Data and Safety Monitoring Board (DSMB) will advise the study leadership on safety aspects and overall progress of the study.

The phase 2 primary endpoint will be assessed during the treatment phase, defined as while hospitalized and up to Day 15. The phase 3 primary endpoint will be assessed during the treatment phase, defined as while hospitalized and up to Day 29. Enrollment of the phase 3 cohort will initiate after safety and proof of concept has been confirmed in the Phase 2 cohort.

4.2 Study Endpoints

4.2.1 Phase 2

4.2.1.1 Primary Endpoint

- Safety (e.g., frequency, intensity, and relationship to study drug of serious adverse events [including unexpected deaths], change from baseline in vital sign and laboratory assessments) at Day 29

4.2.2 Phase 3

4.2.2.1 Primary Efficacy Endpoint

- Proportion of subjects recovered (defined as alive, free of respiratory failure [e.g., need for non-invasive or invasive mechanical ventilation, high flow oxygen, or ECMO], and free of renal replacement therapy [RRT]) at Day 29.

4.2.2.2 Seconday Efficacy Endpoint (assessed at Day 29 unless stated otherwise)

- Number of renal replacement therapy (RRT)-free days
- Number of mechanical ventilation-free days
- All-cause mortality
- Proportion of subjects experiencing a deterioration from baseline (as defined by a 1-point worsening) to end of treatment or Day 29 (whichever comes first) in clinical status using an 11-category ordinal scale:
    - 0 – Uninfected; no viral RNA detected
    - 1 – Asymptomatic; viral RNA detected
    - 2 – Symptomatic; Independent
    - 3 – Symptomatic; assistance needed
    - 4 – Hospitalized; no oxygen therapy
    - 5 – Hospitalized; oxygen by mask or nasal prongs
    - 6 – Hospitalized; oxygen by NIV or High flow
    - 7 – Intubation & Mechanical ventilation; pO2/FIO2 >/= 150 or SpO2/FIO2 >/=200
    - 8 – Mechanical ventilation pO2/FIO2 < 150 (SpO2/FIO2 <200) or vasopressors
    - 9 – Mechanical ventilation pO2/FIO2 < 150 and vasopressors, dialysis or ECMO
    - 10 – Death

4.2.2.3 Exploratory Efficacy Endpoint (assessed at Day 29 unless stated otherwise)

- Change from baseline in eGFR
- Time to recovery
- Recovery at Day 60
- Change from baseline in PaO2/ FiO2 (while hospitalized on Day 5, 8, 15, and end of treatment)
- Change from baseline in D-dimer, C-reactive protein (CRP), LDH, troponin and cytokine levels (while hospitalized on Day 5, 8, 15, and end of treatment)

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Laboratory-confirmed COVID-19 infection as determined by polymerase chain reaction (PCR)
2. Hospitalized patients that meets one of the following conditions:
    a. Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.); OR

b. At rest, blood oxygen saturation ≤ 94%; OR

c. Require supplemental oxygen; OR

d. Requiring non-invasive ventilation; OR

e. Requiring invasive mechanical ventilation for up to 2 days.

3. Age ≥ 18 years. Enrollment of patients ≥70 years of age may be limited (e.g., comprise no more than 10% of all randomized patients), pending safety review by the DSMB and executive committee
4. Participant or legally authorized representative is willing to give informed consent

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Intubated and on invasive mechanical ventilation for three or more days at the time of randomization
2. Known left ventricular ejection fraction (LVEF) <40% or prior hospitalization for heart failure
3. Cardiac arrest
4. Shock
5. Known uncontrolled bacterial, fungal, or non-COVID viral infection
6. eGFR <30 ml/min/1.73 m^2 or requiring dialysis
7. ALT or AST > 5X ULN
8. History of cirrhosis, chronic active hepatitis or severe hepatic disease
9. Pregnant or lactating women
10. Enrolled in other trial of unapproved therapies, unless approved by trial Principal Investigator. In general, co-enrollment will be permitted unless there are safety concerns, mechanistic incompatibility or inability to adjudicate serious adverse events and will be decided on a case by case basis.
11. If in the opinion of the clinical team, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments

5.3 Vulnerable Subjects

The study will include subjects with diminished or lack of capacity to provide consent if their Legally Authorized Representative (LAR) is able to provide consent on their behalf. Due to the known progression of the COVID-19 disease, there is the possibility that a patient may be sedated, under mechanical ventilation, or under the effects of hypoxia, etc. that may contribute to an altered mental status before the study team is able to obtain written consent. We believe that this group of patients will have a potential for direct benefit by participating in the trial. In addition to the standard of care monitoring by their treatment team, there will be additional monitoring for the study. Overall, we believe that participation in this trial will facilitate close monitoring of their clinical status which may improve their clinical care.

As usual, assessment of a subject's capacity will be conducted by the treating physician based on the standard clinical assessment of capacity, which includes assessment of patients understanding of the facts presented, assessment of their appreciation and reasoning about the choice, etc. and communicated to the study team. If it is determined that the subject is unable to provide consent, consent will be obtained from subject's LAR before study-related procedures can begin. The study will be explained to the LAR by the study team using the IRB-approved Informed Consent Form. The hierarchy of identifying the LAR will be in the following order: health care agent, spouse (if not legally separated), domestic partner, adult child, parent, adult sibling, and close friend. The hierarchy may vary from state to state and the local site should refer to their local regulatrions. Identification and verification of the LAR will follow the standard policies and procedures in place at each study site.

Subjects' capacity will be re-assessed at each study visit with the treatment team. Once the participant regains capacity to consent, they will be informed of their participation in the study and will have an opportunity to withdraw from further participation in the study. Subjects who regain the capacity to consent and decline to continue participation will be asked if previously collected data can still be used. If they decline to allow use of previously collected data, their data will be discarded. If a subject provides consent with capacity, and subsequently loses capacity, their participation in the study is expected to continue unless the LAR notifies the study team of study withdrawal.

5.4 Strategies for Recruitment and Retention

Participants will be screened by designated qualified clinical staff in an electronic medical records system, such as EPIC or similar, using the inclusion and exclusion criteria specified for the study. When a potential participant is identified, the Investigator will contact the participant's treating physician (TP), or equivalent, to further verify eligibility for the study. The Investigator and TP will determine the best way to approach the potential participant to introduce the study. The consenting process will occur in an in-patient setting. In addition to screening by the study team, the Principal Investigator and Investigators at participating sites may publicize this study internally to clinical colleagues. Referrals from clinical colleagues will be reviewed to verify eligibility before proceeding to the consenting process.

