CCB-CRISIS-02

STUDY PROTOCOL

The CRISIS2 Study: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2

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Study No: CCB-CRISIS-02

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine amino transferase
AML	Acute myeloid leukemia
ARDS	Acute respiratory disease syndrome
AST	Aspartate amino transferase
BRQ	Brequinar
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus-19 infection
CRP	c-reactive protein
CTCAE	Common terminology criteria for adverse events
CTEP	Cancer Therapy Evaluation Program
CV	Curricula vitae
DHO	Dihydroorotate
DHODH	Dihydroorotate dehydrogenase
DHODHi	Dihydroorotate dehydrogenase inhibitor
DMC	Data Safety Monitoring Board
ECMO	Extra corporeal membrane oxygenation
EHR	Electronic health record
ESR	Erythrocyte Sedimentation Rate
EUA	Emergency Use Authorization
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council on Harmonization
ICU	Intensive care unit
IMP	Inosine-5’ phosphate
IP	Investigational product
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NEWS2	National Early Warning System (NEWS) 2 Score
RNA	Ribonucleic Acid
RdRp	RNA-dependent RNA polymerase
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	SARS Coronavirus 2
SOC	Standard of Care
SUSAR	Suspected unexpected serious adverse reaction
UMP	Uridine 5’-monophosphatase

Abbreviation	Definition
US	United States
XMP	Xanthosine-5’ phosphate
WHO	World Health Organization
WOCBP	Women of childbearing potential

2 SYNOPSIS

CCB-CRISIS-02 SYNOPSIS	
IND	149291
Title	The CRISIS2 Study: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2
Protocol Number	CCB-CRISIS-02
Rationale	Brequinar is a potent DHODH inhibitor that has been previously studied in more than 1,000 cancer, psoriasis, and organ transplant patients. Brequinar has been found to have potent *in vitro* antiviral activity against many RNA viruses including SARS-CoV-2. The antiviral activity of brequinar against SARS-CoV-2 is likely due to DHODH inhibition and shows nanomolar potency and a high selectivity index in inhibiting viral replication in *in vitro* studies. The CRISIS2 trial will study out-patients (non-hospitalized patients) who have a positive SARS-CoV-2 test and are symptomatic. Subjects will be randomized to receive standard of care (SOC) + 5 days of brequinar or SOC + 5 days of placebo. The purpose of this study is to determine if the *in vitro* antiviral activity of brequinar can be duplicated in patients infected with SARS-CoV-2 by measuring the effect of brequinar on viral shedding. Importantly, the safety and tolerability of brequinar will also be determined in these patients. The results of this proof-of-concept study will inform future studies that will help determine if brequinar is a safe and effective drug for the treatment of SARS-CoV-2 infection.
Investigational Product and Dosage	Subjects will be randomized in a 1:1 ratio to either standard of care (SOC) + 5 days of brequinar 100 mg or SOC + 5 days of placebo. Investigational product will be supplied as either brequinar 100 mg oral capsules or placebo capsules. The subjects are to self-administer one capsule on Study Days 1 – 5. Treatment assignment will be randomized, double-blind.
Primary Objectives	● To demonstrate a change from baseline in quantitative SARS-CoV-2 viral load for brequinar-treated subjects compared to placebo-treated subjects through Day 29.
Secondary Objectives	Through Day 29: ● To characterize the safety and tolerability of brequinar in out-patient COVID-19 subjects as measured by frequencies of grade 3 and 4 AEs and SAEs; ● To demonstrate a shorter duration of viral shedding in subjects treated with brequinar compared to subjects who received placebo;

	● To reduce the percentage of subjects requiring hospital admission as an in-patient for > 24 hours for brequinar subjects compared to subjects who received placebo; ● To reduce mortality through Day 29 for brequinar subjects compared to subjects who received placebo.
Exploratory Objectives	● To determine time to viral clearance (two consecutive negative tests); ● To determine time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline; ● To reduce disease severity as measured by the WHO Ordinal Scale score measured for the subset of subject with baseline WHO Ordinal Scale of 2 for brequinar subjects compared to subjects who received placebo.
Design	This will be a phase 2 randomized, double blind, multi-center study with approximately 100 subjects. All subjects will receive SOC per relevant guidelines for treatment of out-patients with COVID-19 infection. In addition to SOC, subjects will self-administer one capsule once daily for 5 days. Subjects will have a Screening Visit followed as soon as possible with Study Day 1. Study procedures are presented in detail in the Schedule of Events. Study visits (virtual or in person) will take place at Screening and on Study Days 1, 8, 15, 22, and 29. The visits that include bloodwork must be conducted at the study site or arrangements made for sample collection at the subject's home or other appropriate location. Other visits/visit activities for that visit may be conducted remotely using telemedicine or other remote technique. Subjects are to self-collect a viral load sample, obtain their respiratory rate, heart rate, body temperature and pO2, and complete a symptom assessment on Days 1, 4, 8, 12, 15, 22, and 29.
Sample Size:	Approximately 100 subjects will be randomized to 5 days of either SOC + brequinar 100 mg or SOC + placebo in a 1:1 ratio (approximately 50 subjects assigned to brequinar 100 mg and 50 subjects to placebo).
Number of Sites:	Approximately 15
Study Period:	An enrollment period of 3 months is expected.
Inclusion Criteria:	1. Willing and able to provide informed consent for the trial, written, electronic, verbal or other method deemed acceptable by the institution and IRB. 2. 18 years of age or older. 3. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other FDA-approved commercial or public health assay within 14 days of randomization.

	4. Out-patient (not currently hospitalized or was hospitalized with duration < 24 hours). 5. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men and women treated or enrolled on this protocol must also agree to use adequate contraception for the duration of study participation, and for 90 days after completion of brequinar administration. 6. Male subjects must agree to refrain from sperm donation and female subjects must agree to refrain from ovum donation from initial study drug administration until 90 days after the last dose of brequinar. 7. Must have at least one COVID-19 symptom including but not limited to fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, shortness of breath, dyspnea, ansomia, dysgeusia, or other symptom commonly associated with COVID-19. 8. Able to swallow capsules.
Exclusion Criteria:	1. Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient 2. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test 3. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide) or other agents known to cause bone marrow suppression leading to thrombocytopenia 4. Platelets ≤150,000 cell/mm^3 5. Hemoglobin < 10 gm/dL for menstruating women and < 12 gm/dL for all other subjects 6. Absolute neutrophil count < 1500 cells/mm^3 7. Renal dysfunction, i.e., creatinine clearance < 30 mL/min 8. AST and/or ALT > 2 x ULN, or total bilirubin > ULN. Gilbert's Syndrome is allowed. 9. Bleeding disorders or blood loss requiring transfusion in the six weeks preceding enrollment 10. Ongoing gastrointestinal ulcer, or gastrointestinal bleeding within 6 weeks of randomization.

	11. Chronic hepatitis B infection, active hepatitis C infection, active liver disease and/or cirrhosis per subject report. 12. Heart failure, current uncontrolled cardiovascular disease, including unstable angina, uncontrolled arrhythmias, major adverse cardiac event within 6 months (e.g. stroke, myocardial infarction, hospitalization due to heart failure, or revascularization procedure).
Treatment	All subjects will receive standard of care (SOC) including symptomatic care. Subjects will be randomly assigned to SOC + brequinar 100 mg daily x 5 or SOC + placebo daily x 5. Study encounters will be conducted remotely whenever possible.
DMC	A Data Monitoring Committee (DMC) will meet periodically to review the safety and scientific conduct of the study. At a minimum, the DMC is to review adverse events and safety laboratory assessments after the first 20 subjects complete Day 8, and again after the first 40 subjects complete Day 8.
Procedures	Study procedures are outlined in the Schedule of Events. Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF.
Safety/ Tolerability	**Safety/Tolerability** Adverse events will be collected from the time of informed consent through Day 29. After Day 29, collect/record only Serious Adverse Events (SAEs) or those judged by the Investigator or designated person to be related to study drug. Treatment-emergent adverse events will be those with an onset after the date and time of first treatment. Subjects who develop Grade 3 or 4 toxicities or SAEs are to be re-evaluated every 2 days, as feasible, until the toxicity returns to Grade ≤ 2 severity.
Stopping Criteria	Individual Criteria: • Participants who develop a Grade 3 toxicity that is assessed by the investigator to be related to the study drug are to be permanently discontinued from study treatment. • Participants who develop a Grade 4 toxicity, regardless of relatedness to study drug, are to be permanently discontinued from study treatment. Study-Level Stopping Criteria: Study enrollment is to be paused if any of the below criteria are met: • If ≥ 3 subjects develop the <u>same</u> related Grade 4 (life-threatening) adverse event or laboratory abnormality;

	• If ≥ 5 subjects develop the same related Grade 3 or 4 adverse event or laboratory abnormality; • If ≥ 10 subjects develop any related Grade 3 or 4 adverse event or laboratory abnormality. Following assessment by the Data Monitoring Committee (DMC), the DMC will determine whether to stop the study, amend the protocol, or continue the study per protocol.
Statistical Analysis	A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. All analyses of safety and efficacy for this study will be descriptive in nature and presented by group. Subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. Summaries for quantitative variables will include the mean, median, quartiles, standard error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the 95% CI, when appropriate. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.4 or higher). Safety and tolerability will be assessed in terms of AEs, SAEs, and safety laboratory data. Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of treatment-emergent adverse events, defined as TEAEs occurring after randomization will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results and other clinical measures will be summarized using appropriate descriptive statistics.

CCB-CRISIS-02 Schedule of Events

CCB-CRISIS-02 Schedule of Events **Procedures**	**Screen**	**D1**	**D2, 3 (± 8 hr)**	**D4 (± 8 hrs)**	**D5 (± 8 hrs)**	**D8 (± 1 day)**	**D12 (± 1 day)**	**D15 (± 1 day)**	**D22 (±1 day)**	**Final Visit D29 (± 2 days)**
Informed Consent (note Date and Time)	X									
AE/Concomitant Medications (dose, route, duration or ongoing)	X	X		X		X	X	X	X	X
Medical history (relevant within one year or ongoing)/ History of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection)	X									
Demographics (subject reported height and weight, date of birth, gender, race, ethnicity)	X									
Check for Physical Exam abnormalities (subject self-reported)	X									
Pregnancy Test (WOCBP)	X (serum)									X (urine)
Hematology/Chemistry[a]	X	X				X		X		
Vital Signs[b]	X	X		X		X	X	X	X	X
Symptom Assessment[c]	X	X		X		X	X	X	X	X
Viral load sample[d]	X	X		X		X	X	X	X	X
Hospital Status						X		X	X	X
WHO Ordinal Scale Assessment		X				X		X	X	X
Randomize subject and dispense Study Medication		X								
Study drug administration[e]		X	X	X	X					
Drug Accountability						X				

[a]Do not repeat if within 48h of Day 1 visit. Send to Covance Central Laboratory Services (CCLS) for analysis.
[b]Vital signs include heart rate, respiratory rate, body temperature, pO2.
[c]Symptom Assessment will be using a checklist provided to the subject with symptoms such as sore throat, cough, GI symptoms (vomting, diarrhea), ansomia, dysgeusia, other (specify), etc.
[d]Sample Day 1 must be obtained prior to dosing. Viral load specimens will be saliva samples self-collected by the subject using an Oragene® collection system or similar. These samples are to be sent to CCLS for analysis. The viral load sample may also be used to perform viral cultures (sample can be split, no additional sample required).
[e]Subject will self-administer study drug once daily Days 1 – 5 and record doses in a medication diary.
Note that any visits/visit activities may be conducted via telephone, telemedicine, or digital media other than serum pregnancy test and chemistry/hematology sample collection. These labs may be collected at the clinical site or another designated out-patient facility/laboratory or collected via home visit. Arrangements for shipping viral load samples will be made by the study team.

STUDY PERSONNEL

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3 INTRODUCTION

3.1 Coronavirus-19 (COVID-19)

Beginning in December 2019, Chinese scientists isolated a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from patients with virus-infected pneumonia which was later designated as coronavirus disease 2019 (COVID-19) by the World Health Organisation (WHO) (Zhou et al., 2020 [2]; Phelan et al., 2020 [3]).

Approximately 14% of those affected with this virus will develop severe disease requiring hospitalization and oxygen support; 5% will require admission to the intensive care unit (Handel et al., 2020 [4]). Severe cases may be complicated by acute respiratory disease syndrome (ARDS), sepsis and septic shock, and multi-organ failure, including acute kidney injury and cardiac injury. Risk factors for death include older age and co-morbid disease such as hypertension and diabetes (Zhou, et al., 2020 [2]). This means that most patients will be treated as out-patients. Reducing viral load in this environment is critically important for both the subjects themselves by preventing worsening of symptoms and possibly avoiding hospitalization, but also to reduce the transmission of the disease to others in the patients' households and their communities.

3.1.1 Coronavirus Biology

Coronaviruses, like other RNA-based viruses, do not have the machinery to synthesize their own nucleotides and thus depend upon the host intracellular pool of nucleotides for viral replication. In essence, viruses steal the host RNA building blocks, and without these building blocks they are unable to replicate. The SARS-CoV-2 is a single-stranded (positive sense) RNA virus with a genome that is 29,811 nucleotides long, quite a lot larger than other RNA-based viruses (e.g. the hepatitis C genome comprises only 9600 nucleotides). The nucleotide composition is broken down as: 29.9% adenosines, 18.4% cytosines, 19.6% guanines, and 32.1% uridines (Sah et al., 2020 [12]).

3.2 Host Nucleotide Synthesis

Host *de novo* pyrimidine synthesis generates uridine monophosphate (UMP) as the building block for all pyrimidine ribonucleotides and deoxyribonucleotides (Figure 3-1). There exists no salvage pathway for the synthesis of UMP, the fundamental building block of pyrimidines. Inhibition of enzymatic steps upstream of UMP (Figure 3-1) leads to a rapid and profound depletion of intracellular pyrimidines.

3.3 Dihydroorotate dehydrogenase (DHODH)

The enzyme dihydroorotate dehydrogenase (DHODH) catalyzes the 4th step of *de novo* pyrimidine synthesis and inhibition of DHODH completely halts all pyrimidine production. As shown in Figure 3-1, DHODH is located on the inner mitochondrial membrane and transfers electrons between DHO and complex III

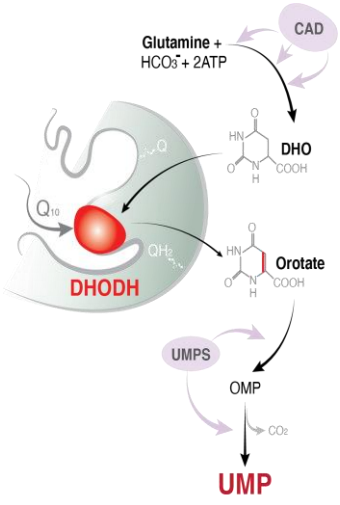

Figure 3-1. DHODH is a mitochondrial enzyme that catalyzes the 4th step of pyrimidine synthesis; it is completely essential for the generation of UMP.

of the electron-transport chain via the reduction of its ubiquinone (coenzyme Q10) cofactor.

DHODH is a clear therapeutic target for the inhibition of host pyrimidine synthesis. The chemical inhibition of DHODH *in vitro* or *in vivo* leads to the rapid depletion of UMP and subsequent depletion of downstream products thymine and cytosine. This forces a cell to rely on the salvage of extracellular pyrimidine nucleotides and this extracellular salvage is not capable of maintaining the cell's normal nucleotide pool (Sykes et al., 2016) [1]).

3.4 Brequinar

Brequinar is an orally available and potent inhibitor of DHODH. Brequinar is one of more than 300 quinoline-carboxylic acid derivatives prepared in an analog synthesis program in the 1980s, which was started after it was found that a compound of this class had antitumor activity. Brequinar was selected by DuPont for further development as a potential clinical drug because of its activity against experimental tumors and because its water solubility made it relatively straightforward to formulate.

In an indication such as treating SARS-CoV-2 infection, brequinar will act as a host-targeting antiviral. It is an orally available and potent inhibitor of dihydroorotate dehydrogenase (DHODH), the enzyme that catalyzes the fourth step in pyrimidine synthesis, namely the conversion of dihydroorotate (DHO) to orotate. DHODH inhibitors, including brequinar, inhibit *de novo* pyrimidine synthesis thereby leading to a depletion of a cell's pool of uridine, cytidine and thymidine ribonucleotides and deoxyribonucleotides.

The antiviral activity of brequinar has been demonstrated in studies of rotavirus replication in human intestinal Caco-2 cells as well as in human primary intestinal organoids (Chen et al., 2019 [6]). Treatment with teriflunomide, another DHODHi, has been effective *in vitro* and *in vivo* in a murine model of foot and mouth disease virus (Mei-Jian et al., 2019 [7]). DHODH inhibition (DHODHi) also inhibited the growth of dengue virus *in vitro* (Wang et al., 2011 [8]). DHODHi also showed antiviral effects against RNA viruses including influenza A, Zika, Ebola and coronavirus SARS-CoV-2 (Xiong et al., 2020 [11])**.** Brequinar has also been shown to inhibit the replication of Ebola virus, vesicular stomatitis virus and Zika virus *in vitro* (Luthra et al., 2018 [9]). Brequinar inhibits the replication of human immunodeficiency virus (HIV) *in vitro* (Andersen et al., 2019 [10]). When considering brequinar as an antiviral for treatment of SARS-CoV-2, oral brequinar is highly bioavailable (>95%) and has good penetration of lung tissue with an average tissue:blood ratio of 0.5 following a single dose of brequinar in the rat. It is therefore expected to achieve a similar period of DHODH inhibition in lung tissue (Brequinar IB [5]).

3.5 Rationale for the Planned Trial

DHODH inhibition has been extensively studied as a potential therapeutic target in the treatment of RNA-based viruses. The inhibition of DHODH is effective in inhibiting viral replication in pre-clinical models involving many RNA-based viruses with nanomolar potency and a high selectivity index (see the Brequinar IB [5], Section 5). In these pre-clinical models, the benefit of DHODH inhibition can be reversed by the supplementation of exogenous nucleotides, confirming that the on-target effect of host pyrimidine depletion is key to the anti-viral activity.

The CCB-CRISIS-02 trial will study standard of care (SOC) with 5 days of brequinar (DHODH inhibition) compared to SOC with 5 days of placebo treatment. Clear Creek Bio hypothesizes that a defined 5-day course of brequinar will inhibit the enzyme DHODH to a degree sufficient to result in the transient depletion of host pyrimidine nucleotides, thereby inhibiting viral replication. A recent publication demonstrated that inhibitors of DHODH could potentiate the activity of inhibitors of RNA-dependent RNA polymerase (RdRp) in the treatment of dengue virus, another single-stranded RNA virus similar to SARS-CoV-2 (Liu et al., 2020 [13]). This inhibition of viral replication may restore the balance in favor of the host immune system for the clearance of SARS-CoV-2.

Marketed DHODHi medications are available, including leflunomide or teriflunomide, however these are very weak inhibitors of DHODH with cellular potency ~500 times lower than brequinar. These low potency inhibitors of DHODH are not expected to have the ability to acutely lower the pool of intracellular pyrimidines to the degree that is required for decreasing the viral load associated with SARS-CoV-2 infection, making brequinar the better choice for acute SARS-CoV-2 infection.

The CRISIS2 study is a proof-of-concept study in patients with SARS-Cov-2 infection and will serve as a basis for future studies to determine the safety and effectiveness of brequinar in COVID-19.

3.5.1 Brequinar Dose Selection

Safety data from previous oncology clinical studies of brequinar with 5 days of consecutive daily dosing suggest that 5 days of daily doses of 100 mg p.o. will be safe and well tolerated. A dose of brequinar 100 mg achieves plasma concentrations of approximately 1 uM (0.4 ug/ml) that should result in sufficient suppression of nucleotide synthesis. When given over 5 days, these plasma concentrations are achieved on a daily basis without accumulation, also assuring the safety of this regimen (see Brequinar IB [5]).

3.5.2 Risk/Benefit of Brequinar

As presented in the Brequinar IB [5], an extensive safety and pharmacokinetic database exists with more than 1,000 patients treated with brequinar. Cancer patients (N = 806) have been exposed to this compound for treatment of a variety of solid tumors at various treatment regimens, doses, and routes including a single dose, once weekly, twice weekly, single dose every 3 weeks, daily times 5 every 4 weeks, and daily times 21 days for multiple courses. Lower doses than used in the cancer studies have also been utilized for patients with psoriasis and organ transplant. The maximum intravenous dose given was 2,250 mg/m^2 every 3 weeks, and the maximum oral dose was 100 mg/m^2 daily for 21 days. There has been limited testing of DHODHi to date in the clinic for infection with SARS-CoV-2. DHODHi therapy at relatively high doses in the context of trials for patients with cancer has the expected safety side-effects of mucositis and bone marrow suppression. Importantly, however, the prior clinical experience in 39 subjects who received daily brequinar for 5 consecutive days at or lower than 100 mg/day show no cases of mucositis and only 1 (2.6%) episode of mild thrombocytopenia. Based on these data the 100 mg per day dose proposed for administration in this study should be within a safe and tolerable range as well as demonstrating the predicted antiviral effect.

The potential benefit in using brequinar to treat SARS-CoV-2 infection is the hypothesis that a 5-day period of brequinar dosing will suppress host *de novo* pyrimidine synthesis for this period thus decreasing viral load. Inhibition of DHODH is expected to reduce the ability of the virus to replicate and it is for this reason that brequinar will be administered to patients with COVID-19 in this study.

3.6 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration of high-dose brequinar in patients with refractory solid tumors, reversible myelosuppression, in particular thrombocytopenia, and mucositis have been the primary dose-limiting toxicities. In addition, skin rash, nausea/vomiting, fatigue, and leukopenia have been dose-limiting in trials utilizing other schedules of brequinar administration. However, these effects were self-limiting, transient, required treatment in few cases, and resolved following discontinuation of dosing. These adverse effects have been associated with higher doses of brequinar given via the intravenous route and for longer durations than the 100 mg dose and 5-day regimen proposed for this study.

In addition to studying a higher risk population with symptomatic COVID-19, a comprehensive safety monitoring plan will be utilized in this study to assess the ongoing safety and well-being of participants (see Section 10.8).

3.7 Possible Interactions with Concomitant Medical Treatments

Brequinar has been administered to subjects taking a variety of concomitant medications that are typical in severely ill cancer patients including antibiotics, antifungals and other critical care medications. No formal interaction studies have been conducted for these medications, however, there have not been any reports of interactions with any medications during the clinical trials with more than 800 cancer patients.

3.7.1 CYP Interactions

No formal clinical drug-drug interaction studies have been performed for brequinar with medications commonly used in treating hematologic malignancies. The nonclinical studies performed to date have demonstrated there is no first-pass metabolism and there have been no apparent hepatotoxic effects in the clinical studies. Brequinar itself does not appear to be a substrate for metabolism by cytochrome P450 enzymes when tested under a variety of conditions. (See Brequinar IB [5]; nonclinical data on file with Clear Creek).

3.8 Steps to be Taken to Control or Mitigate Risks

All subjects will be treated by highly experienced clinicians familiar with the treatment of viral infections and their complications.

4 TRIAL OBJECTIVES

4.1 Primary Objective

To demonstrate a change from baseline in quantitative SARS-CoV-2 viral load for brequinar-treated subjects compared to placebo-treated subjects through Day 29.

4.2 Secondary Objectives

The secondary objectives of this study are:

Through Day 29:

- To characterize the safety and tolerability of brequinar in out-patient COVID-19 subjects as measured by frequencies of grade 3 and 4 AEs and SAEs;
- To demonstrate a shorter duration of viral shedding in subjects treated with brequinar compared to subjects who received placebo;
- To reduce the percentage of subjects requiring hospital admission as an inpatient for >24 hours for brequinar subjects compared to subjects who received placebo;
- To improve survival status through Day 29 for brequinar subjects compared to subjects who received placebo.

4.3 EXPLORATORY OBJECTIVES

- To determine time to viral clearance (two consecutive negative tests);
- To determine time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline;
- To reduce disease severity as measured by the WHO Ordinal Scale score for the subset of subjects with baseline WHO Ordinal Scale of 2 for brequinar subjects compared to subjects who received placebo.

5 TRIAL DESIGN

This will be a phase II randomized, placebo-controlled, double blind, multi-center study with approximately 100 subjects. All subjects will receive standard of care per (SOC) institutional guidelines for treatment of patients with COVID-19 infection. In addition to SOC, the subjects will self-administer one capsule once daily for 5 days.

Subjects will have a Screening Visit followed as soon as possible with Study Day 1. Study procedures are presented in detail in the Schedule of Events (Appendix 15.1). Study visits (virtual or in person) will take place at Screening and on Study Days 1, 8, 15, 22, and 29. The visits that include bloodwork must be conducted at the study site or arrangements made for sample collection at the subject's home or other appropriate location. Other visits/visit activities for that visit may be conducted remotely using telemedicine or other remote technique. Subjects are to self-collect a viral load sample, obtain their respiratory rate, heart rate, body temperature and pO2, and complete a symptom assessment checklist on Days 1, 4, 8, 12, 15, 22, and 29.

6 TRIAL ENDPOINTS

6.1 Primary Endpoint

Quantitative SARS-CoV-2 viral load through Day 29.

6.2 Secondary Endpoints

The secondary endpoints of this study are:

Through Day 29:

- Rates of AEs and SAEs including laboratory assessments;
- Duration of viral shedding;
- Percentage of subjects requiring admission as an inpatient for >24 hours.

6.3 Exploratory Endpoints

- Time to viral clearance (two consecutive negative tests);
- Time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline;
- Disease severity as measured by the WHO Ordinal Scale score for the subset of subjects with baseline WHO Ordinal Scale of 2;

7 TRIAL POPULATION

7.1 Number of Subjects

Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 100 subjects have completed the study. Subjects will be randomized to either standard of care plus brequinar 100 mg or standard of care plus placebo in a 1:1 ratio (approximately 50 subjects assigned to standard of care plus brequinar 100 mg and approximately 50 subjects assigned to standard of care plus placebo).

7.2 Inclusion criteria

1. Willing and able to provide informed consent for the trial, written, electronic, verbal or other method deemed acceptable by the institution and IRB.
2. 18 years of age or older.
3. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other FDA-approved commercial or public health assay within 14 days of randomization.
4. Out-patient (not currently hospitalized or was hospitalized with duration < 24 hours)
5. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men and women treated or enrolled on this protocol must also agree to use adequate contraception for the duration of study participation, and for 90 days after completion of brequinar administration.
6. Male subjects must agree to refrain from sperm donation and female subjects must agree to refrain from ovum donation from initial study drug administration until 90 days after the last dose of brequinar.
7. At least one COVID-19 symptom including but not limited to fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, shortness of breath, dyspnea, anosmia, dysgeusia, or other symptom commonly associated with COVID-19.
8. Able to swallow capsules.

7.3 Exclusion Criteria

1. Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient
2. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test
3. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide) or other agents known to cause bone marrow suppression leading to thrombocytopenia

4. Platelets ≤150,000 cell/mm3
5. Hemoglobin < 10 gm/dL for menstruating women and < 12 gm/dL for all other subjects
6. Absolute neutrophil count < 1500 cells/mm3
7. Renal dysfunction, i.e., creatinine clearance < 30 mL/min
8. AST and/or ALT > 2 x ULN, or total bilirubin > ULN. Gilbert's Syndrome is allowed.
9. Bleeding disorders or blood loss requiring transfusion in the six weeks preceding enrollment
10. Ongoing gastrointestinal ulcer, or gastrointestinal bleeding within 6 weeks of randomization.
11. Chronic hepatitis B infection, active hepatitis C infection, active liver disease and/or cirrhosis per subject report.
12. Heart failure, current uncontrolled cardiovascular disease, including unstable angina, uncontrolled arrhythmias, major adverse cardiac event within 6 months (e.g. stroke, myocardial infarction, hospitalization due to heart failure, or revascularization procedure).

8 STUDY TREATMENTS

8.1 Description of Study Medications

8.1.1 Brequinar

Brequinar and placebo will be supplied as 100 mg capsules. Dosing will be a single 5-day course of brequinar 100 mg capsules or placebo 100 mg capsules once daily for 5 doses.

8.2 Treatment Administration

This will be a phase 2 randomized, placebo-controlled, double blind, multi-center study with approximately 100 subjects. All subjects will receive standard of care (SOC) for COVID-19 infection. Subjects will be randomly assigned in a 1:1 ratio to standard of care plus brequinar or standard of care plus placebo.

8.2.1 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit. The *NIH Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria.

Adverse events (AEs) commonly observed in patients treated with brequinar are provided in the Investigator's Brochure (IB) and include thrombocytopenia, nausea, anemia, diarrhea, vomiting, leukopenia, stomatitis, rash, granulocytopenia, fatigue, and infection. In a study of 209 cancer subjects treated once-weekly (DuP 785-012, see Brequinar IB [5]), the deaths of three patients were attributed to study drug toxicity (two to hemorrhage, one following acute renal failure). Severe toxicities grades (Grades 3 to 4) which typically led to discontinuation in this study included hematologic toxicities (anemia, thrombocytopenia, leukopenia, granulocytopenia), digestive system toxicity (nausea, vomiting, stomatitis, others including gastric hemorrhage) and mucositis.

In three oncology studies with five consecutive days of intravenous (IV) brequinar dosing in 168 subjects (Study 785-001 [14], 785-003 [15], and 785-005 [16]) there were no toxic deaths. For subjects from these three studies who were treated with a daily dose of 100 mg or below (as will be dosed in CCB-CRISIS-02), AEs through 21 days showed that 2 of 39 subjects (5.1%) had a severe (Grades 3 or 4) AE related to study drug (1 subject each with hyperbilirubinemia and hyperglycemia), and no subjects discontinued from the study due to a study drug-related AE. The few study drug related AEs through 21 days at or below the 100 mg dose from these three studies included 2 subjects each with nausea, vomiting, and creatinine elevated and one subject each with thrombocytopenia and diarrhea. When only studies with oral dosing were considered at this dose level (Studies 785-022 [17], 785-031 [18] , and 785-034 [19]), the study drug related AEs through 21 days (each observed in one subject only) included diarrhea, headache, nausea, pruritus, abdominal pain, anorexia, chest pain, dry mouth, fatigue, keratosis, stomatitis, and vomiting. See brequinar IB [5].

In most instances, brequinar-related toxicities were transient, clinically manageable, and reversible upon discontinuation of brequinar treatment. Any of these events reported with brequinar use can be serious in nature and may result in death.

A 5-day course of oral brequinar administered once daily at a low level relative to those administered in the cancer studies is expected to be safe and well tolerated in the COVID-19 population.

8.3 Study Discontinuation

Subjects will remain in the study through at least Study Day 29 (or longer if needed to follow up study drug-related adverse events). Participants may discontinue from the study by withdrawing consent at any time or for any reason as presented in Section 9.7.

8.4 Stopping Criteria

8.4.1 Individual Stopping Criteria

- Participants who develop a Grade 3 toxicity that is assessed by the investigator to be related to the study drug are to be permanently discontinued from study treatment.
- Participants who develop a Grade 4 toxicity, regardless of relatedness to study drug, are to be permanently discontinued from study treatment.
- Subjects who develop Grade 3 or 4 toxicities are to be followed by re-evaluation every 2 days, as feasible, until the toxicity returns to ≤ Grade 2 severity.

8.4.2 Study-Level Stopping Criteria

Study enrollment is to be paused if any of the below criteria are met:

- If ≥ 3 subjects develop the same related Grade 4 (life-threatening) adverse event or laboratory abnormality;
- If ≥ 5 subjects develop the same related Grade 3 or 4 adverse event or laboratory abnormality;
- If ≥ 10 subjects develop any related Grade 3 or 4 adverse event or laboratory abnormality.

Following assessment by the Data Monitoring Committee (DMC, see Section 10.9), the DMC will determine whether to stop the study, amend the protocol, or continue the study per protocol.

8.5 Concomitant Medication/Treatment

Record the name, dose, start/stop date, indication for use, route, and whether ongoing or stopped for medications/treatments taken within two weeks prior to study entry as well as any medications taken during the study are to be recorded. Prohibited medications are identified in Section 8.8.

8.6 Treatment Compliance

Compliance will be assessed by reviewing the subject's medication diary and study records as appropriate.

8.7 Storage, Stability, Labeling and Packaging

8.7.1 Storage and Stability

The study drug is stored at room temperature. Stability testing is ongoing.

8.7.2 Labeling and Packaging

The bulk drug and unit-dose containers will be labeled in accordance with national laws and regulations.

8.7.3 Blinding and Randomization

The trial will be conducted in double blinded, randomized manner with random assignment to standard of care plus brequinar or standard of care plus placebo. The brequinar and placebo capsules will be provided to each participating institution in pre-numbered bottles intended for individual subjects to be dispensed by the institution's pharmacist or designated person. Randomization assignments will be provided by an independent statistician to the drug packaging company. The pharmacist/designated person will dispense the next number in sequence to the next patient who qualifies for the study at an individual site.

8.7.4 Unblinding/Expectedness

Contact the Covance Medical Monitor if it is necessary to break the blind for this blinded study due to an adverse event (AE). Each site will be provided with a sealed envelope containing individual sealed envelopes for subject numbers assigned to that site. Each individual subject number sealed envelope will have the treatment (brequinar or placebo) randomly assigned to that subject number. Do not open the outer envelope or the individual sealed envelope unless it has been agreed with the Medical Monitor and the Sponsor that unblinding is necessary for that particular AE. Unblinding must be documented in the study records. Envelope seals are to be checked to ensure they remain intact during drug accountability monitoring.

If after a discussion with the Medical Monitor, the investigator or treating clinician believes the AE leading to unblinding to be related to the study drug, no further doses of drug should be administered to that subject.

Expectedness will be determined by establishing whether an adverse event is among those identified in the protocol and the brequinar IB or are commonly associated with COVID-19 or similar severe viral illnesses and their complications.

8.7.5 Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator must keep a record of all study medication received, administered, and discarded. It must be clear from the records whether the subject received study medication and what subject number was assigned to which subject. Adequate drug is to be dispensed for the number of subjects expected to be treated at each institution.

The pharmacist/staff member responsible for drug accountability is to document the date and time of dispensing and for what subject the study drug was intended (i.e., record subject initials and birth date or other unique identifier). A pharmacy manual will be provided by the Sponsor.

At the end of the study any unused study drug will be returned to the Sponsor for destruction or may be destroyed locally; disposition of study drug will be documented.

The Sponsor will be permitted access to the trial supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation. Records may be electronic or paper and may be accessed remotely for monitoring/drug accountability purposes.

Each subject will be provided with one bottle with five brequinar or five placebo capsules for the five days of dosing.

8.8 Prohibited Medications

Treatment is prohibited with another DHODH inhibitor (e.g., leflunomide and teriflunomide). Treatment is prohibited with agents known to cause bone marrow suppression leading to thrombocytopenia.

8.9 Study Adjustments Due to COVID-19

Due to the highly contagious nature of COVID-19, multiple adjustments and revised procedures are rapidly evolving regarding clinical trial management and study conduct. Reasonable procedures implemented by study staff to avoid spreading this disease are acceptable to Clear Creek with written permission. Examples include but are not limited to e-consent, telephone consent and study visits conducted by telemedicine, telephone or other digital media.

Background standard of care is to be maintained in both treatment arms. The standard of care is expected to change as additional information, such as that from randomized controlled trials, emerges, and the Sponsor and the treating clinicians will need to address anticipated off-label use of any other drugs, devices, or interventions that might be used to manage COVID-19 (e.g. anticoagulants).

The Sponsor and treating clinicians are to consider changes in SOC over time, for example, overlapping toxicities of brequinar and a SOC treatment expected to be widely used is to be considered. The availability of new standard of care treatment may change over time and vary from one clinical trial site to another. The Sponsor will discuss these issues with FDA should the need arise.

9 CONDUCT OF THE TRIAL

9.1 Ethical and Regulatory Considerations

The trial will be performed in accordance with the Declaration of Helsinki (1964) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Scotland (2000, Note of Clarification 2002 & 2004) and Seoul 2008 (Appendix A), and Fortaleza (Brazil) (2013), and with the International Council on Harmonization (ICH) Tripartite Guideline on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and United States (US) FDA Regulations.

9.2 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki must be implemented in each clinical study before protocol-specified procedures are carried out. Informed consent must be obtained in accordance with US Code of Federal Regulations (21 CFR Part 50), the FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency (March 2020, Updated April 16, 2020) [20], as well as local and national regulations. Information should be given in both oral and written form whenever possible and deemed appropriate by the Institutional Review Board (IRB). Subjects and their relatives, if necessary, must be given ample opportunity to inquire about details of the study.

The Investigator or qualified designated person will verbally inform subjects as to the nature, expected duration and purpose of the trial, the administration of the Investigational Product (IP), and the hazards involved, as well as the potential benefits that may come from treatment with this IP. The trial procedures will be explained in lay language and any questions will be answered. The subjects will be given an IRB-approved consent form. The subjects will be given appropriate time to consider their participation in the trial and have any questions answered prior to signing the consent form. If a subject agrees to participate, he/she will sign and date an informed consent form and be provided with a copy of the signed consent. All subjects who sign an informed consent form are to be recorded on the applicable screening log. If the subject is unable to consent for any reason, a designated family member or healthcare power of attorney or other person may consent per institutional policy.

The subject will be informed that his/her medical records will be subject to review by the Sponsor, Sponsor's representatives, and possibly by a representative of the FDA and other relevant regulatory authorities. Subjects will be informed that they are free to refuse participation in this clinical investigation, and if they should participate, it will be made clear to them that they may withdraw from the trial at any time without prejudicing further medical care they may require. The subject will receive a copy of the consent form as well as an information sheet about the trial.

Informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to completing the informed consent process but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. Documentation of consent will be subject to review by the Sponsor; if in writing, a copy will be given to the subject and a copy will be filed with the subject's medical notes. Verbal consents will be documented by the study team as appropriate and agreed by the IRB.

Note that informed consent procedures have been affected by COVID-19, and the study staff may use any consent method that has been approved by the IRB (e.g., phone consent, verbal consent with witness, e-consent, etc.) of the local institution. In-person consent, written consent signatures and providing hard copies to the subject are examples of procedures that may be foregone under these circumstances.

The study should be discussed with the potential participant only after an initial review of his/her clinical status and appropriateness for participation have been evaluated to determine if he/she meets the subject selection criteria.

A sample subject information sheet and consent form are available from Clear Creek. The final version at each institution may differ depending on institutional requirements and standard formats. This protocol will not be amended for site specific changes as such changes are to be made to the site's consent when required.

9.3 Institutional Review Board

It is the responsibility of the Investigator to submit the protocol, consent form and information sheet to the IRB. An IB will be available for review by the IRB. The protocol and informed consent form (ICF) must be approved by the IRB prior to the recruitment of the first subject. The template consent form may be revised in accordance with site-specific requirements with Sponsor review and approval. A copy of the IRB written approval must be provided to the Sponsor and investigator before the trial may start at that institution. Written approval from the IRB is also required for substantial protocol amendments prior to their implementation.

A substantial amendment may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments are "substantial" when they are likely to have an impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any IP used in the trial.

If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects, the Investigator will notify the Sponsor and the IRB of the new events and the measures taken as soon as possible.

The Investigator will report promptly to the Sponsor and IRB any new information that may adversely affect the safety of the subjects or the conduct of the trial. On completion of the trial, the Investigator will inform the applicable IRB as per local IRB requirements that the trial has ended. If the study is terminated for any reason, the investigator will return all clinical supplies and study-related equipment supplied by the Sponsor to the Sponsor unless otherwise specified.

9.4 Schedule of Events

Study activities will be conducted or supervised by experienced personnel throughout the study based on the Schedule of Events. The subjects may collect the saliva sample for viral load testing and perform other study activities such as body temperature, heart rate, respiratory rate, pO2, and symptom assessments themselves with appropriate training. Telemedicine visits such as phone calls or other remote media are to be utilized as much as possible. Subjects may need to come to an out-patient facility or be visited by a home health professional for some study assessments.

See 15.1 Schedule of Events in Appendix A for the full list of study assessments and timings.

Blood chemistry tests include blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALK), alanine amino transferase (ALT), aspartate amino transferase (AST), total bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium), lactate dehydrogenase (LDH).

Hematology tests include hemoglobin, hematocrit, complete blood count with full differential, and platelet count.

Viral load sampling is to be carried out on Days 1, 4, 8, 12, 15, 22, and 29. The subject is to self-collect saliva samples with appropriate training for this analysis. Samples may be banked for future retrospective analyses.

Hospitalization status after enrollment is to be recorded as not hospitalized or admitted to hospital as an in-patient with admission > 24 hours.

9.5 Study Conduct

The study visits are to be conducted as shown in the Schedule of Events, Appendix 15.1.

Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF.

9.5.1 Unscheduled Visits

Unscheduled visits and tests are permitted as needed to assess AEs/SAEs throughout the study. Unscheduled visits and tests are also permitted as needed to assess AEs/ SAEs with onset within two (2) weeks after the final study visit providing the AE is considered related to study drug

9.6 Compliance with Study Procedures

The time at which study procedures are conducted should follow the protocol timelines as closely as possible. However, it is recognized in a clinical setting that protocol-specified timings may not occur exactly as specified in the protocol, particularly when conducted remotely by the subject. Provided that activities are carried out within the identified windows it will not be necessary to file a protocol deviation. Remote visits such as a telemedicine visit may be conducted to collect as much information as possible remotely. A home visit or return to the clinical site or an out-patient laboratory may be arranged for safety labs or other assessments, when required. Telemedicine or

other remote technique is to be utilized to ensure subject compliance when subject is performing self-collection of study assessments.

9.7 Early Withdrawal from the Study

A subject may withdraw from the study at any time for any reason or for one of the reasons listed below. The Sponsor or Investigator may also terminate a subject's study participation after discussion with the other party if it is believed it would be unsafe for the subject to continue in the study.

Subjects must discontinue study medication if any of the following events occur:

- Significant protocol violation or non-compliance, either on the part of the subject or the investigator or other site personnel;
- Decision of the Investigator or Sponsor that removal is in the subject's best interest;
- Severe unrelated medical illness or complication;
- Safety reasons/ significant adverse event;
- Subject request (withdrawal of consent);
- Sponsor decision.

Collect/conduct all scheduled evaluations even for subjects who discontinue study medication prior to completing the treatment period unless consent is withdrawn.

9.8 Early Termination of the Study

If the Sponsor or an Investigator believes it would be unsafe to continue the study, or for any reason at the Sponsor's request, the study may be terminated at that site or the entire study terminated after discussion with the other parties.

The Sponsor will provide a written statement to the IRB and the relevant regulatory authority with the reasons for termination of the study. This will be conducted within 15 days of the decision to terminate the study.

If the study is terminated, a close out monitoring visit will be performed and applicable procedures will be carried out to close the trial site(s).

9.9 Non-Childbearing Potential

Women of non-childbearing potential are defined as those who have no uterus, ligation of the fallopian tubes, or permanent cessation of ovarian function due to ovarian failure or surgical removal of the ovaries. Documentation of surgical procedure or physical examination is required for subjects who have had a hysterectomy or tubal ligation. A woman is also presumed to be infertile due to natural causes if she has been amenorrheic for greater than 12 months and has an FSH greater than 40 IU/L. In the absence of such documentation, a negative serum pregnancy test is required for inclusion into the study.

10 ADVERSE EVENT REPORTING

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

Events that occur prior to informed consent will be entered as medical history; AEs that occur after informed consent will be entered on the AE form.

Subjects will be questioned and observed for evidence of AEs, whether or not judged by the Investigator or designated person to be related to study drug. All AEs will be documented in the subject's medical record and CRF. For any pre-existing condition or abnormal laboratory finding that changes in severity after dosing, this change should be recorded as an AE. New abnormal laboratory findings that are clinically significant are considered AEs.

All adverse events will be collected from the time of informed consent through Day 29. After Day 29, collect/record only Serious Adverse Events (SAEs) which are assessed by the Investigator or designated person to be related to study drug. AE details are to be documented including start and stop date and times, whether continuous or intermittent, severity, any intervention utilized to correct the event (e.g., medication, surgery, or other therapy), outcome and the relationship to the study drug.

AEs identified in the protocol as critical to the evaluation of safety must be reported to the Sponsor by the Investigator according to the reporting requirements within the time periods specified in the protocol.

AEs determined by the Investigator to be related to study drug must be followed until resolution or until they are considered stable or for at least 30 days after discontinuation of study drug.

Abnormal laboratory values or test results occurring after study enrollment constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, are Grades 3 or 4, or require therapy.

If a death occurs during the SAE reporting period, the cause of death such as pneumonia, ARDS, or respiratory failure, is considered as the AE and the death is considered its outcome. Death should be considered an outcome, not an event. The event or condition leading to death should be recorded and reported as a single medical concept on the AE eCRF. Generally, only one such event should be reported. “Fatal” will be recorded as the outcome of this respective event; death due to an outcome of an AE will not be recorded as separate event. If the primary cause of death is disease progression, the cause of death should be clearly identified as COVID-19.

In cases of surgical or diagnostic procedures, the condition leading to the procedure is considered as the AE instead of the procedure itself. Each AE will be coded by the Sponsor from the verbatim text to a preferred term using a thesaurus based on the Medical Dictionary for Regulatory Activities (MedDRA). For example, record appendicitis, not appendectomy.

The following guidelines will be followed for the recording and reporting of adverse and serious adverse events.

1. The medical history section of the case report form will serve as the source document for baseline events.

    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed.

        i. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.

2. Adverse events occurring after signing consent are to be recorded in the eCRF using the AE form.

3. Serious adverse events will be reported to the local IRB according to institutional policy.

The *NIH Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf) will be used for adverse event reporting.

10.1 Follow Up of Grade 3 or 4 Toxicities

Grade 3 or 4 toxicities are to be followed by re-evaluation every 2 days, as feasible, until the toxicity returns to Grade ≤ 2 severity.

10.2 Infection Follow Up

Any new infection that occurs on study regardless of infecting agent (i.e., viral or non-viral) should be captured. Additionally, the site of infection and source of culture (BAL, tracheal aspirate, sputum, blood, urine, etc.) should also be recorded.

10.3 Classification of Causality

Attribution is the relationship between an adverse event or serious adverse event

and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment

Guidance for assessing causality:

The Investigator will need to determine whether an AE is considered related to ("caused by"') the study drug rather than some underlying condition, for example, COVID-19.

For the purposes of this study, 'drug related' shall mean 'Definite', 'Probable' and 'Possible' relationship to drug as determined by the Investigator.

10.4 Classification of Severity

The NIH Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017) will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria.

AEs that are expected are subject to expedited reporting only if the adverse event varies in nature, intensity or frequency from the expected toxicity information that is provided in the Investigator Brochure.

10.5 Serious Adverse Event (SAE) Reporting

The regulatory definition of an SAE is any untoward medical occurrence or effect that at any dose fulfills one or more of these criteria:

- results in death;
- is life threatening (at the time of the event);
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability / incapacity
- is a congenital anomaly / birth defect;
- or is an event considered medically serious by the Investigator.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

A life-threatening adverse event is one that places the patient/subject, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.

An unexpected adverse event is any adverse drug event, the nature or severity of which is not consistent with the applicable product information (e.g. IB for an unauthorized investigational product or summary of product characteristics for an authorized product).

Enter only one event as the reason for the SAE on the SAE form. Other non-serious events which did not directly result in the SAE should be detailed in the description section on the SAE form and listed separately as AEs if necessary. For fatal SAEs, report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term.

Note that hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of COVID-19 infection, not associated with any deterioration in condition;
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent;
- Social reasons and respite care in the absence of any deterioration in the subject's general condition;
- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above.

ANY SERIOUS ADVERSE EVENT MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) BY EMAIL TO THE SAE REPORTING EMAIL USING THE FORM PROVIDED. ENTER THE SUBJECT'S AVAILABLE INFORMATION INTO THE eCRF WITHIN 48 HOURS.

The subjects are to be identified in the immediate and follow-up reports by unique code numbers supplied by the sponsor. The email address for reporting SAEs can be found below and at the front of this protocol.

Reports relating to the subject's subsequent medical course following an SAE must be submitted to Covance Patient Safety until the event has subsided or, in case of permanent impairment, it stabilizes, and the overall clinical outcome has been ascertained.