5.5 Duration of Study Participation

Bardoxolone methyl or placebo will be administered for the duration of hospitalization (until recovery), for up to a maximum of 29 days. A final follow-up visit will occur 60 days after randomization. Total duration of study participation is estimated to be approximately 2 months.

5.6 Total Number of Participants and Sites

Recruitment will end when approximately 400-440 participants are enrolled. Recruitment is planned to occur at approximately 20 sites.

5.7 Participant Treatment Discontinuation

5.7.1 Reasons for Treatment Discontinuation

Study drug discontinuation refers to a patient's stopping administration of study drug. Participants are free to discontinue study treatment at any time for any reason without prejudice to their medical care. Furthermore, the investigator may disconintue a patient from study drug. The reason for a patient's discontinuation from stu drug will be rcorded in the electronic case report form (eCRF).
Reasons for study drug discontinuation may include the following:

- Adverse event;
- Death;
- Lost to follow-up;
- Physician decision;
- Protocol specified criterion met;
- Withdrawal by subject

Patients who are discontinued from study drug should still continue in the study, complete all study visits, and undergo all scheduled study assessments, if possible.

5.8 Participant Withdrawal or Termination

5.8.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request, without prejudice to their medical care. The reason for a patient's withdrawal or termination will be recorded in an electronic case report form (eCRF). The potential reasons could be:

- Withdrawal of Consent by Participant
- Lost to Follow-up

Discontinuation of treatment is not a withdrawal of participation from the study. If treatment is discontinued, the participant should remain in the study and continue to be assessed at the scheduled study assessments.

5.8.2 Handling of Participant Withdrawals or Termination

If a participant (or legally authorized representative who provided consent) notifies the study team about withdrawing participation from the study, the study team will make all efforts to collect data related to the primary and secondary endpoints.

The investigator will make reasonable efforts to obtain, at a minimum, survival data on all participants lost to follow-up. Before a participant is considered lost to follow-up, study team will use any combination of the following methods to ascertain vital status:

- Multiple phone calls to participant and/or their next-of-kin
- Send certified letters to known addresses
- Search medical records system for recent routine visits

The overall clinical care of this patient will not change as a result of participation in this study nor will it change should the patient be withdrawn for any reason.

5.9 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the Principal Investigator, funding agency, the IND sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

Although Reata intends to complete the study, Reata reserves the right to discontinue the study at any time for clinical or administrative reasons, or if required by regulatory agencies. If Reata discontinues the study, all study drug will be discontinued and the investigator will be responsible for securing any alternative therapy to be administered, as appropriate.

6 Study Agent

6.1 Study Agent(s) and Control Description

Bardoxolone methyl (RTA 402) drug product information is shown in Table 2. Information about the placebo is shown in Table 3.

Table 2: Bardoxolone Methyl Drug Product Information

Description	Bardoxolone methyl capsule (5 mg, 15 mg)

Ingredients	Bardoxolone methyl Methacrylic Acid – Ethyl Acrylate Copolymer (1:1), Type A Silicified Microcrystalline Cellulose Hydroxypropyl Methylcellulose Lactose Monohydrate Sodium Lauryl Sulfate Colloidal Silicon Dioxide Magnesium Stearate Gelatin capsules Titanium Dioxide (capsule pigment)
Route of Administration	Oral

Table 3: Placebo Information

Description	Placebo for bardoxolone methyl capsule (size #4 and size #1)
Ingredients	Silicified Microcrystalline Cellulose Lactose monohydrate Magnesium Stearate Gelatin capsules Titanium Dioxide (capsule pigment)
Route of Administration	Oral

6.1.1 Acquisition

Study drug will be shipped directly to each site prior to the start of the study. Blinded ordering of supplies will be maintained via the IWRS. Shipping contact information will be managed within the IWRS. All requests will require client approval prior to shipment.

6.1.2 Formulation, Appearance, Packaging, and Labeling

The study drug will be supplied in tamper-evident sealed kits containing two high-density polyethylene (HDPE) bottles. The 20mg kit contains two (HDPE) bottles (1) 30ct 15mg bottle and (1) 30ct 5mg bottle. The 20mg dose is attained by taking 1 capsule from each bottle as directed. The 10mg kit contains two (HDPE) bottles (2) 30ct 5mg bottles. The 10mg dose is attained by taking 1 capsule from each bottle as directed. Each bottle will utilize foil induction-seal liners and a child-resistant closure. Each bottle of study drug will contain 30 capsules of 5 mg or 15 mg strength bardoxolone methyl or the matching placebo capsules. Each bottle will also contain a desiccant insert that must not be ingested. Labeling on each bottle will contain at minimum the following information:

- Protocol: s20-00591
- Product name and strength
- Caution: New Drug – Limited by Federal Law to Investigational Use
- Keep out of reach of children
- Control or lot number
- Store at 15° – 25°C (59° – 77°F)

- Reata Pharmaceuticals, Inc., Irving, TX

6.1.3 Product Storage and Stability

The stability of the drug product has been and is currently being evaluated in ongoing studies. Investigative sites must store the investigational product in a secure location with room temperature conditions of 15° - 25°C (59° - 77°F).

6.1.4 Preparation

Patients will be administered one capsule from each bottle included in the study drug kit orally once a day beginning on Day 1 while the patient remains hospitalized. Patients unable to receive oral medications (e.g., due to intubation and/or mechanical ventilation) may receive the contents of the capsule through a nasogastric or orogastric tube flushed with water. Each dose of study drug should be administered at approximately the same time each day, preferably in the morning.

6.1.5 Dosing and Administration

Please refer to Section 7.1.1.7 for details on study drug administration, which will be administered at the time points listed in Table 1. Patients must be instructed to continue taking study drug once daily while hospitalized (until recovery) with an expected duration of 10 days. For patients who are still hospitalized for more than 10 days, treatment can be continued for a maximum treatment duration of 29 days.

6.1.6 Route of Administration

Bardoxolone methyl will be administered orally. Patients unable to receive oral dosing will receive study drug via a nasogastric or orogastric tube.

6.1.7 Starting Dose

Patients will be randomized 1:1 to either 20 mg of bardoxolone methyl or placebo.

6.1.8 Dose Adjustments/Modifications/Delays

The investigator may choose to decrease the patient's dose to a lower dose (*e.g.*, 20 mg to 10 mg), if clinically indicated. Reasons for dose de-escalation should be documented. Once a patient's dose has been reduced, dose re-escalation back to a higher dose is permitted.