SAE REPORTING EMAIL: SAEIntake@covance.com

Medical Monitor:

Norberto Soto, MD	Telephone:	(609) 212-7892
Covance Physician/Medical Monitor	Email:	Norberto.Soto@Covance.com

Sponsor Representative:

Barbara Powers, MSN, Ph.D.	Telephone:	M: (484) 686-0545
VP, Clinical Operations	Email:	bpowers@clearcreekbio.com

All SAEs will be reported to the IRB periodically, at the end of the study, or per local institutional guidelines.

10.6 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected, unexpected, serious adverse reactions (SUSARs) are SAEs that are both related to the study drug (Relationship = Related) and unexpected (not previously described in the investigator's brochure). All SUSARs will be reported in an expedited manner to the Sponsor or designee and IRB by the Investigators and to all relevant regulatory authorities by the Sponsor. Expectedness will be judged by the Covance Physician and site Investigator. It is critical that all SAEs are reported within the 24-hour guideline so that the expectedness determination can be made. SUSARs require immediate attention and expedited reporting to relevant regulatory authorities.

The Sponsor will ensure that all relevant information about **fatal or life-threatening** SUSARs are appropriately recorded and reported to the concerned Regulatory Authority and to the concerned

IRB(s) within seven (7) calendar days of the date of first report to Covance Patient Safety / Sponsor. Follow-up information will be communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs will be reported to the Regulatory Authority and to the IRB(s) concerned as soon as possible within a maximum of fifteen calendar days of first notification to Covance Patient Safety / Sponsor.

The Sponsor or designee will also inform all Investigators studying the investigational medicinal product about SUSARs and ensure that all IRBs have been notified.

For reported deaths of a subject, the Investigator shall supply the Sponsor and the IRB(s) with requested additional information on an expedited basis.

10.7 Pregnancies

Pregnancy occurring in a female subject or a subject's partner during the study period will be documented in the subject's source documents and reported to Covance Patient Safety (by email to SAEIntake@covance.com) and to the IRB by the investigational staff within 1 working day of their knowledge of the event. The collection period for a pregnancy occurring in a subject or a subject's partner will begin at the first dose of study drug and will continue through 90 days after the last dose of study drug. Monitoring of the subject or partner should continue until the conclusion of the pregnancy, if the subject or subject's partner has consented to this. Monitoring of the baby should continue for 3 months after birth, if the subject or subject's partner has consented to this.

Pregnancy itself is not an AE; it should be reported for tracking purposes. The Investigator or designee will discontinue the pregnant subject from the treatment aspects of the study, continue to follow her per protocol for safety outcomes only, and advise her to seek prenatal care and counseling from her primary care provider. Data on fetal outcome and breast-feeding will be collected for regulatory reporting and drug safety evaluation, if the subject has consented to this.

If the pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as (S)AEs.

The site clinical staff will request the pregnant subject to notify the site of the outcome of the pregnancy (i.e., birth, loss, or termination). To help ensure this, the site clinical staff will follow the subject until the end of pregnancy, with the subject's consent. This request and the subject's response will be documented in the subject's source document.

10.8 Safety Monitoring for Hematologic Toxicities

Myelosuppression is a known effect of DHODH inhibition that is associated with prolonged exposure and high doses. To reduce the risk of this effect with brequinar in COVID-19 subjects, the extensive brequinar safety database with over 1,000 patients has been evaluated to select a dose

level expected to be safe and well tolerated with regard to hematologic toxicity. In addition to enhancing safety by selecting a relatively brief 5-day exposure and a low brequinar dose, all subjects in the clinical trial will be under the care of highly qualified medical personnel. Clinically significant out-of-range laboratory results will be reported as adverse events.

In addition to real time assessments by the treating clinical team, the Covance Medical Monitor will assess the available hematology data on a periodic basis to identify any pathologic trends or safety issues. Any apparent increase in the expected rate or severity of hematologic safety events will be discussed with the Principal Investigators and the Sponsor. In addition, the Data Monitoring Committee (DMC) will assess available hematology data on a periodic basis to independently assess any pathologic trends or safety issues. If the rate or severity of hematologic toxicities appears to be above the expected rate or the severity appears worse than that expected, the trial enrollment will be suspended and no further subjects will be treated while a comprehensive data review is conducted. Depending on the outcome of the safety review the study may be stopped, the design adjusted, or the study may continue as designed. Individual and Study stopping rules are provided in Section 8.4.

Safety laboratory results are to be initially assessed in real time by the Principal Investigator or designated person. Any study drug-related clinically significant out-of-range laboratories or study drug-related adverse events will be followed as needed until resolution or stable.

The in-clinic assessments and telemedicine/phone call visits will specifically ask about possible hematologic toxicity including any evidence of the list below. Subjects will be provided with a list of the following events in lay terms and will be instructed to call the research team if any of these events occur.

- Ecchymosis/purpura/petechiae
- Epistaxis
- Hemoptysis
- Hematuria
- Gingival bleeding
- Prolonged bleeding time from needle sticks, abrasions or lacerations
- Hematemesis
- Rectal bleeding
- Blood in stool
- Any other unusual bleeding noted by the subject or caregiver

Any of these symptoms considered clinically significant will be recorded as an adverse event and must be followed until resolved or stable.

10.9 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established to provide independent oversight to this trial. The primary responsibility of the DMC will be to review the progress and conduct of the trial in order to maintain scientific rigor and to ensure the wellbeing of subjects participating in the trial. The specific responsibilities of the DMC will be detailed in a separate DMC charter. The DMC will include at a minimum at least one statistician and two clinicians who will perform

periodic data review to assess whether there are clinically significant differences between treatment arms that could affect participant safety. Following such a review, the DMC Chair will advise the Sponsor that the study be stopped, the design changed, or that the study may continue per protocol.

10.9.1 DMC Safety Review Schedule

The DMC is to review adverse events and safety laboratory assessments after the first 20 subjects complete the Day 8 visit, and again after the first 40 subjects complete the Day 8 visit.

11 STATISTICAL CONSIDERATIONS

A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. All analyses will be descriptive in nature and presented by group.

Summaries for quantitative variables will include the mean, median, quartiles, standard error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and 95% confidence interval (CI), when appropriate. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.4 or higher).

Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. The following sections will briefly summarize of the planned statistical analyses and analysis sets for the primary and secondary endpoints.

11.1 Study Populations for Analysis

All safety analyses will be based on the ITT population, which is defined as all randomized subjects. As will be described in the SAP, efficacy analyses of changes in viral load will be based on the population of subjects with detectable viral load at baseline or similar qualification. Sample size may be adjusted if an inadequate number of subjects have detectable viral load at baseline.

11.2 Safety Analyses

Safety and tolerability will be assessed in terms of AEs, SAEs, WHO Assessments, and safety laboratory data.

Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of post-randomization adverse events will be tabulated by MedDRA preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results and study assessments will be summarized using appropriate descriptive statistics.

11.3 Efficacy Analyses

Efficacy will primarily be assessed via viral load changes.

11.4 Sample Size Considerations

Formal sample size calculations are not applicable for this proof-of-concept study. The sample size of approximately 100 subjects planned to be entered in this trial is expected to be adequate to provide safety and efficacy information to advise future study design.

11.5 Randomization

A randomization scheme will be provided by an independent statistician to the drug packaging company to ensure subjects are randomly assigned to SOC + brequinar or SOC + placebo in a 1:1 ratio.

11.6 Pooling of Study Centers

Not applicable to this small, early phase study.

11.7 Interim Analysis

No interim analysis is planned for this trial.

12 INVESTIGATOR RESPONSIBILITIES

12.1 Investigator's Performance

The Investigator will ensure that all those concerned with conducting the trial are:

- provided with copies of the protocol and all safety information prior to the start of the trial;
- trained regarding the conduct of the study and the training has been documented.

The Investigator will sign the Investigator's Statement and Agreement found in Section 15.2 to indicate commitment to comply with the contents.

12.2 Confidentiality

The Investigator shall assure the subject that his/her identity will be protected and confidentiality will be maintained during all audits and inspections of the trial site and documentation. A unique number will be assigned to each subject at the start of the trial and this, with the subject's initials, will be used to identify the subject. In some cases, a further step may be taken to assign "fake initials" to the subject, per individual site requirements. The subject's number will be the site number followed by the number of this subject at this site and will be used as the unique identifier in the source records and on the eCRF, on all trial correspondence and in the trial database. The Investigator will keep a list of identification codes or initials used for each subject along with the unique number assigned.

All information provided to the Investigator relevant to the investigational product (IP), as well as information obtained during the course of the trial will be regarded as confidential. The Investigator and members of his/her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the Sponsor which will not be unreasonably withheld, except as required by law, or as permitted by the Publications section of this protocol, Section 12.7.

The Investigator will take all measures to ensure subject's confidentiality will be maintained at all times.

12.3 Source Documentation

Investigators are to maintain adequate source documentation of the original study data, for example medication records, laboratory reports and pharmacy records as appropriate. The Investigator will allow inspections of the trial site and documentation by clinical research and audit personnel from the Sponsor, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the eCRFs. In order to do this, direct access to the subjects' medical or clinic records is necessary. The Investigator will ensure that certain information is contained in the medical or clinic written or electronic records of the subject and that the entries are signed and dated, as follows:

- sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories;

- a note on the day the subject entered the trial describing the trial number, the IP being

evaluated, the trial number assigned to that subject and a statement that consent was obtained;

- a note of each subsequent trial visit including any concerns about AEs and their resolution;
- notes of all concomitant medication taken by the subject, including start and stop dates;
- a note of when the subject terminated from the trial, the reason for termination and the subject's general condition at termination;
- a copy of the signed informed consent form should be kept in the medical records of each subject during the clinical phase of the study. A signed copy should also be filed in the investigator file.

12.4 Data Collection

Suitably qualified and trained personnel at the trial site will ensure compliance with the protocol, adherence to ICH GCP obligations, proper maintenance of trial records including IP accountability records, correct administration of IP including storage conditions and accurate reporting of AEs. In addition, suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. All queries and discrepancies relating to the data collection are to be resolved at the completion of the trial. Remote data capture is encouraged whenever possible.

12.5 Case Report Forms, Investigator's Site File and Record Retention

The Sponsor may provide the CRFs in paper, electronic (eCRF), or other media. The forms will be reviewed against source documentation at each monitoring visit. All CRFs and supporting source documentation must be completed and available to the Sponsor in a timely manner. Changes or corrections due to data clarification and resolutions will be tracked by paper or electronically with an audit trail.

Prior to review of the case report forms by the Sponsor's representative, they should be reviewed for completeness and accuracy by the Investigator or a member of the research team.

The Investigator must maintain an Investigator Site File which includes, but is not limited to, the IB, the protocol plus any amendments, all correspondence with the IRB including the approval for the trial to proceed, Regulatory Authority approval/ notification (if applicable) including a sample of an approved informed consent, IP accountability, Source Documents, investigator and staff curricula vitae (CVs,) trial documentation, and all trial correspondence. The original signed informed consent forms and the final report will be kept in the Investigator Site File.

The Investigator will archive all essential documents. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The Investigator has a responsibility to retain essential documents for as long as is required by the Sponsor and applicable regulatory authorities. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained. Investigators will be asked to contact the Sponsor prior to the destruction of any data or removal to another site if this occurs prior to the Sponsor

notification that the documentation is no longer required. Any transfer of ownership of the data or of documents will be documented in writing. The new owner will assume responsibility for data retention and archiving.

Should the Investigator retire, relocate, or for other reasons withdraw from the responsibility of keeping the trial essential documents, custody must be transferred to a person who will accept that responsibility, and the Sponsor must be notified in writing of the name and address of said person.

12.6 Non-Protocol Research

No investigational procedures other than those outlined in this protocol may be undertaken on the subjects in this trial without the prior written permission of the subject, the Sponsor, the IRB and, when appropriate, the regulatory authority.

12.7 Publication

The Sponsor acknowledges the benefit of making widely available the results of all clinical trials and intends to publish the results of this trial. All publications resulting from the clinical trial must be in a form that does not reveal technical information that the Sponsor considers confidential or proprietary. A copy of any abstract, presentation or manuscript proposed for publication must be submitted to the Sponsor for review at least 30 days before its submission for any meeting or journal. In addition, if deemed necessary by the Sponsor for protection of proprietary information prior to patent filing, the Investigator agrees to a further delay of 60 days before any presentation or publication is submitted. The Sponsor reserves the right to include the report of this trial in any regulatory documentation or submission or in any informational materials prepared for the medical profession.

Authorship determination will be at the discretion of the Sponsor and will include evaluation of the following criteria: Investigator must participate in the review of and content of the protocol; review and comment on the study results; participate in the writing, reviewing and commenting of the manuscript; and approve the final manuscript for submission.

13 SPONSOR RESPONSIBILITIES

13.1 General

The Sponsor agrees to adhere to the ICH Note for Guidance on GCP (CPMP/ICH/135/95, Jan.97) and US FDA Regulations. It is the Sponsor's responsibility to obtain appropriate regulatory approval to perform the trial (if applicable). The Sponsor should notify promptly all concerned investigator(s), IRB(s) and the Regulatory Authority of findings that could adversely affect the health of the patients/ subjects, impact on the conduct of the trial or alter the Regulatory Authority's authorization to continue the trial. If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects the Sponsor will notify the relevant regulatory authority and relevant IRB of the new events, the measures taken and the plan for further action as soon as possible. This will be by telephone in the first instance followed by a written report.

On completion of the trial, the Sponsor will inform the regulatory authority that the trial has ended. If the study is terminated for any reason the Sponsor will provide a written statement to the relevant regulatory authority and the IRB with the reasons for termination of the trial. This will be conducted within 15 days of the decision to terminate the trial. The Sponsor will report in an expeditious manner all SUSARs to the relevant regulatory authority and IRBs.

13.2 Indemnity

The Sponsor will provide compensation insurance against any risk incurred by a subject as a result of participation in this trial. The Sponsor will indemnify the Investigators as detailed in a separate document.

13.3 Data Monitoring

Suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site or will access the electronic health record (EHR) or conduct remote monitoring visits at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. CRFs and source documentation will be available for review during monitoring visits to the trial site. The function of this monitoring is to ensure compliance with the protocol, adherence to regulatory and GCP obligations, proper maintenance of records including IP accountability records, correct administration of IP including storage conditions and accurate reporting of AEs. On-site visits are not required for any monitoring visits for this study.

Once the data from the case report forms have been entered onto the database, they will be reviewed, and the data verified against the subject's source data. Any discrepancies will be tracked by paper or electronically with an electronic audit trail.

13.4 Audit

The Sponsor has an obligation to audit a proportion of studies. A department other than the clinical department will undertake this obligation. Therefore, the Sponsor, an independent auditor or a regulatory authority may audit the trial site and trial documentation. These audits may take place while the trial is being conducted or up to several years later.

13.5 Confidentiality

The Sponsor will not keep any material on file bearing any subject's name, and subjects' confidentiality will be maintained at all times.

13.6 Finance

This will be the subject of a separate agreement between the Investigator/Institution and Sponsor.

14 REFERENCES

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14. Study DUP 785-001 Clinical Study Report (on file with Clear Creek)
15. Study DUP 785-003 Clinical Study Report (on file with Clear Creek)
16. Study DUP 785-005 Clinical Study Report (on file with Clear Creek)
17. Study DUP 785-022 Clinical Study Report (on file with Clear Creek)
18. Study DUP 785-031 Clinical Study Report (on file with Clear Creek)
19. Study DUP 785-034 Clinical Study Report (on file with Clear Creek)
20. FDA Guidance "COVID-19: Developing Drugs and Biological Products for the Treatment or Prevention (https://www.fda.gov/media/137926/download)

15 APPENDICES

15.1 Appendix A: CCB-CRISIS-02 Schedule of Events

CCB-CRISIS-02 Schedule of Events **Procedures**	**Screen**	**D1**	**D2, 3 (± 8 hr)**	**D4 (± 8 hrs)**	**D5 (± 8 hrs)**	**D8 (± 1 day)**	**D12 (± 1 day)**	**D15 (± 1 day)**	**D22 (±1 day)**	**Final Visit D29 (± 2 days)**
Informed Consent (note Date and Time)	X									
AE/Concomitant Medications (dose, route, duration or ongoing)	X	X		X		X	X	X	X	X
Medical history (relevant within one year or ongoing)/ History of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection)	X									
Demographics (subject reported height and weight, date of birth, gender, race, ethnicity)	X									
Check for Physical Exam abnormalities (subject self-reported)	X									
Pregnancy Test (WOCBP)	X (serum)									X (urine)
Hematology/Chemistry[a]	X	X				X		X		
Vital Signs[b]	X	X		X		X	X	X	X	X
Symptom Assessment[c]	X	X		X		X	X	X	X	X
Viral load sample[d]	X	X		X		X	X	X	X	X
Hospital Status						X		X	X	X
WHO Ordinal Scale Assessment		X				X		X	X	X
Randomize subject and dispense Study Medication		X								
Study drug administration[e]		X	X	X	X					
Drug Accountability						X				

[a]Do not repeat if within 48h of Day 1 visit. Send to Covance Central Laboratory Services (CCLS) for analysis.
[b]Vital signs include heart rate, respiratory rate, body temperature, pO2.
[c]Symptom Assessment will be using a checklist provided to the subject with symptoms such as sore throat, cough, GI symptoms (vomiting, diarrhea), anosmia, dysgeusia, other (specify), etc.
[d]Sample Day 1 must be obtained prior to dosing. Viral load specimens will be saliva samples self-collected by the subject using an Oragene® collection system or similar. These samples are to be sent to CCLS for analysis. The viral load sample may also be used to perform viral cultures (sample can be split, no additional sample required).
[e]Subject will self-administer study drug once daily Days 1 – 5 and record doses in a medication diary.
Note that any visits/visit activities may be conducted via telephone, telemedicine, or digital media other than serum pregnancy test and chemistry/hematology sample collection. These labs may be collected at the clinical site or another designated out-patient facility/laboratory or collected via home visit. Arrangements for shipping viral load samples will be made by the study team.

15.2 Appendix B: Investigator's Statement and Agreement

STUDY NUMBER: CCB-CRISIS-02

The CRISIS2 Study: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2.

INVESTIGATOR'S STATEMENT AND AGREEMENT

I (*the Investigator*) have read this protocol and hereby agree to conduct the trial in accord with all of its provisions. It is further agreed that the details of this trial and all information provided to me by Clear Creek Bio, Inc. (*the Sponsor*) will be held in the strictest confidence and will not be revealed for any reason without written authorization from Clear Creek Bio, Inc. except to those who are to participate in the conduct of the trial.

I agree that all data, the case report forms, and all materials provided for the conduct of the trial are the property of Clear Creek Bio, Inc. unless specified otherwise in writing. It is understood that Clear Creek Bio, Inc. will utilize the information derived from this trial in various ways, such as for submission to government regulatory agencies, required internal reports, and presentations without violating patient/ subject confidentiality in any way.

I further agree that Clear Creek Bio, Inc. or its representatives will be permitted access, in accordance with current Good Clinical Practice Guidelines, to all data generated by this trial and the source documents from which case report form data were generated.

PRINCIPAL INVESTIGATOR

Printed Name: _____

Signature: _____ Date: _____

15.3 Appendix C: WHO Ordinal Scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

WHO clinical progression scale

STUDY PROTOCOL

The CRISIS2 Study: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2

Study No: CCB-CRISIS-02

Version: 2.0

Version Date: 15 September 2020

Sponsor:

Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

Sponsor Telephone: (617) 765-2252

Sponsor Facsimile: (617) 863-2082

IND Number: 149291

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine amino transferase
AML	Acute myeloid leukemia
ARDS	Acute respiratory disease syndrome
AST	Aspartate amino transferase
BRQ	Brequinar
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus-19 infection
CRP	c-reactive protein
CTCAE	Common terminology criteria for adverse events
CTEP	Cancer Therapy Evaluation Program
CV	Curricula vitae
DHO	Dihydroorotate
DHODH	Dihydroorotate dehydrogenase
DHODHi	Dihydroorotate dehydrogenase inhibitor
DMC	Data Safety Monitoring Board
ECMO	Extra corporeal membrane oxygenation
EHR	Electronic health record
ESR	Erythrocyte Sedimentation Rate
EUA	Emergency Use Authorization
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council on Harmonization
ICU	Intensive care unit
IMP	Inosine-5’ phosphate
IP	Investigational product
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NEWS2	National Early Warning System (NEWS) 2 Score
RNA	Ribonucleic Acid
RdRp	RNA-dependent RNA polymerase
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	SARS Coronavirus 2
SOC	Standard of Care
SUSAR	Suspected unexpected serious adverse reaction
SpO_2	Peripheral capillary oxygen saturation

Abbreviation	Definition
UMP	Uridine 5'-monophosphatase
US	United States
XMP	Xanthosine-5' phosphate
WHO	World Health Organization
WOCBP	Women of childbearing potential

2 SYNOPSIS

CCB-CRISIS-02 SYNOPSIS	
IND	149291
Title	The CRISIS2 Study: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2
Protocol Number	CCB-CRISIS-02
Rationale	Brequinar is a potent DHODH inhibitor that has been previously studied in more than 1,000 cancer, psoriasis, and organ transplant patients. Brequinar has been found to have potent *in vitro* antiviral activity against many RNA viruses including SARS-CoV-2. The antiviral activity of brequinar against SARS-CoV-2 is likely due to DHODH inhibition and shows nanomolar potency and a high selectivity index in inhibiting viral replication in *in vitro* studies. The CRISIS2 trial will study out-patients (non-hospitalized patients) who have a positive SARS-CoV-2 test and are symptomatic. Subjects will be randomized to receive standard of care (SOC) + 5 days of brequinar or SOC + 5 days of placebo. The purpose of this study is to determine if the *in vitro* antiviral activity of brequinar can be duplicated in patients infected with SARS-CoV-2 by measuring the effect of brequinar on viral shedding. Importantly, the safety and tolerability of brequinar will also be determined in these patients. The results of this proof-of-concept study will inform future studies that will help determine if brequinar is a safe and effective drug for the treatment of SARS-CoV-2 infection.
Investigational Product and Dosage	Subjects will be randomized in a 1:1 ratio to either standard of care (SOC) + 5 days of brequinar 100 mg or SOC + 5 days of placebo. Investigational product will be supplied as either brequinar 100 mg oral capsules or placebo capsules. The subjects are to self-administer one capsule on Study Days 1 – 5. Treatment assignment will be randomized, double-blind.
Primary Objectives	● To demonstrate a change from baseline in quantitative SARS-CoV-2 viral load for brequinar-treated subjects compared to placebo-treated subjects through Day 29.
Secondary Objectives	Through Day 29: ● To characterize the safety and tolerability of brequinar in out-patient COVID-19 subjects as measured by frequencies of grade 3 and 4 AEs and SAEs; ● To demonstrate a shorter duration of viral shedding in subjects treated with brequinar compared to subjects who received placebo;

	● To reduce the percentage of subjects requiring hospital admission as an in-patient for > 24 hours for brequinar subjects compared to subjects who received placebo; ● To reduce all-cause mortality through Day 29 for brequinar subjects compared to subjects who received placebo.
Exploratory Objectives	Through Day 29: ● To determine time to viral clearance (two consecutive negative tests); ● To determine time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline; ● To determine time to clinical improvement as measured by a favorable shift in the WHO Ordinal Scale score measured for the subset of subjects with baseline WHO Ordinal Scale of 2 for brequinar subjects compared to subjects who received placebo.
Design	This will be a phase 2 randomized, double blind, multi-center study with approximately 100 subjects. All subjects will receive SOC per relevant guidelines for treatment of out-patients with COVID-19 infection. In addition to SOC, subjects will self-administer one capsule once daily for 5 days. Subjects will have a Screening Visit followed as soon as possible with Study Day 1. Study procedures are presented in detail in the Schedule of Events. Study visits (virtual or in person) will take place at Screening and on Study Days 1, 8, 15, 22, and 29. The visits that include bloodwork must be conducted at the study site or arrangements made for sample collection at the subject's home or other appropriate location. Other visits/visit activities for that visit may be conducted remotely using telemedicine or other remote technique. Subjects are to self-collect a viral load sample, obtain their respiratory rate, heart rate, body temperature and SpO2, and complete a symptom assessment on Days 1, 4, 8, 12, 15, 22, and 29. A home health nurse will visit the subject at Screening and on study Days 1, 8, 15, 22, and 29. Telemedicine visits will be conducted by site staff on study Days 4 and 12.
Sample Size:	Approximately 100 subjects will be randomized to 5 days of either SOC + brequinar 100 mg or SOC + placebo in a 1:1 ratio (approximately 50 subjects assigned to brequinar 100 mg and 50 subjects to placebo).
Number of Sites:	Approximately 15
Study Period:	An enrollment period of 3 months is expected.
Inclusion Criteria:	1. Willing and able to provide informed consent for the trial, written, electronic, verbal, or other method deemed acceptable by the institution and IRB. 2. 18 years of age or older.

	3. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other FDA-approved commercial or public health assay within 14 days of first dose. 4. Out-patient (never hospitalized as an in-patient for COVID-19 or was evaluated/treated for COVID-19 only in the Emergency Room with a stay of < 24 hours). 5. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men and women treated or enrolled on this protocol must also agree to use adequate contraception for the duration of study participation, and for 90 days after completion of brequinar administration. 6. Male subjects must agree to refrain from sperm donation and female subjects must agree to refrain from ovum donation from initial study drug administration until 90 days after the last dose of brequinar. 7. Must have at least one COVID-19 symptom including but not limited to fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, shortness of breath, dyspnea, anosmia, dysgeusia, or other symptom commonly associated with COVID-19. 8. Able to swallow capsules.
Exclusion Criteria:	1. Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient 2. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test 3. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide) or other agents known to cause bone marrow suppression leading to thrombocytopenia 4. Platelets ≤150,000 cell/mm^3 5. Hemoglobin < 10 gm/dL 6. Absolute neutrophil count < 1500 cells/mm^3 7. Renal dysfunction, i.e., creatinine clearance < 30 mL/min 8. AST and/or ALT > 2 x ULN, or total bilirubin > ULN. Gilbert's Syndrome is allowed. 9. Bleeding disorders or blood loss requiring transfusion in the six weeks preceding enrollment

	10. Ongoing gastrointestinal ulcer, or gastrointestinal bleeding within 6 weeks of first dose. 11. Chronic hepatitis B infection, active hepatitis C infection, active liver disease and/or cirrhosis per subject report. 12. Heart failure, current uncontrolled cardiovascular disease, including unstable angina, uncontrolled arrhythmias, major adverse cardiac event within 6 months (e.g. stroke, myocardial infarction, hospitalization due to heart failure, or revascularization procedure).
Treatment	All subjects will receive standard of care (SOC) including symptomatic care. Subjects will be randomly assigned to SOC + brequinar 100 mg daily x 5 or SOC + placebo daily x 5. Study encounters will be conducted remotely whenever possible.
DMC	A Data Monitoring Committee (DMC) will meet periodically to review the safety and scientific conduct of the study. At a minimum, the DMC is to review adverse events and safety laboratory assessments after the first 20 subjects complete Day 8, and again after the first 40 subjects complete Day 8.
Procedures	Study procedures are outlined in the Schedule of Events. Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF.
Safety/ Tolerability	**Safety/Tolerability** Adverse events will be collected from the time of first dose through Day 29. After Day 29, collect/record only Serious Adverse Events (SAEs) or those judged by the Investigator or designated person to be related to study drug. Treatment-emergent adverse events will be those with an onset after the date and time of first treatment. Subjects who develop Grade 3 or 4 toxicities or SAEs are to be re-evaluated every 2 days, as feasible, until the toxicity returns to Grade ≤ 2 severity.
Stopping Criteria	Individual Criteria: • Participants who develop a Grade 3 toxicity that is assessed by the investigator to be related to the study drug are to be permanently discontinued from study treatment. • Participants who develop a Grade 4 toxicity, regardless of relatedness to study drug, are to be permanently discontinued from study treatment. Study-Level Stopping Criteria: Study enrollment is to be paused if any of the below criteria are met: • If ≥ 3 subjects develop the <u>same</u> related Grade 4 (life-threatening) adverse event or laboratory abnormality;

	• If ≥ 5 subjects develop the same related Grade 3 or 4 adverse event or laboratory abnormality; • If ≥ 10 subjects develop any related Grade 3 or 4 adverse event or laboratory abnormality. Following assessment by the Data Monitoring Committee (DMC), the DMC will determine whether to stop the study, amend the protocol, or continue the study per protocol.
Statistical Analysis	A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. All analyses of safety and efficacy for this study will be descriptive in nature and presented by group. Subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. Summaries for quantitative variables will include the mean, median, quartiles, standard error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the 95% CI, when appropriate. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.4 or higher). Safety and tolerability will be assessed in terms of AEs, SAEs, and safety laboratory data. Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of treatment-emergent adverse events, defined as TEAEs occurring after first dose will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results and other clinical measures will be summarized using appropriate descriptive statistics.

CCB-CRISIS-02 Schedule of Events

CCB-CRISIS-02 Schedule of Events **Windows are relative to first dose time** **Procedures**	**Screen (days -14 to -1)**	**D1**	**D2, 3 (± 8 hrs)**	**D4 (± 8 hrs)**	**D5 (± 8 hrs)**	**D8 (± 1 day)**	**D12 (± 1 day)**	**D15 (± 1 day)**	**D22 (±1 day)**	**Final Visit D29 (± 2 days)**
Informed Consent (note Date and Time)	X									
AE/Concomitant Medications (dose, route, duration or ongoing)	X	X		X		X	X	X	X	X
Medical history (relevant within one year or ongoing)/ History of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection)	X									
Demographics (subject reported height and weight, date of birth, gender, race, ethnicity)	X									
Check for Physical Exam abnormalities (subject self-reported)	X									
Pregnancy Test (WOCBP)	X (serum)									X (urine)
Hematology/Chemistry[a]	X	X				X		X		
Vital Signs[b]	X	X		X		X	X	X	X	X
Symptom Assessment[c]	X	X		X		X	X	X	X	X
SARS-CoV-2 RT-PCR/Viral load sample[d]	X	X		X		X	X	X	X	X
Hospital Status						X		X	X	X
WHO Ordinal Scale Assessment		X				X		X	X	X
Confirm Eligibility		X								
Randomize subject and dispense Study Medication		X								
Study drug administration[e]		X	X	X	X					
Drug Accountability						X				

[a]Do not repeat if within 48h of Day 1 visit. Send to Covance Central Laboratory Services (CCLS) for analysis.

[b]Vital signs include heart rate, respiratory rate, body temperature, SpO2. Subject will be provided with a thermometer and pulse oximeter with heart rate monitoring capability. Training will be provided during the first visit by the home health nurse. Vital signs parameters will be observed and recorded by study staff via telemedicine or during a visit by the home health nurse.

[c]Symptom Assessment will use a checklist provided to the subject with symptoms such as sore throat, cough, GI symptoms (vomiting, diarrhea), anosmia, dysgeusia, other (specify), etc. Severity Mild, Moderate, or Severe will be collected.

[d]RT-PCR at Screening may be performed by the site if the subject cannot provide documentation of a positive SARS-CoV-2 result. Samples collected after Screening will be saliva samples sent for viral load analysis. Day 1 sample must be obtained prior to dosing. Viral load specimens after Screening will be saliva samples self-collected by the subject using an Oragene® collection system or similar. The home health nurse will train the subject and observe sample collection on Day 1. These samples are to be sent to CCLS for analysis. The viral load sample may also be used to perform viral cultures (sample can be split by the central laboratory, no additional sample required).

[e]Subject will self-administer study drug once daily Days 1 – 5 and record doses in a medication diary. Note that any visits/visit activities may be conducted via telephone, telemedicine, or digital media other than serum pregnancy test and chemistry/hematology sample collection. These labs may be collected at the clinical site or another designated out-patient facility/laboratory or collected via home visit. Arrangements for shipping viral load samples will be made by the study team.

STUDY PERSONNEL

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3 INTRODUCTION

3.1 Coronavirus-19 (COVID-19)

Beginning in December 2019, Chinese scientists isolated a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from patients with virus-infected pneumonia which was later designated as coronavirus disease 2019 (COVID-19) by the World Health Organisation (WHO) (Zhou et al., 2020 [2]; Phelan et al., 2020 [3]).

Approximately 14% of those affected with this virus will develop severe disease requiring hospitalization and oxygen support; 5% will require admission to the intensive care unit (Handel et al., 2020 [4]). Severe cases may be complicated by acute respiratory disease syndrome (ARDS), sepsis and septic shock, and multi-organ failure, including acute kidney injury and cardiac injury. Risk factors for death include older age and co-morbid disease such as hypertension and diabetes (Zhou, et al., 2020 [2]). This means that most patients will be treated as out-patients. Reducing viral load in this environment is critically important for both the subjects themselves by preventing worsening of symptoms and possibly avoiding hospitalization, but also to reduce the transmission of the disease to others in the patients' households and their communities.

3.1.1 Coronavirus Biology

Coronaviruses, like other RNA-based viruses, do not have the machinery to synthesize their own nucleotides and thus depend upon the host intracellular pool of nucleotides for viral replication. In essence, viruses steal the host RNA building blocks, and without these building blocks they are unable to replicate. The SARS-CoV-2 is a single-stranded (positive sense) RNA virus with a genome that is 29,811 nucleotides long, quite a lot larger than other RNA-based viruses (e.g. the hepatitis C genome comprises only 9600 nucleotides). The nucleotide composition is broken down as: 29.9% adenosines, 18.4% cytosines, 19.6% guanines, and 32.1% uridines (Sah et al., 2020 [12]).

3.2 Host Nucleotide Synthesis

Host *de novo* pyrimidine synthesis generates uridine monophosphate (UMP) as the building block for all pyrimidine ribonucleotides and deoxyribonucleotides (Figure 3-1). There exists no salvage pathway for the synthesis of UMP, the fundamental building block of pyrimidines. Inhibition of enzymatic steps upstream of UMP (Figure 3-1) leads to a rapid and profound depletion of intracellular pyrimidines.

3.3 Dihydroorotate dehydrogenase (DHODH)

The enzyme dihydroorotate dehydrogenase (DHODH) catalyzes the 4th step of *de novo* pyrimidine synthesis and inhibition of DHODH completely halts all pyrimidine production. As shown in Figure 3-1, DHODH is located on the inner mitochondrial membrane and transfers electrons between DHO and complex III of the electron-

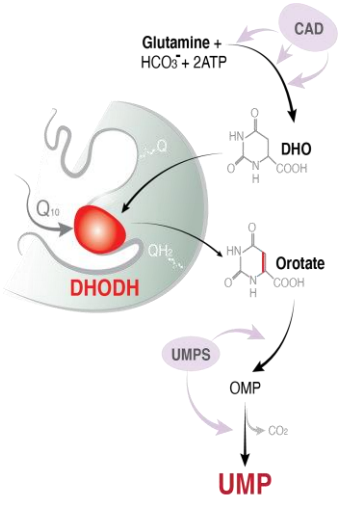

Figure 3-1. DHODH is a mitochondrial enzyme that catalyzes the 4th step of pyrimidine synthesis; it is completely essential for the generation of UMP.

transport chain via the reduction of its ubiquinone (coenzyme Q10) cofactor.

DHODH is a clear therapeutic target for the inhibition of host pyrimidine synthesis. The chemical inhibition of DHODH *in vitro* or *in vivo* leads to the rapid depletion of UMP and subsequent depletion of downstream products thymine and cytosine. This forces a cell to rely on the salvage of extracellular pyrimidine nucleotides and this extracellular salvage is not capable of maintaining the cell's normal nucleotide pool (Sykes et al., 2016) [1]).

3.4 Brequinar

Brequinar is an orally available and potent inhibitor of DHODH. Brequinar is one of more than 300 quinoline-carboxylic acid derivatives prepared in an analog synthesis program in the 1980s, which was started after it was found that a compound of this class had antitumor activity. Brequinar was selected by DuPont for further development as a potential clinical drug because of its activity against experimental tumors and because its water solubility made it relatively straightforward to formulate.

In an indication such as treating SARS-CoV-2 infection, brequinar will act as a host-targeting antiviral. It is an orally available and potent inhibitor of dihydroorotate dehydrogenase (DHODH), the enzyme that catalyzes the fourth step in pyrimidine synthesis, namely the conversion of dihydroorotate (DHO) to orotate. DHODH inhibitors, including brequinar, inhibit *de novo* pyrimidine synthesis thereby leading to a depletion of a cell's pool of uridine, cytidine and thymidine ribonucleotides and deoxyribonucleotides.

The antiviral activity of brequinar has been demonstrated in studies of rotavirus replication in human intestinal Caco-2 cells as well as in human primary intestinal organoids (Chen et al., 2019 [6]). Treatment with teriflunomide, another DHODHi, has been effective *in vitro* and *in vivo* in a murine model of foot and mouth disease virus (Mei-Jian et al., 2019 [7]). DHODH inhibition (DHODHi) also inhibited the growth of dengue virus *in vitro* (Wang et al., 2011 [8]). DHODHi also showed antiviral effects against RNA viruses including influenza A, Zika, Ebola and coronavirus SARS-CoV-2 (Xiong et al., 2020 [11]**).** Brequinar has also been shown to inhibit the replication of Ebola virus, vesicular stomatitis virus and Zika virus *in vitro* (Luthra et al., 2018 [9]). Brequinar inhibits the replication of human immunodeficiency virus (HIV) *in vitro* (Andersen et al., 2019 [10]). When considering brequinar as an antiviral for treatment of SARS-CoV-2, oral brequinar is highly bioavailable (>95%) and has good penetration of lung tissue with an average tissue:blood ratio of 0.5 following a single dose of brequinar in the rat. It is therefore expected to achieve a similar period of DHODH inhibition in lung tissue (Brequinar IB [5]).

3.5 Rationale for the Planned Trial

DHODH inhibition has been extensively studied as a potential therapeutic target in the treatment of RNA-based viruses. The inhibition of DHODH is effective in inhibiting viral replication in pre-clinical models involving many RNA-based viruses with nanomolar potency and a high selectivity index (see the Brequinar IB [5], Section 5). In these pre-clinical models, the benefit of DHODH inhibition can be reversed by the supplementation of exogenous nucleotides, confirming that the on-target effect of host pyrimidine depletion is key to the anti-viral activity.

The CCB-CRISIS-02 trial will study standard of care (SOC) with 5 days of brequinar (DHODH inhibition) compared to SOC with 5 days of placebo treatment. Clear Creek Bio hypothesizes that a defined 5-day course of brequinar will inhibit the enzyme DHODH to a degree sufficient to result in the transient depletion of host pyrimidine nucleotides, thereby inhibiting viral replication. A recent publication demonstrated that inhibitors of DHODH could potentiate the activity of inhibitors of RNA-dependent RNA polymerase (RdRp) in the treatment of dengue virus, another single-stranded RNA virus similar to SARS-CoV-2 (Liu et al., 2020 [13]). This inhibition of viral replication may restore the balance in favor of the host immune system for the clearance of SARS-CoV-2.

Marketed DHODHi medications are available, including leflunomide or teriflunomide, however these are very weak inhibitors of DHODH with cellular potency ~500 times lower than brequinar. These low potency inhibitors of DHODH are not expected to have the ability to acutely lower the pool of intracellular pyrimidines to the degree that is required for decreasing the viral load associated with SARS-CoV-2 infection, making brequinar the better choice for acute SARS-CoV-2 infection.

The CRISIS2 study is a proof-of-concept study in patients with SARS-Cov-2 infection and will serve as a basis for future studies to determine the safety and effectiveness of brequinar in COVID-19.

3.5.1 Brequinar Dose Selection

Safety data from previous oncology clinical studies of brequinar with 5 days of consecutive daily dosing suggest that 5 days of daily doses of 100 mg p.o. will be safe and well tolerated. A dose of brequinar 100 mg achieves plasma concentrations of approximately 1 uM (0.4 ug/ml) that should result in sufficient suppression of nucleotide synthesis. When given over 5 days, these plasma concentrations are achieved on a daily basis without accumulation, also assuring the safety of this regimen (see Brequinar IB [5]).

3.5.2 Risk/Benefit of Brequinar

As presented in the Brequinar IB [5], an extensive safety and pharmacokinetic database exists with more than 1,000 patients treated with brequinar. Cancer patients (N = 806) have been exposed to this compound for treatment of a variety of solid tumors at various treatment regimens, doses, and routes including a single dose, once weekly, twice weekly, single dose every 3 weeks, daily times 5 every 4 weeks, and daily times 21 days for multiple courses. Lower doses than used in the cancer studies have also been utilized for patients with psoriasis and organ transplant. The maximum intravenous dose given was 2,250 mg/m^2 every 3 weeks, and the maximum oral dose was 100 mg/m^2 daily for 21 days. There has been limited testing of DHODHi to date in the clinic for infection with SARS-CoV-2. DHODHi therapy at relatively high doses in the context of trials for patients with cancer has the expected safety side-effects of mucositis and bone marrow suppression. Importantly, however, the prior clinical experience in 39 subjects who received daily brequinar for 5 consecutive days at or lower than 100 mg/day show no cases of mucositis and only 1 (2.6%) episode of mild thrombocytopenia. Based on these data the 100 mg per day dose proposed for administration in this study should be within a safe and tolerable range as well as demonstrating the predicted antiviral effect.

The potential benefit in using brequinar to treat SARS-CoV-2 infection is the hypothesis that a 5-day period of brequinar dosing will suppress host *de novo* pyrimidine synthesis for this period thus decreasing viral load. Inhibition of DHODH is expected to reduce the ability of the virus to replicate

and it is for this reason that brequinar will be administered to patients with COVID-19 in this study.

3.6 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration of high-dose brequinar in patients with refractory solid tumors, reversible myelosuppression, in particular thrombocytopenia, and mucositis have been the primary dose-limiting toxicities. In addition, skin rash, nausea/vomiting, fatigue, and leukopenia have been dose-limiting in trials utilizing other schedules of brequinar administration. However, these effects were self-limiting, transient, required treatment in few cases, and resolved following discontinuation of dosing. These adverse effects have been associated with higher doses of brequinar given via the intravenous route and for longer durations than the 100 mg dose and 5-day regimen proposed for this study.

In addition to studying a higher risk population with symptomatic COVID-19, a comprehensive safety monitoring plan will be utilized in this study to assess the ongoing safety and well-being of participants (see Section 10.8).

3.7 Possible Interactions with Concomitant Medical Treatments

Brequinar has been administered to subjects taking a variety of concomitant medications that are typical in severely ill cancer patients including antibiotics, antifungals and other critical care medications. No formal interaction studies have been conducted for these medications, however, there have not been any reports of interactions with any medications during the clinical trials with more than 800 cancer patients.

3.7.1 CYP Interactions

No formal clinical drug-drug interaction studies have been performed for brequinar with medications commonly used in treating hematologic malignancies. The nonclinical studies performed to date have demonstrated there is no first-pass metabolism and there have been no apparent hepatotoxic effects in the clinical studies. Brequinar itself does not appear to be a substrate for metabolism by cytochrome P450 enzymes when tested under a variety of conditions. (See Brequinar IB [5]; nonclinical data on file with Clear Creek).

3.8 Steps to be Taken to Control or Mitigate Risks

All subjects will be treated by highly experienced clinicians familiar with the treatment of viral infections and their complications.

4 TRIAL OBJECTIVES

4.1 Primary Objective

To demonstrate a change from baseline in quantitative SARS-CoV-2 viral load for brequinar-treated subjects compared to placebo-treated subjects through Day 29.

4.2 Secondary Objectives

The secondary objectives of this study are:

Through Day 29:

- To characterize the safety and tolerability of brequinar in out-patient COVID-19 subjects as measured by frequencies of grade 3 and 4 AEs and SAEs;
- To demonstrate a shorter duration of viral shedding in subjects treated with brequinar compared to subjects who received placebo;
- To reduce the percentage of subjects requiring hospital admission as an inpatient for >24 hours for brequinar subjects compared to subjects who received placebo;
- To reduce all-cause mortality through Day 29 for brequinar subjects compared to subjects who received placebo.

4.3 EXPLORATORY OBJECTIVES

Through Day 29:

- To determine time to viral clearance (two consecutive negative tests);
- To determine time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline;
- To determine time to clinical improvement as measured by a favorable shift in the WHO Ordinal Scale score for the subset of subjects with baseline WHO Ordinal Scale of 2 for brequinar subjects compared to subjects who received placebo.

5 TRIAL DESIGN

This will be a phase II randomized, placebo-controlled, double blind, multi-center study with approximately 100 subjects. All subjects will receive standard of care per (SOC) institutional guidelines for treatment of patients with COVID-19 infection. In addition to SOC, the subjects will self-administer one capsule once daily for 5 days.

Subjects will have a Screening Visit followed as soon as possible with Study Day 1. Study procedures are presented in detail in the Schedule of Events (Appendix 15.1). Study visits (virtual or in person) will take place at Screening and on Study Days 1, 8, 15, 22, and 29. The visits that include bloodwork must be conducted at the study site or arrangements made for sample collection at the subject's home or other appropriate location. Other visits/visit activities for that visit may be conducted remotely using telemedicine or other remote technique. Subjects are to self-collect a viral load sample, obtain their respiratory rate, heart rate, body temperature and SpO2, and complete a symptom assessment checklist on Days 1, 4, 8, 12, 15, 22, and 29.

6 TRIAL ENDPOINTS

6.1 Primary Endpoint

Quantitative SARS-CoV-2 viral load through Day 29.

6.2 Secondary Endpoints

The secondary endpoints of this study are:

Through Day 29:

- Rates of AEs and SAEs including laboratory assessments;
- Duration of viral shedding;
- Percentage of subjects requiring admission as an inpatient for >24 hours.
- All-cause mortality.

6.3 Exploratory Endpoints

Through Day 29:

- Time to viral clearance (two consecutive negative tests);
- Time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline;
- Time to clinical improvement measured by a favorable shift in WHO Ordinal Scale score for the subset of subjects with baseline WHO Ordinal Scale of 2.

7 TRIAL POPULATION

7.1 Number of Subjects

Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 100 subjects have completed the study. Subjects will be randomized to either standard of care plus brequinar 100 mg or standard of care plus placebo in a 1:1 ratio (approximately 50 subjects assigned to standard of care plus brequinar 100 mg and approximately 50 subjects assigned to standard of care plus placebo).

7.2 Inclusion criteria

1. Willing and able to provide informed consent for the trial, written, electronic, verbal or other method deemed acceptable by the institution and IRB.
2. 18 years of age or older.
3. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other FDA-approved commercial or public health assay within 14 days of first dose.
4. Out-patient (never hospitalized as an in-patient for COVID-19 or was evaluated/treated for COVID-19 only in the Emergency Room with a stay of < 24 hours).
5. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men and women treated or enrolled on this protocol must also agree to use adequate contraception for the duration of study participation, and for 90 days after completion of brequinar administration.
6. Male subjects must agree to refrain from sperm donation and female subjects must agree to refrain from ovum donation from initial study drug administration until 90 days after the last dose of brequinar.
7. At least one COVID-19 symptom including but not limited to fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, shortness of breath, dyspnea, anosmia, dysgeusia, or other symptom commonly associated with COVID-19.
8. Able to swallow capsules.

7.3 Exclusion Criteria

1. Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient
2. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test
3. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide) or other agents known to cause bone marrow suppression leading to thrombocytopenia
4. Platelets $\leq$150,000 cell/mm^3

5. Hemoglobin < 10 gm/dL
6. Absolute neutrophil count < 1500 cells/mm^3
7. Renal dysfunction, i.e., creatinine clearance < 30 mL/min
8. AST and/or ALT > 2 x ULN, or total bilirubin > ULN. Gilbert's Syndrome is allowed.
9. Bleeding disorders or blood loss requiring transfusion in the six weeks preceding enrollment
10. Ongoing gastrointestinal ulcer, or gastrointestinal bleeding within 6 weeks of first dose.
11. Chronic hepatitis B infection, active hepatitis C infection, active liver disease and/or cirrhosis per subject report.
12. Heart failure, current uncontrolled cardiovascular disease, including unstable angina, uncontrolled arrhythmias, major adverse cardiac event within 6 months (e.g. stroke, myocardial infarction, hospitalization due to heart failure, or revascularization procedure).

8 STUDY TREATMENTS

8.1 Description of Study Medications

8.1.1 Brequinar

Brequinar and placebo will be supplied as 100 mg capsules. Dosing will be a single 5-day course of brequinar 100 mg capsules or placebo 100 mg capsules once daily for 5 doses.

8.2 Treatment Administration

This will be a phase 2 randomized, placebo-controlled, double blind, multi-center study with approximately 100 subjects. All subjects will receive standard of care (SOC) for COVID-19 infection. Subjects will be randomly assigned in a 1:1 ratio to standard of care plus brequinar or standard of care plus placebo.