6.1.9 Duration of Therapy

Patients will receive study drug while hospitalized (until recovery) with an expected duration of 10 days. For patients who are still hospitalized for more than 10 days, treatment can be continued for a maximum treatment duration of 29 days.

6.1.10 Tracking of Dose

Study drug administration should be recorded in patient source record.

6.2 Study Agent Accountability Procedures

The investigator, or designee, will maintain a record of all study drug received, dispensed, and returned. Study drug bottles and any unused capsules from dispensed kits should be disposed as biohazardous waste. At the conclusion of the study or in an instance of planned study drug replacement, Reata or its designee will direct the site regarding the final disposition of study drug.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

7.1.1.1 Informed Consent

Informed consent (see Section **Error! Reference source not found.**) must be obtained from the patient or the legally authorized representative (for patients who cannot consent, for example, those who are intubated) before any study-related procedures are performed, and again if there is a change in the study procedures that would affect the patient's willingness to participate.

7.1.1.2 Inclusion/Exclusion

Inclusion and exclusion criteria must be reviewed as indicated in Table 1. Patients must meet all of the inclusion and none of the exclusion criteria for entry in the study. Investigators should contact the Reata Medical Monitor or the Clinical Coordinating Center with any questions regarding eligibility prior to randomizing the patient on Day 1.

7.1.1.3 Demographics and Baseline Disease Characteristics

Demographic data including sex, age, race, and ethnicity, will be collected as indicated in Table 1. Baseline disease characteristics will be collected as indicated in Table 1.

7.1.1.4 Prior and Current Concomitant Medications

The name, dose, and frequency must be recorded for all medications that the patient is taking. Trade or generic drug names should be used where possible. Concomitant medications will be reviewed as indicated in Table 1 and all changes will be recorded.

7.1.1.5 Medical History

A complete medical history that includes all available medical history must be collected. Medical history will be recorded as indicated in Table 1.

7.1.1.6 Pregnancy Test

WOCBP will complete a pregnancy test as indicated in Table 1, or at any time if pregnancy is suspected. Any patient who becomes pregnant during the study must discontinue taking study drug immediately. See Section 8.4.4 for a description of procedures to be followed in case of pregnancy.

7.1.1.7 Study Drug Administration

Patients will be administered one capsule from each bottle included in the study drug kit orally once a day beginning on Day 1 while the patient remains hospitalized, as indicated in Table 1. Each dose of study drug should be administered at approximately the same time each day, preferably in the morning. Patients unable to receive oral medications (e.g., due to intubation and/or mechanical ventilation) may receive the contents of the capsule through a nasogastric or orogastric tube flushed with water. A vomited dose must not be replaced. A double dose (*e.g.*, missed dose from previous day and dose for current day) must not be taken.

7.1.1.8 SARS CoV-2 PCR Test

A sample will be collected from the patient to test for presence of viral load as indicated in Table 1. At the screening visit, study team is required to confirm there is a positive SARS CoV-2 PCR test to satisfy the study's inclusion criteria. If feasible per local clinical care, SARS CoV-2 PCR test is requested to be collected at Day 15 or End of Treatment, whichever is earlier.

7.1.1.9 In-person/Telephone Contact

Patients will have a follow-up on Day 29, regardless of treatment adherence and recovery status prior to Day 29, and a safety follow-up 60 days after randomization, which may be conducted by in-person visit (preferable) or telephone call (if there are quarantine and other restrictions). The call will include questions on health status including new adverse events, continuing adverse events, hospital visits, continued care, reinfection or death following exposure to bardoxolone methyl or placebo in the trial.

7.1.1.10 Adverse Event Collection

All adverse events will be recorded as indicated in Table 1.

7.1.1.11 Clinical Status Assessment

Clinical status of the patient will be assessed as indicated in Table 1. The assessment will include collection of data related to critical events and other data to support the safety reporting criteria set by the DSMB. An 11-category ordinal scale defined in Section 4.2.2.3 will be used to support data collection for the exploratory endpoint.

7.1.1.12 Recovery Assessment

Each of the following patient recovery components will be assessed as indicated in Table 4:

- Alive (yes/no)
- Free of respiratory failure (yes/no)
- Free of RRT (yes/no)

7.1.1.13 eGFR

The eGFR value will be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation:

$$\text{eGFR (mL/min/1.73 m}^2) = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

Where the patient's age on the date of consent is used, S_{cr} is serum creatinine (mg/dL), κ is 0.7 for females or 0.9 for males, and α is -0.329 for females or -0.411 for males. Min indicates the minimum of S_{cr}/κ or 1 and max indicates the maximum of S_{cr}/κ or 1.

7.1.1.14 PaO_2/FiO_2 Ratio

PaO_2/FiO_2 ratio will be collected as indicated in Table 1 and calculated by using the PaO_2 from the arterial blood gas and then dividing by the estimated FiO_2 for that oxygen delivery method (0.21 for room air, 0.21 + (oxygen flow rate * 0.03) for nasal cannula, 0.80 for non-rebreather mask or the recorded FiO_2 for non-invasive or invasive ventilation) (Brown SM et al. Chest 2016;150:307-13).

7.1.2 Standard of Care Study Procedures

7.1.2.1 Vital Sign Measurements

Vital sign measurements include the patient's heart rate, respiration rate, and body temperature. Vital sign measurements should be taken as indicated in Table 1. Data related to vitals signs will be used to calculate a National Early Warning Score (NEWS) at each assessment. If feasible, vital sign measurements will be taken during outpatient study visits.

7.1.2.2 Laboratory Assessments

Samples will be collected for specified clinical chemistry and hemoatology analyses as indicated in Table 1. If feasible, available laboratory assessments will be reviewed during outpatient visits. The analyses will include the following:

- Clinical Chemistry and biomarkers
  - Comprehensive metabolic panel
  - Lipid panel
  - Cytokines (if feasible per local clinical care)
  - Ferritin
  - Lactate dehydrogenase
  - C-reactive protein
  - Cardiac markers (Troponin)
  - B-type natriuretic peptide (BNP)
- Hematology
  - Complete blood count (CBC)
  - CBC differential
  - Coagulation testing (including PT, INR, fibrinogen, D-dimer, etc.)

7.1.2.3 Chest Imaging

Chest imaging test performed as part of standard of care will be reviewed for eligibility. .

7.2 Study Schedule

All patients enrolled in the Phase 2 and Phase 3 portions of the trial will follow the same study schedule.