8.2.1 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit. The *NIH Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria.

Adverse events (AEs) commonly observed in patients treated with brequinar are provided in the Investigator's Brochure (IB) and include thrombocytopenia, nausea, anemia, diarrhea, vomiting, leukopenia, stomatitis, rash, granulocytopenia, fatigue, and infection. In a study of 209 cancer subjects treated once-weekly (DuP 785-012, see Brequinar IB [5]), the deaths of three patients were attributed to study drug toxicity (two to hemorrhage, one following acute renal failure). Severe toxicities grades (Grades 3 to 4) which typically led to discontinuation in this study included hematologic toxicities (anemia, thrombocytopenia, leukopenia, granulocytopenia), digestive system toxicity (nausea, vomiting, stomatitis, others including gastric hemorrhage) and mucositis.

In three oncology studies with five consecutive days of intravenous (IV) brequinar dosing in 168 subjects (Study 785-001 [14], 785-003 [15], and 785-005 [16]) there were no toxic deaths. For subjects from these three studies who were treated with a daily dose of 100 mg or below (as will be dosed in CCB-CRISIS-02), AEs through 21 days showed that 2 of 39 subjects (5.1%) had a severe (Grades 3 or 4) AE related to study drug (1 subject each with hyperbilirubinemia and hyperglycemia), and no subjects discontinued from the study due to a study drug-related AE. The few study drug related AEs through 21 days at or below the 100 mg dose from these three studies included 2 subjects each with nausea, vomiting, and creatinine elevated and one subject each with thrombocytopenia and diarrhea. When only studies with oral dosing were considered at this dose level (Studies 785-022 [17], 785-031 [18] , and 785-034 [19]), the study drug related AEs through 21 days (each observed in one subject only) included diarrhea, headache, nausea, pruritus, abdominal pain, anorexia, chest pain, dry mouth, fatigue, keratosis, stomatitis, and vomiting. See brequinar IB [5].

In most instances, brequinar-related toxicities were transient, clinically manageable, and reversible upon discontinuation of brequinar treatment. Any of these events reported with brequinar use can be serious in nature and may result in death.

A 5-day course of oral brequinar administered once daily at a low level relative to those administered in the cancer studies is expected to be safe and well tolerated in the COVID-19 population.

8.3 Study Discontinuation

Subjects will remain in the study through at least Study Day 29 (or longer if needed to follow up study drug-related adverse events). Participants may discontinue from the study by withdrawing consent at any time or for any reason as presented in Section 9.7.

8.4 Stopping Criteria

8.4.1 Individual Stopping Criteria

- Participants who develop a Grade 3 toxicity that is assessed by the investigator to be related to the study drug are to be permanently discontinued from study treatment.
- Participants who develop a Grade 4 toxicity, regardless of relatedness to study drug, are to be permanently discontinued from study treatment.
- Subjects who develop Grade 3 or 4 toxicities are to be followed by re-evaluation every 2 days, as feasible, until the toxicity returns to ≤ Grade 2 severity.

8.4.2 Study-Level Stopping Criteria

Study enrollment is to be paused if any of the below criteria are met:

- If ≥ 3 subjects develop the same related Grade 4 (life-threatening) adverse event or laboratory abnormality;
- If ≥ 5 subjects develop the same related Grade 3 or 4 adverse event or laboratory abnormality;
- If ≥ 10 subjects develop any related Grade 3 or 4 adverse event or laboratory abnormality.

Following assessment by the Data Monitoring Committee (DMC, see Section 10.9), the DMC will determine whether to stop the study, amend the protocol, or continue the study per protocol.

8.5 Concomitant Medication/Treatment

Record the name, dose, start/stop date, indication for use, route, and whether ongoing or stopped for medications/treatments taken within two weeks prior to study entry as well as any medications taken during the study are to be recorded. Prohibited medications are identified in Section 8.8.

8.6 Treatment Compliance

Compliance will be assessed by reviewing the subject's medication diary and study records as appropriate.

8.7 Storage, Stability, Labeling and Packaging

8.7.1 Storage and Stability

The study drug is stored at room temperature. Stability testing is ongoing.

8.7.2 Labeling and Packaging

The bulk drug and unit-dose containers will be labeled in accordance with national laws and regulations.

8.7.3 Blinding and Randomization

The trial will be conducted in double blinded, randomized manner with random assignment to standard of care plus brequinar or standard of care plus placebo. The brequinar and placebo capsules will be provided to each participating institution in pre-numbered bottles intended for individual subjects to be dispensed by the institution's pharmacist or designated person. Randomization assignments will be provided by an independent statistician to the drug packaging company. The pharmacist/designated person will dispense the next number in sequence to the next patient who qualifies for the study at an individual site.

8.7.4 Unblinding/Expectedness

Contact the Covance Medical Monitor if it is necessary to break the blind for this blinded study due to an adverse event (AE). Each site will be provided with a sealed envelope containing individual sealed envelopes for subject numbers assigned to that site. Each individual subject number sealed envelope will have the treatment (brequinar or placebo) randomly assigned to that subject number. Do not open the outer envelope or the individual sealed envelope unless it has been agreed with the Medical Monitor and the Sponsor that unblinding is necessary for that particular AE. Unblinding must be documented in the study records. Envelope seals are to be checked to ensure they remain intact during drug accountability monitoring.

If after a discussion with the Medical Monitor, the investigator or treating clinician believes the AE leading to unblinding to be related to the study drug, no further doses of drug should be administered to that subject.

Expectedness will be determined by establishing whether an adverse event is among those identified in the protocol and the brequinar IB or are commonly associated with COVID-19 or similar severe viral illnesses and their complications.

8.7.5 Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator must keep a record of all study medication received, administered, and discarded. It must be clear from the records whether the subject received study medication and what subject number was assigned to which subject. Adequate drug is to be dispensed for the number of subjects expected to be treated at each institution.

The pharmacist/staff member responsible for drug accountability is to document the date and time of dispensing and for what subject the study drug was intended (i.e., record subject initials and birth date or other unique identifier). A pharmacy manual will be provided by the Sponsor.

At the end of the study any unused study drug will be returned to the Sponsor for destruction or may be destroyed locally; disposition of study drug will be documented.

The Sponsor will be permitted access to the trial supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation. Records may be electronic or paper and may be accessed remotely for monitoring/drug accountability purposes.

Each subject will be provided with one bottle with five brequinar or five placebo capsules for the five days of dosing.

8.8 Prohibited Medications

Treatment is prohibited with another DHODH inhibitor (e.g., leflunomide and teriflunomide). Treatment is prohibited with agents known to cause bone marrow suppression leading to thrombocytopenia.

8.9 Study Adjustments Due to COVID-19

Due to the highly contagious nature of COVID-19, multiple adjustments and revised procedures are rapidly evolving regarding clinical trial management and study conduct. Reasonable procedures implemented by study staff to avoid spreading this disease are acceptable to Clear Creek with written permission. Examples include but are not limited to e-consent, telephone consent and study visits conducted by telemedicine, telephone or other digital media.

Background standard of care is to be maintained in both treatment arms. The standard of care is expected to change as additional information, such as that from randomized controlled trials, emerges, and the Sponsor and the treating clinicians will need to address anticipated off-label use of any other drugs, devices, or interventions that might be used to manage COVID-19 (e.g. anticoagulants).

The Sponsor and treating clinicians are to consider changes in SOC over time, for example, overlapping toxicities of brequinar and a SOC treatment expected to be widely used is to be considered. The availability of new standard of care treatment may change over time and vary from one clinical trial site to another. The Sponsor will discuss these issues with FDA should the need arise.

9 CONDUCT OF THE TRIAL

9.1 Ethical and Regulatory Considerations

The trial will be performed in accordance with the Declaration of Helsinki (1964) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Scotland (2000, Note of Clarification 2002 & 2004) and Seoul 2008 (Appendix A), and Fortaleza (Brazil) (2013), and with the International Council on Harmonization (ICH) Tripartite Guideline on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and United States (US) FDA Regulations.

9.2 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki must be implemented in each clinical study before protocol-specified procedures are carried out. Informed consent must be obtained in accordance with US Code of Federal Regulations (21 CFR Part 50), the FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency (March 2020, Updated April 16, 2020) [20], as well as local and national regulations. Information should be given in both oral and written form whenever possible and deemed appropriate by the Institutional Review Board (IRB). Subjects and their relatives, if necessary, must be given ample opportunity to inquire about details of the study.

The Investigator or qualified designated person will verbally inform subjects as to the nature, expected duration and purpose of the trial, the administration of the Investigational Product (IP), and the hazards involved, as well as the potential benefits that may come from treatment with this IP. The trial procedures will be explained in lay language and any questions will be answered. The subjects will be given an IRB-approved consent form. The subjects will be given appropriate time to consider their participation in the trial and have any questions answered prior to signing the consent form. If a subject agrees to participate, he/she will sign and date an informed consent form and be provided with a copy of the signed consent. All subjects who sign an informed consent form are to be recorded on the applicable screening log. If the subject is unable to consent for any reason, a designated family member or healthcare power of attorney or other person may consent per institutional policy.

The subject will be informed that his/her medical records will be subject to review by the Sponsor, Sponsor's representatives, and possibly by a representative of the FDA and other relevant regulatory authorities. Subjects will be informed that they are free to refuse participation in this clinical investigation, and if they should participate, it will be made clear to them that they may withdraw from the trial at any time without prejudicing further medical care they may require. The subject will receive a copy of the consent form as well as an information sheet about the trial.

Informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to completing the informed consent process but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. Documentation of consent will be subject to review by the Sponsor; if in writing, a copy will be given to the subject and a copy will be filed with the subject's medical notes. Verbal consents will be documented by the study team as appropriate and agreed by the IRB.

Note that informed consent procedures have been affected by COVID-19, and the study staff may use any consent method that has been approved by the IRB (e.g., phone consent, verbal consent with

witness, e-consent, etc.) of the local institution. In-person consent, written consent signatures and providing hard copies to the subject are examples of procedures that may be foregone under these circumstances.

The study should be discussed with the potential participant only after an initial review of his/her clinical status and appropriateness for participation have been evaluated to determine if he/she meets the subject selection criteria.

A sample subject information sheet and consent form are available from Clear Creek. The final version at each institution may differ depending on institutional requirements and standard formats. This protocol will not be amended for site specific changes as such changes are to be made to the site's consent when required.

9.3 Institutional Review Board

It is the responsibility of the Investigator to submit the protocol, consent form and information sheet to the IRB. An IB will be available for review by the IRB. The protocol and informed consent form (ICF) must be approved by the IRB prior to the recruitment of the first subject. The template consent form may be revised in accordance with site-specific requirements with Sponsor review and approval. A copy of the IRB written approval must be provided to the Sponsor and investigator before the trial may start at that institution. Written approval from the IRB is also required for substantial protocol amendments prior to their implementation.

A substantial amendment may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments are "substantial" when they are likely to have an impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any IP used in the trial.

If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects, the Investigator will notify the Sponsor and the IRB of the new events and the measures taken as soon as possible.

The Investigator will report promptly to the Sponsor and IRB any new information that may adversely affect the safety of the subjects or the conduct of the trial. On completion of the trial, the Investigator will inform the applicable IRB as per local IRB requirements that the trial has ended. If the study is terminated for any reason, the investigator will return all clinical supplies and study-related equipment supplied by the Sponsor to the Sponsor unless otherwise specified.

9.4 Schedule of Events

Study activities will be conducted or supervised by experienced personnel throughout the study based on the Schedule of Events. The subjects may collect the saliva sample for viral load testing and perform other study activities such as body temperature, heart rate, respiratory rate, SpO2, and symptom

assessments themselves with appropriate training. Equipment will be provided to the subject for study purposes including a pulse oximeter with heart rate monitoring capability and a thermometer. Telemedicine visits such as phone calls or other remote media are to be utilized as much as possible. Subjects may need to come to an out-patient facility or be visited by a home health professional for some study assessments.

See 15.1 Schedule of Events in Appendix A for the full list of study assessments and timings.

Blood chemistry tests include blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALK), alanine amino transferase (ALT), aspartate amino transferase (AST), total bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium), lactate dehydrogenase (LDH).

Hematology tests include hemoglobin, hematocrit, complete blood count with full differential, and platelet count.

Viral load sampling is to be carried out on Days 1, 4, 8, 12, 15, 22, and 29. The subject is to self-collect saliva samples with appropriate training for this analysis. Samples may be banked for future analyses. If the subject cannot provide documentation of the previous positive COVID-19 test, the site may perform an additional RT-PCR test. The subject must have a documented positive result to be eligible for the study.

Hospitalization status after enrollment is to be recorded as not hospitalized or admitted to hospital as an in-patient with admission > 24 hours.

As much of the study as possible will be conducted via telemedicine remote from the site (e.g., consent, medical history, concomitant medications may be collected remotely). Subjects will be visited at home (or place of residence) by a home health nurse at Screening and on study Days 1, 8, 15, 22, and 29. On study Days 4 and 12 the vital signs collection will be observed via telemedicine by the study site staff. Subjects will be provided with a pulse oximeter and thermometer during the Screening in-home visit, as well as being trained on the use of these devices during that visit. Training will also be provided by the home health nurse for the saliva collection required for viral load testing. Assessments will be recorded by the home nurse during home visits and by the site staff during telemedicine visits. These data will be entered in the eCRF by the site staff or as determined by the study team.

9.5 Study Conduct

The study visits are to be conducted as shown in the Schedule of Events, Appendix 15.1.

Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF.

9.5.1 Unscheduled Visits

Unscheduled visits and tests are permitted as needed to assess AEs/SAEs throughout the study. Unscheduled visits and tests are also permitted as needed to assess AEs/ SAEs with onset within two (2) weeks after the final study visit providing the AE is considered related to study drug

9.6 Compliance with Study Procedures

The time at which study procedures are conducted should follow the protocol timelines as closely as possible. However, it is recognized in a clinical setting that protocol-specified timings may not occur exactly as specified in the protocol, particularly when conducted remotely by the subject. Provided that activities are carried out within the identified windows it will not be necessary to file a protocol deviation. Remote visits such as a telemedicine visit may be conducted to collect as much information as possible remotely. A home visit or return to the clinical site or an out-patient laboratory may be arranged for safety labs or other assessments, when required. Telemedicine or other remote technique is to be utilized to ensure subject compliance when subject is performing self-collection of study assessments.

9.7 Early Withdrawal from the Study

A subject may withdraw from the study at any time for any reason or for one of the reasons listed below. The Sponsor or Investigator may also terminate a subject's study participation after discussion with the other party if it is believed it would be unsafe for the subject to continue in the study.

Subjects must discontinue study medication if any of the following events occur:

- Significant protocol violation or non-compliance, either on the part of the subject or the investigator or other site personnel;
- Decision of the Investigator or Sponsor that removal is in the subject's best interest;
- Severe unrelated medical illness or complication;
- Safety reasons/ significant adverse event;
- Subject request (withdrawal of consent);
- Sponsor decision.

Collect/conduct all scheduled evaluations even for subjects who discontinue study medication prior to completing the treatment period unless consent is withdrawn.

9.8 Early Termination of the Study

If the Sponsor or an Investigator believes it would be unsafe to continue the study, or for any reason at the Sponsor's request, the study may be terminated at that site or the entire study terminated after discussion with the other parties.

The Sponsor will provide a written statement to the IRB and the relevant regulatory authority with the reasons for termination of the study. This will be conducted within 15 days of the decision to terminate the study.

If the study is terminated, a close out monitoring visit will be performed and applicable procedures will be carried out to close the trial site(s).

9.9 Non-Childbearing Potential

Women of non-childbearing potential are defined as those who have no uterus, ligation of the fallopian tubes, or permanent cessation of ovarian function due to ovarian failure or surgical removal of the ovaries. Documentation of surgical procedure or physical examination is required for subjects who have had a hysterectomy or tubal ligation. A woman is also presumed to be infertile due to natural causes if she has been amenorrheic for greater than 12 months and has an FSH greater than 40 IU/L. In the absence of such documentation, a negative serum pregnancy test is required for inclusion into the study.

10 ADVERSE EVENT REPORTING

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

Events that occur prior to first dose will be entered as medical history; events that occur after first dose will be entered as adverse events (AEs) on the AE form.

Subjects will be questioned and observed for evidence of AEs, whether or not judged by the Investigator or designated person to be related to study drug. All AEs will be documented in the subject's medical record and CRF. For any pre-existing condition or abnormal laboratory finding that changes in severity after dosing, this change should be recorded as an AE. New abnormal laboratory findings that are clinically significant are considered AEs.

Adverse events will be collected from the time of first dose through Day 29. After Day 29, collect/record only Serious Adverse Events (SAEs) which are assessed by the Investigator or designated person to be related to study drug. AE details are to be documented including start and stop date and times, whether continuous or intermittent, severity, any intervention utilized to correct the event (e.g., medication, surgery, or other therapy), outcome and the relationship to the study drug.

AEs identified in the protocol as critical to the evaluation of safety must be reported to the Sponsor by the Investigator according to the reporting requirements within the time periods specified in the protocol.

AEs determined by the Investigator to be related to study drug must be followed until resolution or until they are considered stable or for at least 30 days after discontinuation of study drug.

Abnormal laboratory values or test results occurring after study enrollment constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, are Grades 3 or 4, or require therapy.

If a death occurs during the SAE reporting period, the cause of death such as pneumonia, ARDS, or respiratory failure, is considered as the AE and the death is considered its outcome. Death should be considered an outcome, not an event. The event or condition leading to death should be recorded and reported as a single medical concept on the AE eCRF. Generally, only one such event should be reported. “Fatal” will be recorded as the outcome of this respective event; death due to an outcome of an AE will not be recorded as separate event. If the primary cause of death is disease progression, the cause of death should be clearly identified as COVID-19.

In cases of surgical or diagnostic procedures, the condition leading to the procedure is considered as the AE instead of the procedure itself. Each AE will be coded by the Sponsor from the verbatim text to a preferred term using a thesaurus based on the Medical Dictionary for Regulatory Activities (MedDRA). For example, record appendicitis, not appendectomy.

The following guidelines will be followed for the recording and reporting of adverse and serious

adverse events.

1. The medical history section of the case report form will serve as the source document for baseline events.

    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed.

        i. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.

2. Adverse events occurring after first dose are to be recorded in the eCRF using the AE form.

3. Serious adverse events will be reported to the local IRB according to institutional policy.

The *NIH Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf) will be used for adverse event reporting.

10.1 Follow Up of Grade 3 or 4 Toxicities

Grade 3 or 4 toxicities are to be followed by re-evaluation every 2 days, as feasible, until the toxicity returns to Grade ≤ 2 severity.

10.2 Infection Follow Up

Any new infection that occurs on study regardless of infecting agent (i.e., viral or non-viral) should be captured. Additionally, the site of infection and source of culture (BAL, tracheal aspirate, sputum, blood, urine, etc.) should also be recorded.

10.3 Classification of Causality

Attribution is the relationship between an adverse event or serious adverse event

and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment

Guidance for assessing causality:

The Investigator will need to determine whether an AE is considered related to ("caused by"') the study drug rather than some underlying condition, for example, COVID-19.

For the purposes of this study, 'drug related' shall mean 'Definite', 'Probable' and 'Possible' relationship to drug as determined by the Investigator.

10.4 Classification of Severity

The NIH Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017) will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria.

AEs that are expected are subject to expedited reporting only if the adverse event varies in nature, intensity or frequency from the expected toxicity information that is provided in the Investigator Brochure.

10.5 Serious Adverse Event (SAE) Reporting

The regulatory definition of an SAE is any untoward medical occurrence or effect that at any dose fulfills one or more of these criteria:

- results in death;
- is life threatening (at the time of the event);
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability / incapacity
- is a congenital anomaly / birth defect;
- or is an event considered medically serious by the Investigator.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

A life-threatening adverse event is one that places the patient/subject, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.

An unexpected adverse event is any adverse drug event, the nature or severity of which is not consistent with the applicable product information (e.g. IB for an unauthorized investigational product or summary of product characteristics for an authorized product).

Enter only one event as the reason for the SAE on the SAE form. Other non-serious events which did not directly result in the SAE should be detailed in the description section on the SAE form and listed separately as AEs if necessary. For fatal SAEs, report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term.

Note that hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of COVID-19 infection, not associated with any deterioration in condition;
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent;
- Social reasons and respite care in the absence of any deterioration in the subject's general condition;
- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above.

ANY SERIOUS ADVERSE EVENT MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) BY EMAIL TO THE SAE REPORTING EMAIL USING THE FORM PROVIDED. ENTER THE SUBJECT'S AVAILABLE INFORMATION INTO THE eCRF WITHIN 48 HOURS.

The subjects are to be identified in the immediate and follow-up reports by unique code numbers supplied by the sponsor. The email address for reporting SAEs can be found below and at the front of this protocol.

Reports relating to the subject's subsequent medical course following an SAE must be submitted to Covance Patient Safety until the event has subsided or, in case of permanent impairment, it stabilizes, and the overall clinical outcome has been ascertained.

SAE REPORTING EMAIL: SAEIntake@covance.com

Medical Monitor:

Norberto Soto, MD	Telephone:	(609) 212-7892
Covance Physician/Medical Monitor	Email:	Norberto.Soto@Covance.com

Sponsor Representative:

Barbara Powers, MSN, Ph.D.	Telephone:	M: (484) 686-0545
VP, Clinical Operations	Email:	bpowers@clearcreekbio.com

All SAEs will be reported to the IRB periodically, at the end of the study, or per local institutional guidelines.

10.6 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected, unexpected, serious adverse reactions (SUSARs) are SAEs that are both related to the study drug (Relationship = Related) and unexpected (not previously described in the investigator's brochure). All SUSARs will be reported in an expedited manner to the Sponsor or designee and IRB by the Investigators and to all relevant regulatory authorities by the Sponsor. Expectedness will be judged by the Covance Physician and site Investigator. It is critical that all SAEs are reported within the 24-hour guideline so that the expectedness determination can be made. SUSARs require immediate attention and expedited reporting to relevant regulatory authorities.

The Sponsor will ensure that all relevant information about **fatal or life-threatening** SUSARs are appropriately recorded and reported to the concerned Regulatory Authority and to the concerned

IRB(s) within seven (7) calendar days of the date of first report to Covance Patient Safety / Sponsor. Follow-up information will be communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs will be reported to the Regulatory Authority and to the IRB(s) concerned as soon as possible within a maximum of fifteen calendar days of first notification to Covance Patient Safety / Sponsor.

The Sponsor or designee will also inform all Investigators studying the investigational medicinal product about SUSARs and ensure that all IRBs have been notified.

For reported deaths of a subject, the Investigator shall supply the Sponsor and the IRB(s) with requested additional information on an expedited basis.

10.7 Pregnancies

Pregnancy occurring in a female subject or a subject's partner during the study period will be documented in the subject's source documents and reported to Covance Patient Safety (by email to SAEIntake@covance.com) and to the IRB by the investigational staff within 1 working day of their knowledge of the event. The collection period for a pregnancy occurring in a subject or a subject's partner will begin at the first dose of study drug and will continue through 90 days after the last dose of study drug. Monitoring of the subject or partner should continue until the conclusion of the pregnancy, if the subject or subject's partner has consented to this. Monitoring of the baby should continue for 3 months after birth, if the subject or subject's partner has consented to this.

Pregnancy itself is not an AE; it should be reported for tracking purposes. The Investigator or designee will discontinue the pregnant subject from the treatment aspects of the study, continue to follow her per protocol for safety outcomes only, and advise her to seek prenatal care and counseling from her primary care provider. Data on fetal outcome and breast-feeding will be collected for regulatory reporting and drug safety evaluation, if the subject has consented to this.

If the pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as (S)AEs.

The site clinical staff will request the pregnant subject to notify the site of the outcome of the pregnancy (i.e., birth, loss, or termination). To help ensure this, the site clinical staff will follow the subject until the end of pregnancy, with the subject's consent. This request and the subject's response will be documented in the subject's source document.