7.2.1 Screening/Enrollment

Screening/Enrollment Visit (Day -3 to 1)

- Obtain informed consent of potential participant, or legally authorized representative verified by signature on study informed consent form. Written and/or electronic signature are acceptable.
- Review medical history and medications history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Verify inclusion/exclusion criteria.
- Obtain blood or urine for pregnancy test if subject is WOCBP.
- Obtain demographic information, medical history, medication history, alcohol and tobacco use history.
- Review and record vital signs, results of medical examinations, results of laboratory assessment, and other assessments as indicated in Table 1.

7.2.2 Intermediate Visits

7.2.2.1 Visit 1 (Day 1)

- Verify inclusion/exclusion criteria.

- Administer first dose of the study treatment in accordance with Section 6 of protocol.
- Review and record concurrent medications.
- Review and record available laboratory assessments as indicated in Table 1.
- Review and record vital signs, results of medical examinations, results of laboratory assessment, and other assessments as indicated in Table 1.
- Assess clinical status.
- Record adverse events as reported by participant or observed by investigator following first dose of study treatment.

7.2.2.2 Visit 2 (Day 3)

- Verify study drug was administered in accordance with Section 6 of protocol since the last visit.
- Review and record concurrent medications.
- Review and record available laboratory assessments as indicated in Table 1.
- Review and record vital signs, results of medical examinations, results of laboratory assessment, and other assessments as indicated in Table 1.
- Assess clinical status.
- Record adverse events as reported by participant or observed by investigator.

7.2.2.3 Visit 3 (Day 5)

- Verify study drug was administered in accordance with Section 6 of protocol since the last visit
- Review and record concurrent medications.
- Review and record available laboratory assessments as indicated in Table 1.
- Review and record vital signs, results of medical examinations, results of laboratory assessment, and other assessments as indicated in Table 1.
- Assess clinical status.
- Record adverse events as reported by participant or observed by investigator.

7.2.2.4 Visit 4 (Day 8)

- Verify study drug was administered in accordance with Section 6 of protocol since the last visit.
- Review and record concurrent medications.
- Review and record available laboratory assessments as indicated in Table 1.
- Review and record vital signs, results of medical examinations, results of laboratory assessment, and other assessments as indicated in Table 1.
- Assess clinical status.
- Record adverse events as reported by participant or observed by investigator.

7.2.2.5 Visit 5 (Day 11)

- Verify study drug was administered in accordance with Section 6 of protocol since the last visit.
- Review and record concurrent medications.
- Review and record available laboratory assessments as indicated in Table 1.
- Review and record vital signs, results of medical examinations, results of laboratory assessment, and other assessments as indicated in Table 1.
- Assess clinical status.
- Record adverse events as reported by participant or observed by investigator.

7.2.2.6 Visit 6 (Day 15)

- Verify study drug was administered in accordance with Section 6 of protocol since the last visit.
- Review and record concurrent medications.
- Review and record available laboratory assessments as indicated in Table 1.
- Review and record vital signs, results of medical examinations, results of laboratory assessment, and other assessments as indicated in Table 1.
- Assess clinical status.

- Record adverse events as reported by participant or observed by investigator.

7.2.2.7 Visit 7 (Day 22)

- Verify study drug was administered in accordance with Section 6 of protocol since the last visit.
- Review and record concurrent medications.
- Review and record available laboratory assessments as indicated in Table 1.
- Review and record vital signs, results of medical examinations, results of laboratory assessment, and other assessments as indicated in Table 1.
- Assess clinical status.
- Record adverse events as reported by participant or observed by investigator.

7.2.2.8 Visit 8 (Day 29)

- If patient is receiving treatment on Day 29, verify study drug was administered in accordance with Section 6 of protocol since the last visit.
- If patient was discharged prior to Day 29, make arrangements for outpatient follow-up visit.
- Review and record available laboratory assessments as indicated in Table 1.
- Review and record vital signs, results of medical examinations, results of laboratory assessment, and other assessments as indicated in Table 1.
- Assess clinical status.
- Assess recovery status.
- Record adverse events as reported by participant or observed by investigator.

7.2.2.9 End of Treatment Visit (or Day of Recovery if prior to Day 29)

- Due to the nature of this visit (end of treatment or day of recovery), study drug will not be administered at this visit.
- Verify study drug was administered in accordance with Section 6 of protocol since the last visit.
- Review and record concurrent medications.
- Review and record available laboratory assessments as indicated in Table 1.
- Review and record vital signs, results of medical examinations, results of laboratory assessment, and other assessments as indicated in Table 1.
- Assess clinical status.
- Assess recovery status.
- Record adverse events as reported by participant or observed by investigator.

7.2.3 Final Safety Follow-up

Final Safety Follow-up (Visit 10, Day 60)

- Safety follow-up with participant 60 days after randomization.
- Review and record available laboratory assessments as indicated in Table 1.
- Review and record vital signs, results of medical examinations, results of laboratory assessment, and other assessments as indicated in Table 1.
- Assess clinical status.
- Assess recovery status.
- Record adverse events as reported by participant or observed by investigator.

7.2.4 Withdrawal/Early Termination Visit

Withdrawal/Early Termination Visit

- Review and record concurrent medications.
- Record adverse events as reported by participant or observed by investigator.
- Assess clinical status.
- If study treatment is ongoing at time of withdrawal:

- Verify study drug was administered in accordance with Section 6 of protocol since the last visit.
- Review and record available laboratory assessments as indicated in Table 1.
- Review and record vital signs, results of medical examinations, results of laboratory assessment, and other assessments as indicated in Table 1.

Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

7.3 Justification for Sensitive Procedures

The use of placebo as the comparator will provide an objective assessment of bardoxolone methyl's treatment effect on proportion recovered in patients with COVID-19.

7.3.1 Precautionary Medications, Treatments, and Procedures

The investigator may choose to decrease the patient's dose to a lower dose (*e.g.*, 20 mg to 10 mg), if clinically indicated. Reasons for dose de-escalation should be documented. Once a patient's dose has been reduced, dose re-escalation back to a higher dose is permitted.

7.4 Prohibited Medications, Treatments, and Procedures

Patient enrolled in other trials of unapproved therapies will ineligble for enrollment unless approved by trial Principal Investigator. Given the nature of the clinical situation in patients with COVID-19 and the evolving status of therapies for the illness, this study will permit simultaneous enrollment (co-enrollment) in other studies. Permission to co-enroll will be decided on a case by case basis weighing in any additional safety concerns, mechanistic incompatibility and ability to adjudicate serious adverse events. Data on co-enrollment will be captured in the EDC and SAE/AE in this subset will be tracked through the length of the trial (see section 8.4.1). Moreover, subgroup analysis will be performed in the cohort of patients co-enrolled in other trials (see section 10.4.8). In general, co-enrollment will be permitted unless there are safety concerns, mechanistic incompatibility or inability to adjudicate serious adverse events and will be decided on a case by case basis.

Concomitant use with strong CYP3A4 inhibitors is prohibited. If a strong CYP3A4 inhibitor is medically necessary, study drug should be temporarily discontinued. Concomitant study drug use with moderate CYP3A4 inhibitors should be avoided whenever possible, and switching to an alternative agent should be considered.

8 Assessment of Safety

8.1 Specification of Safety Parameters

The following safety endpoints will be assessed during the study:

- All adverse events that are serious, unexpected, and have a reasonable possibility of having been related to the study drug
- All unexpected deaths

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

Severity for each adverse event will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) system. All adverse events will be recorded:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

8.2.2 Relationship to Study Agent

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – The event follows: (a) a reasonable, temporal sequence from study drug or a study procedure; and (b) cannot be explained by the known characteristics of the participant's clinical state or other therapies; and (c) evaluation of the participant's clinical state indicates to the investigator that the experience is definitely related to study procedures.
- **Probably Related** – The event should be assessed following the same criteria for "Definitely Related". If in the investigator's opinion at least one or more of the criteria are not present, then is can be assessed as "probably" related.
- **Possibly Related** – The event should be assessed following the same criteria for "Definitely Related". If in the investigator's opinion at least one or more of the criteria are not present, then it can be assessed as "possibly" related.
- **Probably Not Related** – The event occurred while the participant was receiving study drug/intervention or undergoing study procedures but can reasonably be explained by the known characteristics of the participant's clinical state or other therapies.
- **Definitely Not Related** – The event is definitely produced by the participant's clinical state or by other therapies administered to the participant.
- **Uncertain Relationship**: The event does not meet any of the criteria previously outlined.

8.2.3 Expectedness

The investigator responsible at each local site will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

There are a plethora of adverse events expected that will be related to COVID-19 infection and not the use of the drug, including death. Some examples of expected COVID-19 related AE include (but not limited to) death, intubation, need for pressors, mechanical circulatory support, resuscitated cardiac arrest, acute kidney injury, infection (non COVID-19), LFTs >5x ULN, disseminated intravascular coagulation, and symptomatic venous thromboembolism.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All adverse events will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study that may reasonably be related to this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Serious Adverse Event Reporting

The cumulative incidence of adverse events that are serious, unexpected, and have a reasonable possibility of having been related to a study drug (from time of administration of the first dose at the Day 1 visit until the final visit indicated in Table 4) must be reported.

The investigator is responsible for reporting all SAEs that are observed or reported by the patient during the study (from the time of administration of the first dose of study drug until the final visit indicated in Table 1, as appropriate). Additional information from the investigator may be requested to ensure the timely completion of accurate safety reports. Serious adverse events related to COVID-19 infections will not be reported.

All SAEs reported or observed during the study must be followed to resolution or until the investigator deems the event to be chronic or the patient to be stable. The investigator may be contacted for additional information on any SAE which has not resolved at the time the patient completes the study.

A summary of SAEs and AEs experienced by subjects co-enrolled in other clinical trials will be reported to the IRB on a monthly basis. The report will include a statement from the PI regarding whether or not there are any safety concerns to the co-enrolled group as compared to the not co-enrolled group.

8.4.2 Unanticipated Problem Reporting

Incidents or events that meet the criteria for UPs in Section 8.1.3 require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC/study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 72 hours of the investigator becoming aware of the problem.

8.4.3 Reporting of Pregnancy

During the study, and for 30 days following administration of the final dose of study medication, all WOCBP must practice one of the following acceptable methods of birth control:

- Use double barrier contraception method defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream, diaphragm [always use with spermicidal jelly/cream]);
- Use of hormonal contraceptives (oral, parenteral, vaginal, or transdermal);
- Use of an intrauterine device;
- Abstain from sexual intercourse completely.

Males who have female partners of childbearing potential must practice one of the following methods of birth control during the study, and for 30 days following administration of the final dose of study medication:

- Have had a vasectomy;
- Use double barrier contraception method, defined as male use of a condom and female use of a barrier method (e.g., contraceptive sponge, spermicidal jelly or cream, diaphragm [always use with spermicidal jelly/cream]);
- Partner use of an intrauterine device;
- Partner use of hormonal contraceptives (oral, parenteral, vaginal or transdermal);
- Abstain from sexual intercourse completely.

WOCBP must be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, late or missed menstrual period). Male patients must be instructed to contact the investigator if a sexual partner suspects she may be pregnant.

If a patient or investigator suspects that the patient may be pregnant, the study drug must be withheld until the results of a serum pregnancy test are available. If the serum pregnancy test confirms the pregnancy, the patient must permanently discontinue taking study drug. The investigator must immediately report to the Reata Medical Monitor a pregnancy associated with study drug exposure. The early discontinuation protocol-required procedures outlined for End-of-treatment and Follow-up visits must be performed on the patient.

Pregnancy is not considered an AE; however, the investigator must follow a pregnant patient, or the pregnant female partner of a male patient (if consenting), and report follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants resulting from such pregnancies should be followed for a minimum of 8 weeks. Reata or designee may contact the investigator to request additional information throughout the course of the pregnancy.

The following pregnancy outcomes must be considered SAEs and will require additional reporting in the eCRF and reported as a serious AE:

- Congenital anomaly/birth defect;
- Stillbirth;
- Spontaneous miscarriage.

8.5 Reporting Procedures – Notifying the Study Sponsor

The study clinician will complete a SAE Form within the following timelines:

- All unexpected deaths and immediately life-threatening events, will be recorded on the SAE Form and submitted to the DCC/study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the DCC/study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC/study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

8.6 Reporting Procedures – Notifying the FDA

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These mandatory written notifications of adverse events are referred to as IND safety reports.

The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

- ***As soon as possible but no later than 7 calendar days***
  Any adverse experience that is:
  - suspected, *and*
  - unexpected, *and*
  - fatal or life-threatening

- ***As soon as possible but no later than 15 calendar days***
  Any adverse experience that is:
  - suspected, *and*
  - unexpected, *and*
  - serious, but not fatal or life-threatening
    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

Definitions:

- **Suspected:** there is reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event.
- **Unexpected:** refers to an event or reaction that is not listed in the investigator's brochure or is not listed at the specificity or severity that has not been observed / is not consistent with the risk information described in the IND application.
- **Life-threatening:** the sponsor determines that adverse event or suspected adverse reaction is considered life-threatening if its occurrence places the participant at immediate risk of death.