10.8 Safety Monitoring for Hematologic Toxicities

Myelosuppression is a known effect of DHODH inhibition that is associated with prolonged exposure and high doses. To reduce the risk of this effect with brequinar in COVID-19 subjects, the extensive brequinar safety database with over 1,000 patients has been evaluated to select a dose level expected to be safe and well tolerated with regard to hematologic toxicity. In addition to enhancing safety by

selecting a relatively brief 5-day exposure and a low brequinar dose, all subjects in the clinical trial will be under the care of highly qualified medical personnel. Clinically significant out-of-range laboratory results will be reported as adverse events.

In addition to real time assessments by the treating clinical team, the Covance Medical Monitor will assess the available hematology data on a periodic basis to identify any pathologic trends or safety issues. Any apparent increase in the expected rate or severity of hematologic safety events will be discussed with the Principal Investigators and the Sponsor. In addition, the Data Monitoring Committee (DMC) will assess available hematology data on a periodic basis to independently assess any pathologic trends or safety issues. If the rate or severity of hematologic toxicities appears to be above the expected rate or the severity appears worse than that expected, the trial enrollment will be suspended and no further subjects will be treated while a comprehensive data review is conducted. Depending on the outcome of the safety review the study may be stopped, the design adjusted, or the study may continue as designed. Individual and Study stopping rules are provided in Section 8.4.

Safety laboratory results are to be initially assessed in real time by the Principal Investigator or designated person. Any study drug-related clinically significant out-of-range laboratories or study drug-related adverse events will be followed as needed until resolution or stable.

The in-clinic assessments and telemedicine/phone call visits will specifically ask about possible hematologic toxicity including any evidence of the list below. Subjects will be provided with a list of the following events in lay terms and will be instructed to call the research team if any of these events occur.

- Ecchymosis/purpura/petechiae
- Epistaxis
- Hemoptysis
- Hematuria
- Gingival bleeding
- Prolonged bleeding time from needle sticks, abrasions or lacerations
- Hematemesis
- Rectal bleeding
- Blood in stool
- Any other unusual bleeding noted by the subject or caregiver

Any of these symptoms considered clinically significant will be recorded as an adverse event and must be followed until resolved or stable.

10.9 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established to provide independent oversight to this trial. The primary responsibility of the DMC will be to review the progress and conduct of the trial in order to maintain scientific rigor and to ensure the wellbeing of subjects participating in the trial. The specific responsibilities of the DMC will be detailed in a separate DMC charter. The DMC will include at a minimum at least one statistician and two clinicians who will perform periodic data review to assess whether there are clinically significant differences between treatment arms that could affect

participant safety. Following such a review, the DMC Chair will advise the Sponsor that the study be stopped, the design changed, or that the study may continue per protocol.

10.9.1 DMC Safety Review Schedule

The DMC is to review adverse events and safety laboratory assessments after the first 20 subjects complete the Day 8 visit, and again after the first 40 subjects complete the Day 8 visit.

11 STATISTICAL CONSIDERATIONS

A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. All analyses will be descriptive in nature and presented by group.

Summaries for quantitative variables will include the mean, median, quartiles, standard error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and 95% confidence interval (CI), when appropriate. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.4 or higher).

Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. The following sections will briefly summarize of the planned statistical analyses and analysis sets for the primary and secondary endpoints.

11.1 Study Populations for Analysis

All safety analyses will be based on the ITT population, which is defined as all randomized subjects. As will be described in the SAP, efficacy analyses of changes in viral load will be based on the population of subjects with detectable viral load at baseline or similar qualification. Sample size may be adjusted if an inadequate number of subjects have detectable viral load at baseline.

11.2 Safety Analyses

Safety and tolerability will be assessed in terms of AEs, SAEs, WHO Assessments, and safety laboratory data.

Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of post-first dose (treatment-emergent) adverse events will be tabulated by MedDRA preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results and study assessments will be summarized using appropriate descriptive statistics.

11.3 Efficacy Analyses

Efficacy will primarily be assessed via viral load changes.

11.4 Sample Size Considerations

Formal sample size calculations are not applicable for this proof-of-concept study. The sample size of approximately 100 subjects planned to be entered in this trial is expected to be adequate to provide safety and efficacy information to advise future study design.

11.5 Randomization

A randomization scheme will be provided by an independent statistician to the drug packaging company to ensure subjects are randomly assigned to SOC + brequinar or SOC + placebo in a 1:1 ratio.

11.6 Pooling of Study Centers

Not applicable to this small, early phase study.

11.7 Interim Analysis

No interim analysis is planned for this trial.

12 INVESTIGATOR RESPONSIBILITIES

12.1 Investigator's Performance

The Investigator will ensure that all those concerned with conducting the trial are:

- provided with copies of the protocol and all safety information prior to the start of the trial;
- trained regarding the conduct of the study and the training has been documented.

The Investigator will sign the Investigator's Statement and Agreement found in Section 15.2 to indicate commitment to comply with the contents.

12.2 Confidentiality

The Investigator shall assure the subject that his/her identity will be protected and confidentiality will be maintained during all audits and inspections of the trial site and documentation. A unique number will be assigned to each subject at the start of the trial and this, with the subject's initials, will be used to identify the subject. In some cases, a further step may be taken to assign "fake initials" to the subject, per individual site requirements. The subject's number will be the site number followed by the number of this subject at this site and will be used as the unique identifier in the source records and on the eCRF, on all trial correspondence and in the trial database. The Investigator will keep a list of identification codes or initials used for each subject along with the unique number assigned.

All information provided to the Investigator relevant to the investigational product (IP), as well as information obtained during the course of the trial will be regarded as confidential. The Investigator and members of his/her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the Sponsor which will not be unreasonably withheld, except as required by law, or as permitted by the Publications section of this protocol, Section 12.7.

The Investigator will take all measures to ensure subject's confidentiality will be maintained at all times.

12.3 Source Documentation

Investigators are to maintain adequate source documentation of the original study data, for example medication records, laboratory reports and pharmacy records as appropriate. The Investigator will allow inspections of the trial site and documentation by clinical research and audit personnel from the Sponsor, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the eCRFs. In order to do this, direct access to the subjects' medical or clinic records is necessary. The Investigator will ensure that certain information is contained in the medical or clinic written or electronic records of the subject and that the entries are signed and dated, as follows:

- sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories;
- a note on the day the subject entered the trial describing the trial number, the IP being evaluated, the trial number assigned to that subject and a statement that consent was obtained;

- a note of each subsequent trial visit including any concerns about AEs and their resolution;
- notes of all concomitant medication taken by the subject, including start and stop dates;
- a note of when the subject terminated from the trial, the reason for termination and the subject's general condition at termination;
- a copy of the signed informed consent form should be kept in the medical records of each subject during the clinical phase of the study. A signed copy should also be filed in the investigator file.

12.4 Data Collection

Suitably qualified and trained personnel at the trial site will ensure compliance with the protocol, adherence to ICH GCP obligations, proper maintenance of trial records including IP accountability records, correct administration of IP including storage conditions and accurate reporting of AEs. In addition, suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. All queries and discrepancies relating to the data collection are to be resolved at the completion of the trial. Remote data capture is encouraged whenever possible.

12.5 Case Report Forms, Investigator's Site File and Record Retention

The Sponsor may provide the CRFs in paper, electronic (eCRF), or other media. The forms will be reviewed against source documentation at each monitoring visit. All CRFs and supporting source documentation must be completed and available to the Sponsor in a timely manner. Changes or corrections due to data clarification and resolutions will be tracked by paper or electronically with an audit trail.

Prior to review of the case report forms by the Sponsor's representative, they should be reviewed for completeness and accuracy by the Investigator or a member of the research team.

The Investigator must maintain an Investigator Site File which includes, but is not limited to, the IB, the protocol plus any amendments, all correspondence with the IRB including the approval for the trial to proceed, Regulatory Authority approval/ notification (if applicable) including a sample of an approved informed consent, IP accountability, Source Documents, investigator and staff curricula vitae (CVs,) trial documentation, and all trial correspondence. The original signed informed consent forms and the final report will be kept in the Investigator Site File.

The Investigator will archive all essential documents. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The Investigator has a responsibility to retain essential documents for as long as is required by the Sponsor and applicable regulatory authorities. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained. Investigators will be asked to contact the Sponsor prior to the destruction of any data or removal to another site if this occurs prior to the Sponsor notification that the documentation is no longer required. Any transfer of ownership of the data or of documents will be documented in writing. The new owner will assume responsibility for data retention and archiving.

Should the Investigator retire, relocate, or for other reasons withdraw from the responsibility of keeping the trial essential documents, custody must be transferred to a person who will accept that responsibility, and the Sponsor must be notified in writing of the name and address of said person.

12.6 Non-Protocol Research

No investigational procedures other than those outlined in this protocol may be undertaken on the subjects in this trial without the prior written permission of the subject, the Sponsor, the IRB and, when appropriate, the regulatory authority.

12.7 Publication

The Sponsor acknowledges the benefit of making widely available the results of all clinical trials and intends to publish the results of this trial. All publications resulting from the clinical trial must be in a form that does not reveal technical information that the Sponsor considers confidential or proprietary. A copy of any abstract, presentation or manuscript proposed for publication must be submitted to the Sponsor for review at least 30 days before its submission for any meeting or journal. In addition, if deemed necessary by the Sponsor for protection of proprietary information prior to patent filing, the Investigator agrees to a further delay of 60 days before any presentation or publication is submitted. The Sponsor reserves the right to include the report of this trial in any regulatory documentation or submission or in any informational materials prepared for the medical profession.

Authorship determination will be at the discretion of the Sponsor and will include evaluation of the following criteria: Investigator must participate in the review of and content of the protocol; review and comment on the study results; participate in the writing, reviewing and commenting of the manuscript; and approve the final manuscript for submission.

13 SPONSOR RESPONSIBILITIES

13.1 General

The Sponsor agrees to adhere to the ICH Note for Guidance on GCP (CPMP/ICH/135/95, Jan.97) and US FDA Regulations. It is the Sponsor's responsibility to obtain appropriate regulatory approval to perform the trial (if applicable). The Sponsor should notify promptly all concerned investigator(s), IRB(s) and the Regulatory Authority of findings that could adversely affect the health of the patients/ subjects, impact on the conduct of the trial or alter the Regulatory Authority's authorization to continue the trial. If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects the Sponsor will notify the relevant regulatory authority and relevant IRB of the new events, the measures taken and the plan for further action as soon as possible. This will be by telephone in the first instance followed by a written report.

On completion of the trial, the Sponsor will inform the regulatory authority that the trial has ended. If the study is terminated for any reason the Sponsor will provide a written statement to the relevant regulatory authority and the IRB with the reasons for termination of the trial. This will be conducted within 15 days of the decision to terminate the trial. The Sponsor will report in an expeditious manner all SUSARs to the relevant regulatory authority and IRBs.

13.2 Indemnity

The Sponsor will provide compensation insurance against any risk incurred by a subject as a result of participation in this trial. The Sponsor will indemnify the Investigators as detailed in a separate document.

13.3 Data Monitoring

Suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site or will access the electronic health record (EHR) or conduct remote monitoring visits at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. CRFs and source documentation will be available for review during monitoring visits to the trial site. The function of this monitoring is to ensure compliance with the protocol, adherence to regulatory and GCP obligations, proper maintenance of records including IP accountability records, correct administration of IP including storage conditions and accurate reporting of AEs. On-site visits are not required for any monitoring visits for this study.

Once the data from the case report forms have been entered onto the database, they will be reviewed, and the data verified against the subject's source data. Any discrepancies will be tracked by paper or electronically with an electronic audit trail.

13.4 Audit

The Sponsor has an obligation to audit a proportion of studies. A department other than the clinical department will undertake this obligation. Therefore, the Sponsor, an independent auditor or a regulatory authority may audit the trial site and trial documentation. These audits may take place while the trial is being conducted or up to several years later.

13.5 Confidentiality

The Sponsor will not keep any material on file bearing any subject's name, and subjects' confidentiality will be maintained at all times.

13.6 Finance

This will be the subject of a separate agreement between the Investigator/Institution and Sponsor.

14 REFERENCES

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14. Study DUP 785-001 Clinical Study Report (on file with Clear Creek)
15. Study DUP 785-003 Clinical Study Report (on file with Clear Creek)
16. Study DUP 785-005 Clinical Study Report (on file with Clear Creek)
17. Study DUP 785-022 Clinical Study Report (on file with Clear Creek)
18. Study DUP 785-031 Clinical Study Report (on file with Clear Creek)
19. Study DUP 785-034 Clinical Study Report (on file with Clear Creek)
20. FDA Guidance "COVID-19: Developing Drugs and Biological Products for the Treatment or Prevention (https://www.fda.gov/media/137926/download)

15 APPENDICES

15.1 Appendix A: CCB-CRISIS-02 Schedule of Events

CCB-CRISIS-02 Schedule of Events **Windows are relative to first dose time Procedures**	**Screen (days -14 to -1)**	**D1**	**D2, 3 (± 8 hrs)**	**D4 (± 8 hrs)**	**D5 (± 8 hrs)**	**D8 (± 1 day)**	**D12 (± 1 day)**	**D15 (± 1 day)**	**D22 (±1 day)**	**Final Visit D29 (± 2 days)**
Informed Consent (note Date and Time)	X									
AE/Concomitant Medications (dose, route, duration or ongoing)	X	X		X		X	X	X	X	X
Medical history (relevant within one year or ongoing)/ History of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection)	X									
Demographics (subject reported height and weight, date of birth, gender, race, ethnicity)	X									
Check for Physical Exam abnormalities (subject self-reported)	X									
Pregnancy Test (WOCBP)	X (serum)									X (urine)
Hematology/Chemistry[a]	X	X				X		X		
Vital Signs[b]	X	X		X		X	X	X	X	X
Symptom Assessment[c]	X	X		X		X	X	X	X	X
SARS-CoV-2 RT-PCR/Viral load sample[d]	X	X		X		X	X	X	X	X
Hospital Status						X		X	X	X
WHO Ordinal Scale Assessment		X				X		X	X	X
Confirm Eligibility		X								
Randomize subject and dispense Study Medication		X								
Study drug administration[e]		X	X	X	X					
Drug Accountability						X				

[a]Do not repeat if within 48h of Day 1 visit. Send to Covance Central Laboratory Services (CCLS) for analysis.

[b]Vital signs include heart rate, respiratory rate, body temperature, and SpO2. Subject will be provided with a thermometer and pulse oximeter with heart rate monitoring capability. Training will be provided during the first visit by the home health nurse. Vital signs parameters will be observed and recorded by study staff via telemedicine or during a visit by the home health nurse.

[c]Symptom Assessment will use a checklist provided to the subject with symptoms such as sore throat, cough, GI symptoms (vomiting, diarrhea), anosmia, dysgeusia, other (specify), etc. Severity Mild, Moderate, or Severe will be collected.

[d] RT-PCR at Screening may be performed by the site if the subject cannot provide documentation of a positive SARS-CoV-2 result. Samples collected after Screening will be saliva samples sent for viral load analysis. Day 1 sample must be obtained prior to dosing. Viral load specimens after Screening will be saliva samples self-collected by the subject using an Oragene® collection system or similar. The home health nurse will train the subject and observe sample collection on Day 1. These samples are to be sent to CCLS for analysis. The viral load sample may also be used to perform viral cultures (sample can be split by the central laboratory, no additional sample required).

[e]Subject will self-administer study drug once daily Days 1 – 5 and record doses in a medication diary.

Note that any visits/visit activities may be conducted via telephone, telemedicine, or digital media other than serum pregnancy test and chemistry/hematology sample collection. These labs may be collected at the clinical site or another designated out-patient facility/laboratory or collected via home visit. Arrangements for shipping viral load samples will be made by the study team.

15.2 Appendix B: Investigator's Statement and Agreement

STUDY NUMBER: CCB-CRISIS-02

The CRISIS2 Study: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2.

INVESTIGATOR'S STATEMENT AND AGREEMENT

I (*the Investigator*) have read this protocol and hereby agree to conduct the trial in accord with all of its provisions. It is further agreed that the details of this trial and all information provided to me by Clear Creek Bio, Inc. (*the Sponsor*) will be held in the strictest confidence and will not be revealed for any reason without written authorization from Clear Creek Bio, Inc. except to those who are to participate in the conduct of the trial.

I agree that all data, the case report forms, and all materials provided for the conduct of the trial are the property of Clear Creek Bio, Inc. unless specified otherwise in writing. It is understood that Clear Creek Bio, Inc. will utilize the information derived from this trial in various ways, such as for submission to government regulatory agencies, required internal reports, and presentations without violating patient/ subject confidentiality in any way.

I further agree that Clear Creek Bio, Inc. or its representatives will be permitted access, in accordance with current Good Clinical Practice Guidelines, to all data generated by this trial and the source documents from which case report form data were generated.

PRINCIPAL INVESTIGATOR

Printed Name: _____

Signature: _____ Date: _____

15.3 Appendix C: WHO Ordinal Scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized: moderate disease	Hospitalized; no oxygen therapy*	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: severe disease	Hospitalized; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	8
	Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

WHO clinical progression scale

STUDY PROTOCOL

The CRISIS2 Study: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2

Study No: CCB-CRISIS-02

Version: 3.0

Version Date: 23 September 2020

Sponsor:

Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

Sponsor Telephone: (617) 765-2252

Sponsor Facsimile: (617) 863-2082

IND Number: 149291

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine amino transferase
AML	Acute myeloid leukemia
ARDS	Acute respiratory disease syndrome
AST	Aspartate amino transferase
BRQ	Brequinar
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus-19 infection
CRP	c-reactive protein
CTCAE	Common terminology criteria for adverse events
CTEP	Cancer Therapy Evaluation Program
CV	Curricula vitae
DHO	Dihydroorotate
DHODH	Dihydroorotate dehydrogenase
DHODHi	Dihydroorotate dehydrogenase inhibitor
DMC	Data Safety Monitoring Board
ECMO	Extra corporeal membrane oxygenation
EHR	Electronic health record
ESR	Erythrocyte Sedimentation Rate
EUA	Emergency Use Authorization
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council on Harmonization
ICU	Intensive care unit
IMP	Inosine-5’ phosphate
IP	Investigational product
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NEWS2	National Early Warning System (NEWS) 2 Score
RNA	Ribonucleic Acid
RdRp	RNA-dependent RNA polymerase
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	SARS Coronavirus 2
SOC	Standard of Care
SUSAR	Suspected unexpected serious adverse reaction
SpO_2	Peripheral capillary oxygen saturation

Abbreviation	Definition
UMP	Uridine 5'-monophosphatase
US	United States
XMP	Xanthosine-5' phosphate
WHO	World Health Organization
WOCBP	Women of childbearing potential

2 SYNOPSIS

CCB-CRISIS-02 SYNOPSIS	
IND	149291
Title	The CRISIS2 Study: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2
Protocol Number	CCB-CRISIS-02
Rationale	Brequinar is a potent DHODH inhibitor that has been previously studied in more than 1,000 cancer, psoriasis, and organ transplant patients. Brequinar has been found to have potent *in vitro* antiviral activity against many RNA viruses including SARS-CoV-2. The antiviral activity of brequinar against SARS-CoV-2 is likely due to DHODH inhibition and shows nanomolar potency and a high selectivity index in inhibiting viral replication in *in vitro* studies. The CRISIS2 trial will study out-patients (non-hospitalized patients) who have a positive SARS-CoV-2 test and are symptomatic. Subjects will be randomized to receive standard of care (SOC) + 5 days of brequinar or SOC + 5 days of placebo. The purpose of this study is to determine if the *in vitro* antiviral activity of brequinar can be duplicated in patients infected with SARS-CoV-2 by measuring the effect of brequinar on viral shedding. Importantly, the safety and tolerability of brequinar will also be determined in these patients. The results of this proof-of-concept study will inform future studies that will help determine if brequinar is a safe and effective drug for the treatment of SARS-CoV-2 infection.
Investigational Product and Dosage	Subjects will be randomized in a 1:1 ratio to either standard of care (SOC) + 5 days of brequinar 100 mg or SOC + 5 days of placebo. Investigational product will be supplied as either brequinar 100 mg oral capsules or placebo capsules. The subjects are to self-administer one capsule on Study Days 1 – 5. Treatment assignment will be randomized, double-blind.
Primary Objectives	● To demonstrate a change from baseline in quantitative SARS-CoV-2 viral load for brequinar-treated subjects compared to placebo-treated subjects through Day 29.
Secondary Objectives	Through Day 29: ● To characterize the safety and tolerability of brequinar in out-patient COVID-19 subjects as measured by frequencies of grade 3 and 4 AEs and SAEs; ● To demonstrate a shorter duration of viral shedding in subjects treated with brequinar compared to subjects who received placebo;

	● To reduce the percentage of subjects requiring hospital admission as an in-patient for > 24 hours for brequinar subjects compared to subjects who received placebo; ● To reduce all-cause mortality through Day 29 for brequinar subjects compared to subjects who received placebo.
Exploratory Objectives	Through Day 29: ● To determine time to viral clearance (two consecutive negative tests); ● To determine time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline; ● To determine time to clinical improvement as measured by a favorable shift in the WHO Ordinal Scale score measured for the subset of subjects with baseline WHO Ordinal Scale of 2 for brequinar subjects compared to subjects who received placebo.
Design	This will be a phase 2 randomized, double blind, multi-center study with approximately 100 subjects. All subjects will receive SOC per relevant guidelines for treatment of out-patients with COVID-19 infection. In addition to SOC, subjects will self-administer one capsule once daily for 5 days. Subjects will have a Screening Visit followed as soon as possible with Study Day 1. Study procedures are presented in detail in the Schedule of Events. Study visits (virtual or in person) will take place at Screening and on Study Days 1 - 8, 12, 15, 22, and 29. The visits that include bloodwork must be conducted at the study site or arrangements made for sample collection at the subject's home or other appropriate location. Other visits/visit activities for that visit may be conducted remotely using telephone, telemedicine or other remote technique. Subjects are to self-collect a viral load sample, obtain their respiratory rate, heart rate, body temperature and SpO2, and complete a symptom assessment with the site via telemedicine on Days 1, 4, 8, 12, 15, 22, and 29. The site will also have a telephone call with the subject on Study Days 2, 3, 5, 6, and 7 for changes in concomitant medications and assessment of adverse events, especially those that may indicate thrombocytopenia and mucositis. A home health nurse will visit the subject at Screening and on study Days 1, 8, 15, and 29. Telemedicine only visits will be conducted by site staff on study Days 4, 12, and 22.
Sample Size:	Approximately 100 subjects will be randomized to 5 days of either SOC + brequinar 100 mg or SOC + placebo in a 1:1 ratio (approximately 50 subjects assigned to brequinar 100 mg and 50 subjects to placebo).
Number of Sites:	Approximately 15
Study Period:	An enrollment period of 3 months is expected.