Note: Serious adverse events related to COVID-19 infections will not be reported to the FDA unless it meets the criteria above. There is a plethora of adverse events expected in the patient population being evaluated that will be related to the COVID-19 infection and not associated with the use of bardoxolone methyl. These adverse events include death, which is expected in severe cases of COVID-19.

Follow-up Safety Reporting
Sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Adverse events may be submitted on FDA Form 3500A (MEDWATCH Form: https://www.fda.gov/media/76299/download), or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 8.3.

Study Halting Rules
At a designated time during Phase 3 of the trial (~40% and ~70% of projected sample size has accrued) interim analysis will be performed for safety, harm and futility. Safety and harm stopping rules will be based on one-tailed group sequential Z-testing with three stages and boundaries calculated from an O'Brien-Fleming spending function. Futility stopping rules will be based on symmetric, two-tailed group sequential Z-testing with three stages and boundaries calculated from an O'Brien-Fleming spending function. The Executive Committee can request to be unblinded after receiving the recommendation from the DSMB after the Phase 2 portion of the trial. If the Phase 2 portion is unblinded, participants enrolled during Phase 2 portion will not be included in the total for the Phase 3 portion of the trial, which will require an additional 400 patients to be enrolled. If Phase 2 portion remains blinded, an additional 360 patients will be enrolled. Detailed plans for interim monitoring will be documented in a separate DSMB analysis plan.

8.7 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events. All study information will be communicated between the PI and study sites on an as-needed basis via emails, phone calls, teleconferences, webinars, and in-person meetings. All attempts will be made to ensure communications are timely with respect to the topic of the communication.

Safety oversight will be under the direction of the NYU Langone Health COVID-19 DSMB. This DSMB committee will be comprised of individuals with expertise across a broad range of disciplines. The DSMB will operate under the rules of an approved charter. The DSMB charter will specify the meeting frequency when safety data on each arm of the study will be assessed.

9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by designated staff at the Coordinating Center at NYU Langone Health.
- Monitoring will be performed centrally at specified time points throughout the study. For-cause on-site monitoring will be performed when needed. A random review of certain data points related to endpoint, safety, and other key data variables will be performed. Monitoring related to protocol adherence will be performed on an ongoing basis.
- Details of clinical site monitoring will be documented in a CMP. The CMP will describe the frequency of monitoring, which data points will be monitored, and the distribution of monitoring reports.

10 Statistical Considerations

10.1 Statistical and Analytical Plans (SAP)

A formal SAP detailing the analyses will be developed and finalized prior to database lock and unblinding of the study. All statistical analyses and data summaries will be performed using SAS® (Version 9.4 or higher) or other validated software. The SAP will serve as the final arbiter of all statistical analyses.

10.2 Statistical Hypotheses

10.2.1 Phase 2

In a given group of 20 subjects the probability of not observing an adverse event when the underlying rate is 10%, 20%, 30%, 40%, and 50% is 0.12, 0.01, 0.001, 0, and 0, respectively. This indicates that in a sample of 20 subjects, the study is sufficiently sized to observe AEs that occur at a rate of 10% or greater.

10.2.2 Phase 3

All statistical hypotheses will be tested using a two-sided significance level of 0.05. The Phase 3 primary outcome is recovery at Day 29. The key parameter of interest is the "risk difference," which quantifies the shift in probability of recovery resulting from treatment. A positive risk difference 1 indicates a higher proportion of patients recovering in the bardoxolone methyl group relative to placebo. The null hypothesis to be tested is that the risk difference is the same for the placebo and bardoxolone methyl arms and is stated as H_0: RD = 0, where RD denotes the risk difference.

10.3 Analysis Populations

The following analysis populations will be defined:

- The intention-to-treat (ITT) population includes all randomized patients categorized by their assigned treatment group (whether or not they received study drug). Efficacy analyses of the primary and secondary outcomes will be performed using the ITT population.
- The safety population includes all patients who received at least one dose of randomized study drug. Patients who receive at least one dose of bardoxolone methyl will be classified in the bardoxolone methyl group, and patients who receive at least one dose of placebo and no dose of bardoxolone methyl will be classified in the placebo group.
- Additional analysis populations may be defined in the SAP as appropriate.

10.4 Description of Statistical Methods

The following subsections include brief descriptions of the planned statistical methods. Full detail of the planned analyses will be described in the formal SAP.

10.4.1 General Approach

This is a double-blind placebo controlled randomized trial testing a superiority hypothesis with a two-sided significance level of 0.05. Data for this placebo-controlled trial will be summarized by treatment group using descriptive statistics. Continuous data will be summarized with number of patients (n), mean, median, minimum, maximum, relevant quartiles, standard deviation, coefficient of variation, and geometric mean (where applicable). Categorical data will be summarized using frequency counts and percentages. Handling of missing data will be described in the SAP.

10.4.2 Analysis of the Phase 3 Primary Efficacy Endpoint

The primary efficacy endpoint is recovery, where recovery is defined as meeting all of the following criteria at Day 29:

- Alive,
- Free of respiratory failure, and
- Free of renal replacement therapy (RRT).

Analysis of the Phase 3 primary endpoint will occur after the last patient enrolled has been followed up to Day 29 and the study is complete. The analysis will be based on the test of treatment effect estimated from a generalized linear model analysis accounting for the stratification factors of study center and mechanical ventilation status as covariates. The primary efficacy endpoint will be a covariate-adjusted estimate as specified in the Statistical Analysis Plan. Events will be analyzed and presented as summary tables of proportion recovered with risk differences and 95% confidence intervals (CIs) for the comparison of

bardoxolone methyl to placebo. The SAP will include additional detail of the planned analyses and definitions of sensitivity analyses.

10.4.3 Analysis of the Secondary/Exploratory Endpoints

The secondary endpoints include the following:

- Change in eGFR (mL/min/1.73 m^2) during treatment as calculated using the CKD-EPI formula.
- Number of mechanical ventilation-free days.

The two treatment groups will be compared with respect to the secondary endpoints. The treatment of missing data, and the strategy to preserve the overall Type I error will be described in the SAP.

10.4.4 Safety Analyses

Safety and tolerability are evaluated by AEs, SAEs, clinical laboratory test results, vital sign measurements, and PaO_2/FiO_2 ratio. All analyses of the safety data will be performed using the safety analysis set. Descriptive statistics are presented by treatment group assignment in the safety analysis set.

10.4.4.1 Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be used to classify all AEs reported during the study by system organ class (SOC) and preferred term (PT). All summary tables will include counts of patients with treatment-emergent adverse events (TEAEs). TEAEs are defined as those AEs that have an onset time either at or after the start of study drug administration and no more than 30 days after the last dose of study drug is administered. An overall summary of TEAEs will be presented with the number and percentage of patients having a TEAE, a serious TEAE, a TEAE leading to study discontinuation, a TEAE with an outcome of death, a TEAE related to study drug (definitely, probably, or possibly related), or a severe TEAE. The overall incidence of TEAEs will be summarized by SOC and by SOC and PT using the number and percentage of patients reporting an event and the number of events reported. The incidence of serious TEAEs and TEAEs leading to premature study discontinuation will be summarized in a similar manner. TEAEs will also be summarized by maximum severity (mild, moderate, or severe), and assessed relationship to study drug with the percentage of patients in each category. TEAEs leading to premature study discontinuation, and TEAEs with an outcome of death will also be presented in separate listings.

10.4.5 Adherence and Retention Analyses

The number of patients enrolled and completed or discontinued will be summarized by treatment group and overall. Duration of treatment will be summarized by treatment group as the number of days the patient received randomized treatment and as a percent of the expected number of doses.

10.4.6 Baseline Descriptive Statistics

Summaries of demographic and other baseline characteristic data will be presented by treatment arm for all analysis populations. For continuous measures, the mean, standard deviation, and interquartile range will be summarized. Categorical variables will be described by the proportion in each category, with the corresponding sample sizes.

10.4.7 Planned Interim Analysis

10.4.7.1 Safety Review

A DSMB will be reviewing unblinded data from the study to ensure patient safety. The DSMB charter will describe the scope and frequency for regularly occurring interim safety reviews.

10.4.8 Additional Sub-Group Analyses

The efficacy outcomes will be analyzed for subgroups of interest, including in the subgroup of patients co-enrolled in other trials, as specified in the SAP.

10.4.9 Multiple Comparison/Multiplicity

This study includes a single primary endpoint. The two secondary efficacy endpoints will be tested using a strategy that preserves the overall Type I error rate.

10.4.10 Tabulation of Individual Response Data

Individual patient data will be listed by endpoint and time point.

10.4.11 Exploratory Analyses

The SAP will describe exploratory efficacy analyses.

10.5 Sample Size

A total sample size of approximately 400 participants (Phase 2 combined with Phase 3, or Phase 3 alone, depending on unblinding of Phase 2) randomized 1:1 using block randomization (~200 bardoxolone methyl; ~200 placebo) is expected to provide approximately 80% power at a two-sided 0.05 significance level using a generalized linear model analysis to detect a risk difference of +.14, assuming the following:

- Follow-up for events for 28 days after randomization (at Day 29)
- 2% of patients in each group drop-out prior to Day 29
- Increase in the probability of recovery from 50% for patients randomized to placebo relative to 64% of patients randomized to bardoxolone methyl.

Under these assumptions, approximately 228 (57% of the 400 enrolled) will have recovered at Day 29. The primary analysis will be based on the ITT population. The secondary endpoints will be tested using a strategy that preserves the overall Type I error rate. Analysis of the primary endpoint will occur after the last patient enrolled has been followed to Day 29. The phase 2 analysis for safety will not assess the primary endpoint and will not impact the overall type I error rate of the trial. If the DSMB concludes the trial should continue to the Phase 3 part, then the phase 2 patients will be included in the phase 3 portion of the study.

Table 5 shows effects detectable with 80% power for a total sample size of 400 and a range of proportion of placebo patients recovered at Day 29.

Table 5. Effects detectable with 80% power for a sample size of n=400 and a range of proportion of placebo patients recovered

Placebo Proportion Recovered at Day 29	Bardoxolone Proportion Recovered at Day 29	Risk Difference
0.350	0.488	0.14
0.400	0.539	0.14
0.450	0.590	0.14
0.500	0.638	0.14
0.550	0.686	0.14
0.600	0.732	0.13
0.650	0.776	0.13
0.700	0.819	0.12
0.750	0.861	0.11
0.800	0.900	0.10
0.850	0.936	0.09
0.900	0.969	0.07

10.6 Measures to Minimize Bias

10.6.1 Enrollment/Randomization/Masking Procedures

An IWRS will be utilized to randomize patients 1:1 to once daily administration of bardoxolone methyl or placebo. Randomization will be performed using block randomization with the following strata: center and invasive mechanical ventilation (i.e., mechanical ventilation with endotracheal intubation) at baseline (yes or no). Enrollment of patients ≥70 years of age may be limited (e.g., comprise no more than 10% of all randomized patients), pending safety review by the DSMB and executive committee

All patients, investigators, site personnel, laboratories, and study personnel with direct involvement in the conduct of the study or their designees will be blinded to treatment assignments. To prevent potential bias, appropriate measures will be taken to ensure the blind is maintained for the patients and personnel mentioned previously. To maintain the blind, investigators will distribute blinded study drug treatment to patients as directed by the IWRS system. Investigators and patients will not be blinded to dose level, but will be blinded to treatment assignment (i.e., bardoxolone methyl vs. placebo).

An IWRS will manage treatment assignments and study drug dispensing. The only people with direct access to treatment assignments prior to database lock will be those individuals who develop and maintain the randomization code and the DSMB.

Following database lock after completion of each phase the study, randomization codes will be released to the statistical team for analysis.

10.6.2 Breaking the Study Blind/Participant Code

Although bardoxolone methyl has no known antidote, under rare circumstances unblinding may be considered medically necessary.

The investigator is encouraged to contact the medical monitor to discuss situations in which he or she believes that the blind should be broken, but the investigator has the right to break the blind (e.g., in the event of a serious or life-threatening medical situation). If unblinding is required, the investigator will utilize the IWRS to perform the unblinding. If a study drug assignment is unblinded, the investigator must describe the event that required unblinding in the patient's source documents.

Patients must permanently discontinue taking study drug if their treatment assignment has been unblinded to the investigator (or designee). Such patients must undergo the same study drug discontinuation procedures as those patients who discontinue taking study drug for other reasons. Following permanent study drug discontinuation due to patient unblinding, patients should continue with study follow-up through their scheduled study assessments.