Inclusion Criteria:	1. Willing and able to provide informed consent for the trial, written, electronic, verbal, or other method deemed acceptable by the institution and IRB. 2. 18 years of age or older. 3. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other FDA-approved commercial or public health assay within 14 days of first dose. 4. Out-patient (never hospitalized as an in-patient for COVID-19 or was evaluated/treated for COVID-19 only in the Emergency Room with a stay of < 24 hours). 5. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men and women treated or enrolled on this protocol must also agree to use adequate contraception for the duration of study participation, and for 90 days after completion of brequinar administration. 6. Male subjects must agree to refrain from sperm donation and female subjects must agree to refrain from ovum donation from initial study drug administration until 90 days after the last dose of brequinar. 7. Must have at least one COVID-19 symptom including but not limited to fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, shortness of breath, dyspnea, anosmia, dysgeusia, or other symptom commonly associated with COVID-19. 8. Able to swallow capsules.
Exclusion Criteria:	1. Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient 2. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test 3. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide) or other agents known to cause bone marrow suppression leading to thrombocytopenia 4. Platelets ≤150,000 cell/mm^3 5. Hemoglobin < 10 gm/dL 6. Absolute neutrophil count < 1500 cells/mm^3 7. Renal dysfunction, i.e., creatinine clearance < 30 mL/min

	8. AST and/or ALT > 2 x ULN, or total bilirubin > ULN. Gilbert's Syndrome is allowed. 9. Bleeding disorders or blood loss requiring transfusion in the six weeks preceding enrollment 10. Ongoing gastrointestinal ulcer, or gastrointestinal bleeding within 6 weeks of first dose. 11. Chronic hepatitis B infection, active hepatitis C infection, active liver disease and/or cirrhosis per subject report. 12. Heart failure, current uncontrolled cardiovascular disease, including unstable angina, uncontrolled arrhythmias, major adverse cardiac event within 6 months (e.g. stroke, myocardial infarction, hospitalization due to heart failure, or revascularization procedure).
Treatment	All subjects will receive standard of care (SOC) including symptomatic care. Subjects will be randomly assigned to SOC + brequinar 100 mg daily x 5 or SOC + placebo daily x 5. Study encounters will be conducted remotely whenever possible.
DMC	A Data Monitoring Committee (DMC) will meet periodically to review the safety and scientific conduct of the study. At a minimum, the DMC is to review adverse events and safety laboratory assessments after the first 20 subjects complete Day 8, and again after the first 40 subjects complete Day 8.
Procedures	Study procedures are outlined in the Schedule of Events. Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF.
Safety/ Tolerability	**Safety/Tolerability** Adverse events will be collected from the time of first dose through Day 29. After Day 29, collect/record only Serious Adverse Events (SAEs) or those judged by the Investigator or designated person to be related to study drug. Treatment-emergent adverse events will be those with an onset after the date and time of first treatment. Subjects who develop Grade 3 or 4 toxicities or SAEs are to be re-evaluated every 2 days, as feasible, until the toxicity returns to Grade ≤ 2 severity. During assessment for adverse events, investigators and site staff are to elicit from the subject any signs or symptoms of mucositis or thrombocytopenia, e.g.: • Ecchymosis/purpura/petechiae • Epistaxis • Hemoptysis • Hematuria • Gingival bleeding

	• Prolonged bleeding time from needle sticks, abrasions or lacerations • Hematemesis • Rectal bleeding • Blood in stool • Any other unusual bleeding noted by the subject or caregiver
Stopping Criteria	Individual Criteria: • Participants who develop a Grade 3 toxicity that is assessed by the investigator to be related to the study drug are to be permanently discontinued from study treatment. • Participants who develop a Grade 4 toxicity, regardless of relatedness to study drug, are to be permanently discontinued from study treatment. Study-Level Stopping Criteria: Study enrollment is to be paused if any of the below criteria are met: • If ≥ 3 subjects develop the same related Grade 4 (life-threatening) adverse event or laboratory abnormality; • If ≥ 5 subjects develop the same related Grade 3 or 4 adverse event or laboratory abnormality; • If ≥ 10 subjects develop any related Grade 3 or 4 adverse event or laboratory abnormality. All adverse events will be reviewed by the DMC during their reviews. Following assessment by the Data Monitoring Committee (DMC), the DMC will determine whether to stop the study, amend the protocol, or continue the study per protocol.
Statistical Analysis	A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. All analyses of safety and efficacy for this study will be descriptive in nature and presented by group. Subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. Summaries for quantitative variables will include the mean, median, quartiles, standard error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the 95% CI, when appropriate. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.4 or higher). Safety and tolerability will be assessed in terms of AEs, SAEs, and safety laboratory data. Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of treatment-emergent adverse events, defined as TEAEs occurring after first dose will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results and other clinical measures will be summarized using appropriate descriptive statistics.

CCB-CRISIS-02 Schedule of Events

CCB-CRISIS-02 Schedule of Events **Windows are relative to first dose time** **Procedures**	**Screen (days -14 to -1) HH+TM[f]**	**D1 HH + TM**	**D2, 3 (± 8 hrs) TC[f]**	**D4 (± 8 hrs) TM**	**D5,6, 7 (± 8 hrs) TC**	**D8 (± 1 day) HH+ TM**	**D12 (± 1 day) TM**	**D15 (± 1 day) HH+ TM**	**D22 (±1 day) TM**	**Final Visit D29 (± 2 days) HH+TM**
Informed Consent (note Date and Time)	X									
AE/Concomitant Medications (dose, route, duration or ongoing)	X	X	X	X	X	X	X	X	X	X
Medical history (relevant within one year or ongoing)/ History of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection)	X									
Demographics (subject reported height and weight, date of birth, gender, race, ethnicity)	X									
Check for Physical Exam abnormalities (subject self-reported)	X									
Pregnancy Test (WOCBP)	X (serum)									X (urine)
Hematology/Chemistry[a]	X	X				X		X		
Vital Signs[b]	X	X		X		X	X	X	X	X
Symptom Assessment[c]	X	X		X		X	X	X	X	X
SARS-CoV-2 RT-PCR/Viral load sample[d]	X	X		X		X	X	X	X	X
Hospital Status						X		X	X	X
WHO Ordinal Scale Assessment		X				X		X	X	X
Confirm Eligibility		X								
Randomize subject and dispense Study Medication		X								
Study drug administration[e]		X	X	X	X D5 only					
Drug Accountability						X				

[a]Do not repeat if within 48h of Day 1 visit. Send to Covance Central Laboratory Services (CCLS) for analysis.

[b]Vital signs include heart rate, respiratory rate, body temperature, SpO2. Subject will be provided with a thermometer and pulse oximeter with heart rate monitoring capability. Training will be provided during the first visit by the home health nurse. Vital signs parameters will be observed and recorded by study staff via telemedicine or during a visit by the home health nurse.

[c]Symptom Assessment will use a checklist provided to the subject with symptoms such as sore throat, cough, GI symptoms (vomiting, diarrhea), anosmia, dysgeusia, other (specify), etc. Severity None, Mild, Moderate, or Severe will be collected.

[d]RT-PCR at Screening may be performed by the site if the subject cannot provide documentation of a positive SARS-CoV-2 result. Samples collected after Screening will be saliva samples sent for viral load analysis. Day 1 sample must be obtained prior to dosing. Viral load specimens after Screening will be saliva samples self-collected by the subject using an Omnigene® collection system or similar. The home health nurse will train the subject and observe sample collection on Day 1. These samples are to be sent to CCLS for analysis. The viral load sample may also be used to perform viral cultures (sample can be split by the central laboratory, no additional sample required).

[e]Subject will self-administer study drug once daily Days 1 – 5 and record doses in a medication diary. Note that any visits/visit activities may be conducted via telephone, telemedicine, or digital media other than serum pregnancy test and chemistry/hematology sample collection. These labs may be collected at the clinical site or another designated out-patient facility/laboratory or collected via home visit. Arrangements for shipping viral load samples will be made by the study team.

[f]HH = Home Health in-person visit; TC = Telephone Call with site and subject; TM = Telemedicine with site and subject.

STUDY PERSONNEL

SPONSOR CONTACT

Name:	Barbara Powers, MSN, Ph.D.
Title:	Clinical Operations
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3 INTRODUCTION

3.1 Coronavirus-19 (COVID-19)

Beginning in December 2019, Chinese scientists isolated a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from patients with virus-infected pneumonia which was later designated as coronavirus disease 2019 (COVID-19) by the World Health Organisation (WHO) (Zhou et al., 2020 [2]; Phelan et al., 2020 [3]).

Approximately 14% of those affected with this virus will develop severe disease requiring hospitalization and oxygen support; 5% will require admission to the intensive care unit (Handel et al., 2020 [4]). Severe cases may be complicated by acute respiratory disease syndrome (ARDS), sepsis and septic shock, and multi-organ failure, including acute kidney injury and cardiac injury. Risk factors for death include older age and co-morbid disease such as hypertension and diabetes (Zhou, et al., 2020 [2]). This means that most patients will be treated as out-patients. Reducing viral load in this environment is critically important for both the subjects themselves by preventing worsening of symptoms and possibly avoiding hospitalization, but also to reduce the transmission of the disease to others in the patients' households and their communities.

3.1.1 Coronavirus Biology

Coronaviruses, like other RNA-based viruses, do not have the machinery to synthesize their own nucleotides and thus depend upon the host intracellular pool of nucleotides for viral replication. In essence, viruses steal the host RNA building blocks, and without these building blocks they are unable to replicate. The SARS-CoV-2 is a single-stranded (positive sense) RNA virus with a genome that is 29,811 nucleotides long, quite a lot larger than other RNA-based viruses (e.g. the hepatitis C genome comprises only 9600 nucleotides). The nucleotide composition is broken down as: 29.9% adenosines, 18.4% cytosines, 19.6% guanines, and 32.1% uridines (Sah et al., 2020 [12]).

3.2 Host Nucleotide Synthesis

Host *de novo* pyrimidine synthesis generates uridine monophosphate (UMP) as the building block for all pyrimidine ribonucleotides and deoxyribonucleotides (Figure 3-1). There exists no salvage pathway for the synthesis of UMP, the fundamental building block of pyrimidines. Inhibition of enzymatic steps upstream of UMP (Figure 3-1) leads to a rapid and profound depletion of intracellular pyrimidines.

3.3 Dihydroorotate dehydrogenase (DHODH)

The enzyme dihydroorotate dehydrogenase (DHODH) catalyzes the 4th step of *de novo* pyrimidine synthesis and inhibition of DHODH completely halts all pyrimidine production. As shown in Figure 3-1, DHODH is located on the inner mitochondrial membrane and transfers electrons between DHO and complex III of the electron-

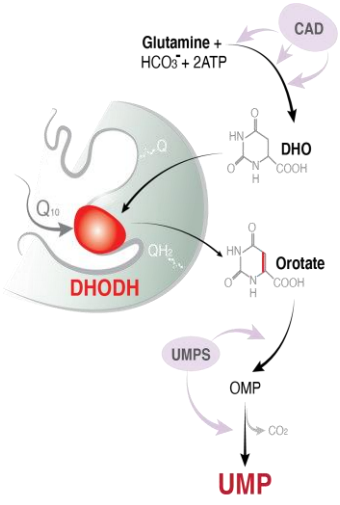

Figure 3-1. DHODH is a mitochondrial enzyme that catalyzes the 4th step of pyrimidine synthesis; it is completely essential for the generation of UMP.

transport chain via the reduction of its ubiquinone (coenzyme Q10) cofactor.

DHODH is a clear therapeutic target for the inhibition of host pyrimidine synthesis. The chemical inhibition of DHODH *in vitro* or *in vivo* leads to the rapid depletion of UMP and subsequent depletion of downstream products thymine and cytosine. This forces a cell to rely on the salvage of extracellular pyrimidine nucleotides and this extracellular salvage is not capable of maintaining the cell's normal nucleotide pool (Sykes et al., 2016) [1]).

3.4 Brequinar

Brequinar is an orally available and potent inhibitor of DHODH. Brequinar is one of more than 300 quinoline-carboxylic acid derivatives prepared in an analog synthesis program in the 1980s, which was started after it was found that a compound of this class had antitumor activity. Brequinar was selected by DuPont for further development as a potential clinical drug because of its activity against experimental tumors and because its water solubility made it relatively straightforward to formulate.

In an indication such as treating SARS-CoV-2 infection, brequinar will act as a host-targeting antiviral. It is an orally available and potent inhibitor of dihydroorotate dehydrogenase (DHODH), the enzyme that catalyzes the fourth step in pyrimidine synthesis, namely the conversion of dihydroorotate (DHO) to orotate. DHODH inhibitors, including brequinar, inhibit *de novo* pyrimidine synthesis thereby leading to a depletion of a cell's pool of uridine, cytidine and thymidine ribonucleotides and deoxyribonucleotides.

The antiviral activity of brequinar has been demonstrated in studies of rotavirus replication in human intestinal Caco-2 cells as well as in human primary intestinal organoids (Chen et al., 2019 [6]). Treatment with teriflunomide, another DHODHi, has been effective *in vitro* and *in vivo* in a murine model of foot and mouth disease virus (Mei-Jian et al., 2019 [7]). DHODH inhibition (DHODHi) also inhibited the growth of dengue virus *in vitro* (Wang et al., 2011 [8]). DHODHi also showed antiviral effects against RNA viruses including influenza A, Zika, Ebola and coronavirus SARS-CoV-2 (Xiong et al., 2020 [11]**).** Brequinar has also been shown to inhibit the replication of Ebola virus, vesicular stomatitis virus and Zika virus *in vitro* (Luthra et al., 2018 [9]). Brequinar inhibits the replication of human immunodeficiency virus (HIV) *in vitro* (Andersen et al., 2019 [10]). When considering brequinar as an antiviral for treatment of SARS-CoV-2, oral brequinar is highly bioavailable (>95%) and has good penetration of lung tissue with an average tissue:blood ratio of 0.5 following a single dose of brequinar in the rat. It is therefore expected to achieve a similar period of DHODH inhibition in lung tissue (Brequinar IB [5]).

3.5 Rationale for the Planned Trial

DHODH inhibition has been extensively studied as a potential therapeutic target in the treatment of RNA-based viruses. The inhibition of DHODH is effective in inhibiting viral replication in pre-clinical models involving many RNA-based viruses with nanomolar potency and a high selectivity index (see the Brequinar IB [5], Section 5). In these pre-clinical models, the benefit of DHODH inhibition can be reversed by the supplementation of exogenous nucleotides, confirming that the on-target effect of host pyrimidine depletion is key to the anti-viral activity.

The CCB-CRISIS-02 trial will study standard of care (SOC) with 5 days of brequinar (DHODH inhibition) compared to SOC with 5 days of placebo treatment. Clear Creek Bio hypothesizes that a defined 5-day course of brequinar will inhibit the enzyme DHODH to a degree sufficient to result in the transient depletion of host pyrimidine nucleotides, thereby inhibiting viral replication. A recent publication demonstrated that inhibitors of DHODH could potentiate the activity of inhibitors of RNA-dependent RNA polymerase (RdRp) in the treatment of dengue virus, another single-stranded RNA virus similar to SARS-CoV-2 (Liu et al., 2020 [13]). This inhibition of viral replication may restore the balance in favor of the host immune system for the clearance of SARS-CoV-2.

Marketed DHODHi medications are available, including leflunomide or teriflunomide, however these are very weak inhibitors of DHODH with cellular potency ~500 times lower than brequinar. These low potency inhibitors of DHODH are not expected to have the ability to acutely lower the pool of intracellular pyrimidines to the degree that is required for decreasing the viral load associated with SARS-CoV-2 infection, making brequinar the better choice for acute SARS-CoV-2 infection.

The CRISIS2 study is a proof-of-concept study in patients with SARS-Cov-2 infection and will serve as a basis for future studies to determine the safety and effectiveness of brequinar in COVID-19.

3.5.1 Brequinar Dose Selection

Safety data from previous oncology clinical studies of brequinar with 5 days of consecutive daily dosing suggest that 5 days of daily doses of 100 mg p.o. will be safe and well tolerated. A dose of brequinar 100 mg achieves plasma concentrations of approximately 1 uM (0.4 ug/ml) that should result in sufficient suppression of nucleotide synthesis. When given over 5 days, these plasma concentrations are achieved on a daily basis without accumulation, also assuring the safety of this regimen (see Brequinar IB [5]).

3.5.2 Risk/Benefit of Brequinar

As presented in the Brequinar IB [5], an extensive safety and pharmacokinetic database exists with more than 1,000 patients treated with brequinar. Cancer patients (N = 806) have been exposed to this compound for treatment of a variety of solid tumors at various treatment regimens, doses, and routes including a single dose, once weekly, twice weekly, single dose every 3 weeks, daily times 5 every 4 weeks, and daily times 21 days for multiple courses. Lower doses than used in the cancer studies have also been utilized for patients with psoriasis and organ transplant. The maximum intravenous dose given was 2,250 mg/m^2 every 3 weeks, and the maximum oral dose was 100 mg/m^2 daily for 21 days. There has been limited testing of DHODHi to date in the clinic for infection with SARS-CoV-2. DHODHi therapy at relatively high doses in the context of trials for patients with cancer has the expected safety side-effects of mucositis and bone marrow suppression. Importantly, however, the prior clinical experience in 39 subjects who received daily brequinar for 5 consecutive days at or lower than 100 mg/day show no cases of mucositis and only 1 (2.6%) episode of mild thrombocytopenia. Based on these data the 100 mg per day dose proposed for administration in this study should be within a safe and tolerable range as well as demonstrating the predicted antiviral effect.

The potential benefit in using brequinar to treat SARS-CoV-2 infection is the hypothesis that a 5-day period of brequinar dosing will suppress host *de novo* pyrimidine synthesis for this period thus decreasing viral load. Inhibition of DHODH is expected to reduce the ability of the virus to replicate

and it is for this reason that brequinar will be administered to patients with COVID-19 in this study.

3.6 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration of high-dose brequinar in patients with refractory solid tumors, reversible myelosuppression, in particular thrombocytopenia, and mucositis have been the primary dose-limiting toxicities. In addition, skin rash, nausea/vomiting, fatigue, and leukopenia have been dose-limiting in trials utilizing other schedules of brequinar administration. However, these effects were self-limiting, transient, required treatment in few cases, and resolved following discontinuation of dosing. These adverse effects have been associated with higher doses of brequinar given via the intravenous route and for longer durations than the 100 mg dose and 5-day regimen proposed for this study.

In addition to studying a higher risk population with symptomatic COVID-19, a comprehensive safety monitoring plan will be utilized in this study to assess the ongoing safety and well-being of participants (see Section 10.8).

3.7 Possible Interactions with Concomitant Medical Treatments

Brequinar has been administered to subjects taking a variety of concomitant medications that are typical in severely ill cancer patients including antibiotics, antifungals and other critical care medications. No formal interaction studies have been conducted for these medications, however, there have not been any reports of interactions with any medications during the clinical trials with more than 800 cancer patients.

3.7.1 CYP Interactions

No formal clinical drug-drug interaction studies have been performed for brequinar with medications commonly used in treating hematologic malignancies. The nonclinical studies performed to date have demonstrated there is no first-pass metabolism and there have been no apparent hepatotoxic effects in the clinical studies. Brequinar itself does not appear to be a substrate for metabolism by cytochrome P450 enzymes when tested under a variety of conditions. (See Brequinar IB [5]; nonclinical data on file with Clear Creek).

3.8 Steps to be Taken to Control or Mitigate Risks

All subjects will be treated by highly experienced clinicians familiar with the treatment of viral infections and their complications.

4 TRIAL OBJECTIVES

4.1 Primary Objective

To demonstrate a change from baseline in quantitative SARS-CoV-2 viral load for brequinar-treated subjects compared to placebo-treated subjects through Day 29.

4.2 Secondary Objectives

The secondary objectives of this study are:

Through Day 29:

- To characterize the safety and tolerability of brequinar in out-patient COVID-19 subjects as measured by frequencies of grade 3 and 4 AEs and SAEs;
- To demonstrate a shorter duration of viral shedding in subjects treated with brequinar compared to subjects who received placebo;
- To reduce the percentage of subjects requiring hospital admission as an inpatient for >24 hours for brequinar subjects compared to subjects who received placebo;
- To reduce all-cause mortality through Day 29 for brequinar subjects compared to subjects who received placebo.

4.3 EXPLORATORY OBJECTIVES

Through Day 29:

- To determine time to viral clearance (two consecutive negative tests);
- To determine time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline;
- To determine time to clinical improvement as measured by a favorable shift in the WHO Ordinal Scale score for the subset of subjects with baseline WHO Ordinal Scale of 2 for brequinar subjects compared to subjects who received placebo.

5 TRIAL DESIGN

This will be a phase II randomized, placebo-controlled, double blind, multi-center study with approximately 100 subjects. All subjects will receive standard of care per (SOC) institutional guidelines for treatment of patients with COVID-19 infection. In addition to SOC, the subjects will self-administer one capsule once daily for 5 days.

Subjects will have a Screening Visit followed as soon as possible with Study Day 1. Study procedures are presented in detail in the Schedule of Events (Appendix 15.1). Study visits (virtual or in person) will take place at Screening and on Study Days 1 - 8, 12, 15, 22, and 29. The visits that include bloodwork must be conducted at the study site or arrangements made for sample collection at the subject's home or other appropriate location. Other visits/visit activities for that visit may be conducted remotely using telephone, telemedicine or other remote technique. Subjects are to self-collect a viral load sample, obtain their respiratory rate, heart rate, body temperature and SpO2, and complete a symptom assessment checklist with the site via telemedicine on Days 1, 4, 8, 12, 15, 22, and 29. The site will also have a telephone call with the subject on Study Days 2, 3, 5, 6, and 7 for changes in concomitant medications and assessment of adverse events, especially those that may indicate thrombocytopenia (see Section 10.8) and mucositis. A home health nurse will visit the subject at Screening and on study Days 1, 8, 15, and 29. Telemedicine only visits will be conducted by site staff on study Days 4, 12, and 22.

6 TRIAL ENDPOINTS

6.1 Primary Endpoint

Quantitative SARS-CoV-2 viral load through Day 29.

6.2 Secondary Endpoints

The secondary endpoints of this study are:

Through Day 29:

- Rates of AEs and SAEs including laboratory assessments;
- Duration of viral shedding;
- Percentage of subjects requiring admission as an inpatient for >24 hours.
- All-cause mortality.

6.3 Exploratory Endpoints

Through Day 29:

- Time to viral clearance (two consecutive negative tests);
- Time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline;
- Time to clinical improvement measured by a favorable shift in WHO Ordinal Scale score for the subset of subjects with baseline WHO Ordinal Scale of 2.

7 TRIAL POPULATION

7.1 Number of Subjects

Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 100 subjects have completed the study. Subjects will be randomized to either standard of care plus brequinar 100 mg or standard of care plus placebo in a 1:1 ratio (approximately 50 subjects assigned to standard of care plus brequinar 100 mg and approximately 50 subjects assigned to standard of care plus placebo).

7.2 Inclusion criteria

1. Willing and able to provide informed consent for the trial, written, electronic, verbal or other method deemed acceptable by the institution and IRB.
2. 18 years of age or older.
3. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other FDA-approved commercial or public health assay within 14 days of first dose.
4. Out-patient (never hospitalized as an in-patient for COVID-19 or was evaluated/treated for COVID-19 only in the Emergency Room with a stay of < 24 hours).
5. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men and women treated or enrolled on this protocol must also agree to use adequate contraception for the duration of study participation, and for 90 days after completion of brequinar administration.
6. Male subjects must agree to refrain from sperm donation and female subjects must agree to refrain from ovum donation from initial study drug administration until 90 days after the last dose of brequinar.
7. At least one COVID-19 symptom including but not limited to fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, shortness of breath, dyspnea, anosmia, dysgeusia, or other symptom commonly associated with COVID-19.
8. Able to swallow capsules.

7.3 Exclusion Criteria

1. Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient
2. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test
3. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide) or other agents known to cause bone marrow suppression leading to thrombocytopenia
4. Platelets $\leq$150,000 cell/mm^3

5. Hemoglobin < 10 gm/dL
6. Absolute neutrophil count < 1500 cells/mm^3
7. Renal dysfunction, i.e., creatinine clearance < 30 mL/min
8. AST and/or ALT > 2 x ULN, or total bilirubin > ULN. Gilbert's Syndrome is allowed.
9. Bleeding disorders or blood loss requiring transfusion in the six weeks preceding enrollment
10. Ongoing gastrointestinal ulcer, or gastrointestinal bleeding within 6 weeks of first dose.
11. Chronic hepatitis B infection, active hepatitis C infection, active liver disease and/or cirrhosis per subject report.
12. Heart failure, current uncontrolled cardiovascular disease, including unstable angina, uncontrolled arrhythmias, major adverse cardiac event within 6 months (e.g. stroke, myocardial infarction, hospitalization due to heart failure, or revascularization procedure).

8 STUDY TREATMENTS

8.1 Description of Study Medications

8.1.1 Brequinar

Brequinar and placebo will be supplied as 100 mg capsules. Dosing will be a single 5-day course of brequinar 100 mg capsules or placebo 100 mg capsules once daily for 5 doses.

8.2 Treatment Administration

This will be a phase 2 randomized, placebo-controlled, double blind, multi-center study with approximately 100 subjects. All subjects will receive standard of care (SOC) for COVID-19 infection. Subjects will be randomly assigned in a 1:1 ratio to standard of care plus brequinar or standard of care plus placebo.

8.2.1 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit. The *NIH Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria.

Adverse events (AEs) commonly observed in patients treated with brequinar are provided in the Investigator's Brochure (IB) and include thrombocytopenia, nausea, anemia, diarrhea, vomiting, leukopenia, stomatitis, rash, granulocytopenia, fatigue, and infection. In a study of 209 cancer subjects treated once-weekly (DuP 785-012, see Brequinar IB [5]), the deaths of three patients were attributed to study drug toxicity (two to hemorrhage, one following acute renal failure). Severe toxicities grades (Grades 3 to 4) which typically led to discontinuation in this study included hematologic toxicities (anemia, thrombocytopenia, leukopenia, granulocytopenia), digestive system toxicity (nausea, vomiting, stomatitis, others including gastric hemorrhage) and mucositis.