Patient treatment assignments must not be unblinded in the case of an AE or SAE, except as described above.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded, unless otherwise noted in the CRF instructions.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (*e.g.*, US Code of Federal Regulations Title 21, European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

The principal investigator agrees to conduct the study in accordance with the International Conference on Harmonization (ICH) for Guidance for Industry on Good Clinical Practice (GCP) ICH E6(R2) [https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf] and the principles of the Declaration of Helsinki [https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/]. The principal investigator must conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent and Other Informational Documents Provided to Participants

Because the study will be conducted under a United States Investigational New Drug Application, a signed informed consent form, in compliance with Title 21 of US CFR Part 50, will be obtained from each patient before the patient enters the study. In the event that the participant is not able to provide consent due to

temporary loss of capacity during critical illness, the legally authorized representative will provide consent. A study team member may conduct the informed consent process via telephone or video (webex) with use of e-consent through REDCap to obtain and document informed consent from the subject or legally authorized representative.

An informed consent template may be provided by the Sponsor or designee to the investigators. The consent must be reviewed by the Sponsor or designee before IRB/EC submission. Once reviewed, the consent will be submitted by the principal investigator to his or her IRB/EC for review and approval before the start of the study. If the informed consent form is revised during the course of the study, all participants affected by the revision must sign the revised IRB/EC-approved consent form.

Before enrollment, each prospective patient or legally authorized representative will be given a full explanation of the study and be allowed to read the approved informed consent form. Once the principal investigator or designee is assured that the patient or legally authorized representative understands the implications of participating in the study, the patient will be asked to give consent to participate in the study.

Eligible patients may only be included in the study after providing IRB/EC-approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

The principal investigator or designee will provide a copy of the informed consent form (signed copy to be provided per applicable law) to the patient or legally authorized representative. The original form will be maintained in the patient's medical records at the site.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

13.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant data capture system, Medidata RAVE, maintained by Reata Pharmaceuticals Inc. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No

records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site PI/study staff to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

14.4 Publication and Data Sharing Policy

The Sponsor supports communication and publication of study results whatever the findings of the study.

The Sponsor reserves the right to review all planned communications and manuscripts based on the results of this study. This reservation of the right is not intended to restrict or hinder publication or any other dissemination of study results, but to allow the Sponsor to confirm the accuracy of the data, to protect proprietary information, and to provide comments based on information that may not yet be available to the study investigators. The Sponsor also encourages disclosure of any conflict of interest from all authors or investigators when manuscripts are submitted for publication. Those individuals who have contributed greatly to this study, including lead external advisors and select principal investigators, may serve on any potential publications committee for the study.

15 Study Finances

15.1 Funding Source

This study is financed by Reata Pharmaceuticals, Inc.

15.2 Costs to the Participant

The patient will not incur costs associated with participation in this study.

15.3 Participant Reimbursements or Payments

No payments or reimbursements will be disbursed to participants in exchange for participation in this study.

16 Study Administration

16.1 Study Leadership

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the study PI, representatives of Reata Pharmaceuticals, Inc., and the PIs of the participating clinical sites. The Steering Committee will meet via teleconference at least monthly or as guided by the need.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore,

persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

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19 Schedule of Events

Table 1: Schedule of Assessments

Assessment	Screening	Day 1[a]	Day 3	Day 5	Day 8	Day 11	Day 15	Day 22	Day 29[k]	End of Treatment [j]	Day 60 Safety Follow-up[b]
Informed consent	X										
Inclusion/ exclusion	X										
Demographics and baseline disease characteristics	X										
Chest imaging	X[h]										
Medical history	X										
Pregnancy test for WOCBP[e]	X										
Concomitant medications	X	X[b,c]	X	X	X	X	X	X		X	
Vital sign measurements	X	X[d,e]	X	X	X	X	X	X	X	X	X
Study drug administration		----------X----------									
Adverse event collection		X[f]	X	X	X	X	X	X	X	X	X
Recovery status assessment									X	X	X
Clinical status assessment	X	X[f,g]	X	X	X	X	X	X	X	X	X
Comprehensive metabolic panel	X	X[c]		X	X			X	X	X	X
Lipid panel		X[c]		X	X			X		X	
Cytokines[l]		X[c]		X	X			X		X	
Ferritin		X[c]		X	X			X		X	
Lacate dehydrogenase (LDH)		X[c]		X	X			X		X	
C-reactive protein (CRP)		X[c]		X	X			X		X	
Cardiac markers (Troponin I, CK)		X[c]		X	X			X		X	
BNP		X[h,i]	X	X	X	X	X	X	X	X	X
Complete blood count (CBC)		X[j,k]	X	X	X	X	X	X	X	X	X
CBC differential		X[l,m]	X	X	X	X	X	X	X	X	X
PT & INR		X[n,o]	X	X	X	X	X	X		X	
Fibrinogen		X[p,q]	X	X	X	X	X	X		X	
D-dimer		X[r,s]	X	X	X	X	X	X	X	X	X
PaO_2/FiO_2		X[c]	X	X	X	X	X	X		X	
SARS CoV-2 PCR Test	X[i]						X[g]			X[g]	

[a] Day 1 is the day of administration of the first dose.

Error! Reference source not found. Patients who discontinue from study drug prior to recovery or prior to Day 29 will have a safety assessment 60 days after randomization. This will be in-person visit when possible or telephone follow-up.

[b] Screening assessments conducted on the same day as randomization (Day 1) do not have to be repeated.

c Performed pre-dose on Day 1.

[e] A serum pregnancy test will be performed at the Screening visit for WOCBP or at any point in time if a pregnancy is suspected. Additional pregnancy assessments will be performed more frequently if required by local law or requested by local regulatory authorities or IRBs/ECs.

Error! Reference source not found. AE assessments on Day 1 should be performed following study drug administration. Only AEs that are serious and have a reasonable possibility of having been related to a study drug will be collected.

[g] If feasible per clinical care at local site, to be performed on Day 15 or End of Treatment, whichever is earlier.

[h] Results available from test performed as per standard of care can be reviewed for eligibility. If not available or not done, it is not required to be performed.

[i] At screening, this test does not need to be performed. Only need to confirm a positive test is available to meet the study's inclusion criteria.

[j] End of Treatment visit can occur on Day 29 or earlier. If the End of Treatment visit is on Day 29, follow schedule of assessments for End of Treatment visit.

[k] All patients, regardless of treatment adherence and recovery status prior to Day 29, will have a follow-up visit at Day 29. This will be in-person visit when possible or telephone follow-up.

[l] Cytokines are to be reported if feasible per clinical care at local site.