In three oncology studies with five consecutive days of intravenous (IV) brequinar dosing in 168 subjects (Study 785-001 [14], 785-003 [15], and 785-005 [16]) there were no toxic deaths. For subjects from these three studies who were treated with a daily dose of 100 mg or below (as will be dosed in CCB-CRISIS-02), AEs through 21 days showed that 2 of 39 subjects (5.1%) had a severe (Grades 3 or 4) AE related to study drug (1 subject each with hyperbilirubinemia and hyperglycemia), and no subjects discontinued from the study due to a study drug-related AE. The few study drug related AEs through 21 days at or below the 100 mg dose from these three studies included 2 subjects each with nausea, vomiting, and creatinine elevated and one subject each with thrombocytopenia and diarrhea. When only studies with oral dosing were considered at this dose level (Studies 785-022 [17], 785-031 [18] , and 785-034 [19]), the study drug related AEs through 21 days (each observed in one subject only) included diarrhea, headache, nausea, pruritus, abdominal pain, anorexia, chest pain, dry mouth, fatigue, keratosis, stomatitis, and vomiting. See brequinar IB [5].

In most instances, brequinar-related toxicities were transient, clinically manageable, and reversible upon discontinuation of brequinar treatment. Any of these events reported with brequinar use can be serious in nature and may result in death.

A 5-day course of oral brequinar administered once daily at a low level relative to those administered in the cancer studies is expected to be safe and well tolerated in the COVID-19 population.

8.3 Study Discontinuation

Subjects will remain in the study through at least Study Day 29 (or longer if needed to follow up study drug-related adverse events). Participants may discontinue from the study by withdrawing consent at any time or for any reason as presented in Section 9.7.

8.4 Stopping Criteria

8.4.1 Individual Stopping Criteria

- Participants who develop a Grade 3 toxicity that is assessed by the investigator to be related to the study drug are to be permanently discontinued from study treatment.
- Participants who develop a Grade 4 toxicity, regardless of relatedness to study drug, are to be permanently discontinued from study treatment.
- Subjects who develop Grade 3 or 4 toxicities are to be followed by re-evaluation every 2 days, as feasible, until the toxicity returns to ≤ Grade 2 severity.

8.4.2 Study-Level Stopping Criteria

Study enrollment is to be paused if any of the below criteria are met:

- If ≥ 3 subjects develop the same related Grade 4 (life-threatening) adverse event or laboratory abnormality;
- If ≥ 5 subjects develop the same related Grade 3 or 4 adverse event or laboratory abnormality;
- If ≥ 10 subjects develop any related Grade 3 or 4 adverse event or laboratory abnormality.

Following assessment by the Data Monitoring Committee (DMC, see Section 10.9), the DMC will determine whether to stop the study, amend the protocol, or continue the study per protocol.

8.5 Concomitant Medication/Treatment

Record the name, dose, start/stop date, indication for use, route, and whether ongoing or stopped for medications/treatments taken within two weeks prior to study entry as well as any medications taken during the study are to be recorded. Prohibited medications are identified in Section 8.8.

8.6 Treatment Compliance

Compliance will be assessed by reviewing the subject's medication diary and study records as appropriate.

8.7 Storage, Stability, Labeling and Packaging

8.7.1 Storage and Stability

The study drug is stored at room temperature. Stability testing is ongoing.

8.7.2 Labeling and Packaging

The bulk drug and unit-dose containers will be labeled in accordance with national laws and regulations.

8.7.3 Blinding and Randomization

The trial will be conducted in double blinded, randomized manner with random assignment to standard of care plus brequinar or standard of care plus placebo. The brequinar and placebo capsules will be provided to each participating institution in pre-numbered bottles intended for individual subjects to be dispensed by the institution's pharmacist or designated person. Randomization assignments will be provided by an independent statistician to the drug packaging company. The pharmacist/designated person will dispense the next number in sequence to the next patient who qualifies for the study at an individual site.

8.7.4 Unblinding/Expectedness

Contact the Covance Medical Monitor if it is necessary to break the blind for this blinded study due to an adverse event (AE). Each site will be provided with a sealed envelope containing individual sealed envelopes for subject numbers assigned to that site. Each individual subject number sealed envelope will have the treatment (brequinar or placebo) randomly assigned to that subject number. Do not open the outer envelope or the individual sealed envelope unless it has been agreed with the Medical Monitor and the Sponsor that unblinding is necessary for that particular AE. Unblinding must be documented in the study records. Envelope seals are to be checked to ensure they remain intact during drug accountability monitoring.

If after a discussion with the Medical Monitor, the investigator or treating clinician believes the AE leading to unblinding to be related to the study drug, no further doses of drug should be administered to that subject.

Expectedness will be determined by establishing whether an adverse event is among those identified in the protocol and the brequinar IB or are commonly associated with COVID-19 or similar severe viral illnesses and their complications.

8.7.5 Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator must keep a record of all study medication received, administered, and discarded. It must be clear from the records whether the subject received study medication and what subject number was assigned to which subject. Adequate drug is to be dispensed for the number of subjects expected to be treated at each institution.

The pharmacist/staff member responsible for drug accountability is to document the date and time of dispensing and for what subject the study drug was intended (i.e., record subject initials and birth date or other unique identifier). A pharmacy manual will be provided by the Sponsor.

At the end of the study any unused study drug will be returned to the Sponsor for destruction or may be destroyed locally; disposition of study drug will be documented.

The Sponsor will be permitted access to the trial supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation. Records may be electronic or paper and may be accessed remotely for monitoring/drug accountability purposes.

Each subject will be provided with one bottle with five brequinar or five placebo capsules for the five days of dosing.

8.8 Prohibited Medications

Treatment is prohibited with another DHODH inhibitor (e.g., leflunomide and teriflunomide). Treatment is prohibited with agents known to cause bone marrow suppression leading to thrombocytopenia.

8.9 Study Adjustments Due to COVID-19

Due to the highly contagious nature of COVID-19, multiple adjustments and revised procedures are rapidly evolving regarding clinical trial management and study conduct. Reasonable procedures implemented by study staff to avoid spreading this disease are acceptable to Clear Creek with written permission. Examples include but are not limited to e-consent, telephone consent and study visits conducted by telemedicine, telephone or other digital media.

Background standard of care is to be maintained in both treatment arms. The standard of care is expected to change as additional information, such as that from randomized controlled trials, emerges, and the Sponsor and the treating clinicians will need to address anticipated off-label use of any other drugs, devices, or interventions that might be used to manage COVID-19 (e.g. anticoagulants).

The Sponsor and treating clinicians are to consider changes in SOC over time, for example, overlapping toxicities of brequinar and a SOC treatment expected to be widely used is to be considered. The availability of new standard of care treatment may change over time and vary from one clinical trial site to another. The Sponsor will discuss these issues with FDA should the need arise.

9 CONDUCT OF THE TRIAL

9.1 Ethical and Regulatory Considerations

The trial will be performed in accordance with the Declaration of Helsinki (1964) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Scotland (2000, Note of Clarification 2002 & 2004) and Seoul 2008 (Appendix A), and Fortaleza (Brazil) (2013), and with the International Council on Harmonization (ICH) Tripartite Guideline on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and United States (US) FDA Regulations.

9.2 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki must be implemented in each clinical study before protocol-specified procedures are carried out. Informed consent must be obtained in accordance with US Code of Federal Regulations (21 CFR Part 50), the FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency (March 2020, Updated April 16, 2020) [20], as well as local and national regulations. Information should be given in both oral and written form whenever possible and deemed appropriate by the Institutional Review Board (IRB). Subjects and their relatives, if necessary, must be given ample opportunity to inquire about details of the study.

The Investigator or qualified designated person will verbally inform subjects as to the nature, expected duration and purpose of the trial, the administration of the Investigational Product (IP), and the hazards involved, as well as the potential benefits that may come from treatment with this IP. The trial procedures will be explained in lay language and any questions will be answered. The subjects will be given an IRB-approved consent form. The subjects will be given appropriate time to consider their participation in the trial and have any questions answered prior to signing the consent form. If a subject agrees to participate, he/she will sign and date an informed consent form and be provided with a copy of the signed consent. All subjects who sign an informed consent form are to be recorded on the applicable screening log. If the subject is unable to consent for any reason, a designated family member or healthcare power of attorney or other person may consent per institutional policy.

The subject will be informed that his/her medical records will be subject to review by the Sponsor, Sponsor's representatives, and possibly by a representative of the FDA and other relevant regulatory authorities. Subjects will be informed that they are free to refuse participation in this clinical investigation, and if they should participate, it will be made clear to them that they may withdraw from the trial at any time without prejudicing further medical care they may require. The subject will receive a copy of the consent form as well as an information sheet about the trial.

Informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to completing the informed consent process but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. Documentation of consent will be subject to review by the Sponsor; if in writing, a copy will be given to the subject and a copy will be filed with the subject's medical notes. Verbal consents will be documented by the study team as appropriate and agreed by the IRB.

Note that informed consent procedures have been affected by COVID-19, and the study staff may use any consent method that has been approved by the IRB (e.g., phone consent, verbal consent with

witness, e-consent, etc.) of the local institution. In-person consent, written consent signatures and providing hard copies to the subject are examples of procedures that may be foregone under these circumstances.

The study should be discussed with the potential participant only after an initial review of his/her clinical status and appropriateness for participation have been evaluated to determine if he/she meets the subject selection criteria.

A sample subject information sheet and consent form are available from Clear Creek. The final version at each institution may differ depending on institutional requirements and standard formats. This protocol will not be amended for site specific changes as such changes are to be made to the site's consent when required.

9.3 Institutional Review Board

It is the responsibility of the Investigator to submit the protocol, consent form and information sheet to the IRB. An IB will be available for review by the IRB. The protocol and informed consent form (ICF) must be approved by the IRB prior to the recruitment of the first subject. The template consent form may be revised in accordance with site-specific requirements with Sponsor review and approval. A copy of the IRB written approval must be provided to the Sponsor and investigator before the trial may start at that institution. Written approval from the IRB is also required for substantial protocol amendments prior to their implementation.

A substantial amendment may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments are "substantial" when they are likely to have an impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any IP used in the trial.

If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects, the Investigator will notify the Sponsor and the IRB of the new events and the measures taken as soon as possible.

The Investigator will report promptly to the Sponsor and IRB any new information that may adversely affect the safety of the subjects or the conduct of the trial. On completion of the trial, the Investigator will inform the applicable IRB as per local IRB requirements that the trial has ended. If the study is terminated for any reason, the investigator will return all clinical supplies and study-related equipment supplied by the Sponsor to the Sponsor unless otherwise specified.

9.4 Schedule of Events

Study activities will be conducted or supervised by experienced personnel throughout the study based on the Schedule of Events. The subjects may collect the saliva sample for viral load testing and perform other study activities such as body temperature, heart rate, respiratory rate, SpO2, and symptom

assessments themselves with appropriate training. Equipment will be provided to the subject for study purposes including a pulse oximeter with heart rate monitoring capability and a thermometer. Telemedicine visits such as phone calls or other remote media are to be utilized as much as possible. Subjects may need to come to an out-patient facility or be visited by a home health professional for some study assessments.

See 15.1 Schedule of Events in Appendix A for the full list of study assessments and timings.

Blood chemistry tests include blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALK), alanine amino transferase (ALT), aspartate amino transferase (AST), total bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium), lactate dehydrogenase (LDH).

Hematology tests include hemoglobin, hematocrit, complete blood count with full differential, and platelet count.

Viral load sampling is to be carried out on Days 1, 4, 8, 12, 15, 22, and 29. The subject is to self-collect saliva samples with appropriate training for this analysis. Samples may be banked for future analyses. If the subject cannot provide documentation of the previous positive COVID-19 test, the site may perform an additional RT-PCR test as part of the Screening visit. The subject must have a documented positive result to be eligible for the study.

Safety laboratory results (chemistry and hematology) are to be reviewed by investigator or designated site personnel within 48 hours of receipt of results.

Hospitalization status after enrollment is to be recorded as not hospitalized or admitted to hospital as an in-patient with admission > 24 hours.

As much of the study as possible will be conducted via telemedicine remote from the site (e.g., consent, medical history, concomitant medications may be collected remotely). Subjects will be visited at home (or place of residence) by a home health nurse at Screening and on study Days 1, 8, 15, and 29. On study Days 4, 12, and 22 the vital signs and saliva collections will be observed via telemedicine by the study site staff. Site staff will have a telephone call with subjects on study days 2, 3, 5, 6, and 7 to assess changes in concomitant medications and to assess adverse events, especially those that may indicate thrombocytopenia, e.g., unusual bruising, epistaxis, gingival bleeding, etc., and mucositis. Subjects will be provided with a pulse oximeter and thermometer during the Screening in-home visit, as well as being trained on the use of these devices during that visit. Training will also be provided by the home health nurse for the saliva collection required for viral load testing. Assessments will be recorded by the home nurse during home visits and by the site staff during telemedicine visits. These data will be entered in the eCRF by the site staff or as determined by the study team.

9.5 Study Conduct

The study visits are to be conducted as shown in the Schedule of Events, Appendix 15.1.

Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF.

9.5.1 Unscheduled Visits

Unscheduled visits and tests are permitted as needed to assess AEs/SAEs throughout the study. Unscheduled visits and tests are also permitted as needed to assess AEs/ SAEs with onset within two (2) weeks after the final study visit providing the AE is considered related to study drug

9.6 Compliance with Study Procedures

The time at which study procedures are conducted should follow the protocol timelines as closely as possible. However, it is recognized in a clinical setting that protocol-specified timings may not occur exactly as specified in the protocol, particularly when conducted remotely by the subject. Provided that activities are carried out within the identified windows it will not be necessary to file a protocol deviation. Remote visits such as a telemedicine visit may be conducted to collect as much information as possible remotely. A home visit or return to the clinical site or an out-patient laboratory may be arranged for safety labs or other assessments, when required. Telemedicine or other remote technique is to be utilized to ensure subject compliance when subject is performing self-collection of study assessments.

9.7 Early Withdrawal from the Study

A subject may withdraw from the study at any time for any reason or for one of the reasons listed below. The Sponsor or Investigator may also terminate a subject's study participation after discussion with the other party if it is believed it would be unsafe for the subject to continue in the study.

Subjects must discontinue study medication if any of the following events occur:

- Significant protocol violation or non-compliance, either on the part of the subject or the investigator or other site personnel;
- Decision of the Investigator or Sponsor that removal is in the subject's best interest;
- Severe unrelated medical illness or complication;
- Safety reasons/ significant adverse event;
- Subject request (withdrawal of consent);
- Sponsor decision.

Collect/conduct all scheduled evaluations even for subjects who discontinue study medication prior to completing the treatment period unless consent is withdrawn.

9.8 Early Termination of the Study

If the Sponsor or an Investigator believes it would be unsafe to continue the study, or for any reason at the Sponsor's request, the study may be terminated at that site or the entire study terminated after discussion with the other parties.

The Sponsor will provide a written statement to the IRB and the relevant regulatory authority with the reasons for termination of the study. This will be conducted within 15 days of the decision to terminate the study.

If the study is terminated, a close out monitoring visit will be performed and applicable procedures will be carried out to close the trial site(s).

9.9 Non-Childbearing Potential

Women of non-childbearing potential are defined as those who have no uterus, ligation of the fallopian tubes, or permanent cessation of ovarian function due to ovarian failure or surgical removal of the ovaries. Documentation of surgical procedure or physical examination is required for subjects who have had a hysterectomy or tubal ligation. A woman is also presumed to be infertile due to natural causes if she has been amenorrheic for greater than 12 months and has an FSH greater than 40 IU/L. In the absence of such documentation, a negative serum pregnancy test is required for inclusion into the study.

10 ADVERSE EVENT REPORTING

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

Events that occur prior to first dose will be entered as medical history; events that occur after first dose will be entered as adverse events (AEs) on the AE form.

Subjects will be questioned and observed for evidence of AEs, whether or not judged by the Investigator or designated person to be related to study drug. All AEs will be documented in the subject's medical record and CRF. For any pre-existing condition or abnormal laboratory finding that changes in severity after dosing, this change should be recorded as an AE. New abnormal laboratory findings that are clinically significant are considered AEs. Investigators and site staff are to elicit from the subject and note any signs or symptoms of mucositis and thrombocytopenia (see Section 10.8).

Adverse events will be collected from the time of first dose through Day 29. After Day 29, collect/record only Serious Adverse Events (SAEs) which are assessed by the Investigator or designated person to be related to study drug. AE details are to be documented including start and stop date and times, whether continuous or intermittent, severity, any intervention utilized to correct the event (e.g., medication, surgery, or other therapy), outcome and the relationship to the study drug.

AEs identified in the protocol as critical to the evaluation of safety must be reported to the Sponsor by the Investigator according to the reporting requirements within the time periods specified in the protocol.

AEs determined by the Investigator to be related to study drug must be followed until resolution or until they are considered stable or for at least 30 days after discontinuation of study drug.

Abnormal laboratory values or test results occurring after study enrollment constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, are Grades 3 or 4, or require therapy.

If a death occurs during the SAE reporting period, the cause of death such as pneumonia, ARDS, or respiratory failure, is considered as the AE and the death is considered its outcome. Death should be considered an outcome, not an event. The event or condition leading to death should be recorded and reported as a single medical concept on the AE eCRF. Generally, only one such event should be reported. “Fatal” will be recorded as the outcome of this respective event; death due to an outcome of an AE will not be recorded as separate event. If the primary cause of death is disease progression, the cause of death should be clearly identified as COVID-19.

In cases of surgical or diagnostic procedures, the condition leading to the procedure is considered as the AE instead of the procedure itself. Each AE will be coded by the Sponsor from the verbatim text to a preferred term using a thesaurus based on the Medical Dictionary for Regulatory Activities (MedDRA). For example, record appendicitis, not appendectomy.

The following guidelines will be followed for the recording and reporting of adverse and serious adverse events.

1. The medical history section of the case report form will serve as the source document for baseline events.

    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed.

        i. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.

2. Adverse events occurring after first dose are to be recorded in the eCRF using the AE form.

3. Serious adverse events will be reported to the local IRB according to institutional policy.

The *NIH Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf) will be used for adverse event reporting.

10.1 Follow Up of Grade 3 or 4 Toxicities

Grade 3 or 4 toxicities are to be followed by re-evaluation every 2 days, as feasible, until the toxicity returns to Grade ≤ 2 severity.

10.2 Infection Follow Up

Any new infection that occurs on study regardless of infecting agent (i.e., viral or non-viral) should be captured. Additionally, the site of infection and source of culture (BAL, tracheal aspirate, sputum, blood, urine, etc.) should also be recorded.

10.3 Classification of Causality

Attribution is the relationship between an adverse event or serious adverse event

and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment

Guidance for assessing causality:

The Investigator will need to determine whether an AE is considered related to ("caused by"') the study drug rather than some underlying condition, for example, COVID-19.

For the purposes of this study, 'drug related' shall mean 'Definite', 'Probable' and 'Possible' relationship to drug as determined by the Investigator.

10.4 Classification of Severity

The NIH Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017) will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria.

AEs that are expected are subject to expedited reporting only if the adverse event varies in nature, intensity or frequency from the expected toxicity information that is provided in the Investigator Brochure.

10.5 Serious Adverse Event (SAE) Reporting

The regulatory definition of an SAE is any untoward medical occurrence or effect that at any dose fulfills one or more of these criteria:

- results in death;
- is life threatening (at the time of the event);
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability / incapacity
- is a congenital anomaly / birth defect;
- or is an event considered medically serious by the Investigator.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

A life-threatening adverse event is one that places the patient/subject, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.

An unexpected adverse event is any adverse drug event, the nature or severity of which is not consistent with the applicable product information (e.g. IB for an unauthorized investigational product or summary of product characteristics for an authorized product).

Enter only one event as the reason for the SAE on the SAE form. Other non-serious events which did not directly result in the SAE should be detailed in the description section on the SAE form and listed separately as AEs if necessary. For fatal SAEs, report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term.

Note that hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of COVID-19 infection, not associated with any deterioration in condition;
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent;
- Social reasons and respite care in the absence of any deterioration in the subject's general condition;
- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above.

ANY SERIOUS ADVERSE EVENT MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) BY EMAIL TO THE SAE REPORTING EMAIL USING THE FORM PROVIDED. ENTER THE SUBJECT'S AVAILABLE INFORMATION INTO THE eCRF WITHIN 48 HOURS.

The subjects are to be identified in the immediate and follow-up reports by unique code numbers supplied by the sponsor. The email address for reporting SAEs can be found below and at the front of this protocol.

Reports relating to the subject's subsequent medical course following an SAE must be submitted to Covance Patient Safety until the event has subsided or, in case of permanent impairment, it stabilizes, and the overall clinical outcome has been ascertained.

SAE REPORTING EMAIL: SAEIntake@covance.com

Medical Monitor:

Norberto Soto, MD	Telephone:	(609) 212-7892
Covance Physician/Medical Monitor	Email:	Norberto.Soto@Covance.com

Sponsor Representative:

Barbara Powers, MSN, Ph.D.	Telephone:	M: (484) 686-0545
VP, Clinical Operations	Email:	bpowers@clearcreekbio.com

All SAEs will be reported to the IRB periodically, at the end of the study, or per local institutional guidelines.

10.6 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected, unexpected, serious adverse reactions (SUSARs) are SAEs that are both related to the study drug (Relationship = Related) and unexpected (not previously described in the investigator's brochure). All SUSARs will be reported in an expedited manner to the Sponsor or designee and IRB by the Investigators and to all relevant regulatory authorities by the Sponsor. Expectedness will be judged by the Covance Physician and site Investigator. It is critical that all SAEs are reported within the 24-hour guideline so that the expectedness determination can be made. SUSARs require immediate attention and expedited reporting to relevant regulatory authorities.

The Sponsor will ensure that all relevant information about **fatal or life-threatening** SUSARs are appropriately recorded and reported to the concerned Regulatory Authority and to the concerned

IRB(s) within seven (7) calendar days of the date of first report to Covance Patient Safety / Sponsor. Follow-up information will be communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs will be reported to the Regulatory Authority and to the IRB(s) concerned as soon as possible within a maximum of fifteen calendar days of first notification to Covance Patient Safety / Sponsor.

The Sponsor or designee will also inform all Investigators studying the investigational medicinal product about SUSARs and ensure that all IRBs have been notified.

For reported deaths of a subject, the Investigator shall supply the Sponsor and the IRB(s) with requested additional information on an expedited basis.

10.7 Pregnancies

Pregnancy occurring in a female subject or a subject's partner during the study period will be documented in the subject's source documents and reported to Covance Patient Safety (by email to SAEIntake@covance.com) and to the IRB by the investigational staff within 1 working day of their knowledge of the event. The collection period for a pregnancy occurring in a subject or a subject's partner will begin at the first dose of study drug and will continue through 90 days after the last dose of study drug. Monitoring of the subject or partner should continue until the conclusion of the pregnancy, if the subject or subject's partner has consented to this. Monitoring of the baby should continue for 3 months after birth, if the subject or subject's partner has consented to this.

Pregnancy itself is not an AE; it should be reported for tracking purposes. The Investigator or designee will discontinue the pregnant subject from the treatment aspects of the study, continue to follow her per protocol for safety outcomes only, and advise her to seek prenatal care and counseling from her primary care provider. Data on fetal outcome and breast-feeding will be collected for regulatory reporting and drug safety evaluation, if the subject has consented to this.

If the pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as (S)AEs.

The site clinical staff will request the pregnant subject to notify the site of the outcome of the pregnancy (i.e., birth, loss, or termination). To help ensure this, the site clinical staff will follow the subject until the end of pregnancy, with the subject's consent. This request and the subject's response will be documented in the subject's source document.

10.8 Safety Monitoring for Hematologic Toxicities

Myelosuppression is a known effect of DHODH inhibition that is associated with prolonged exposure and high doses. To reduce the risk of this effect with brequinar in COVID-19 subjects, the extensive brequinar safety database with over 1,000 patients has been evaluated to select a dose level expected to be safe and well tolerated with regard to hematologic toxicity. In addition to enhancing safety by

selecting a relatively brief 5-day exposure and a low brequinar dose, all subjects in the clinical trial will be under the care of highly qualified medical personnel. Clinically significant out-of-range laboratory results will be reported as adverse events.

In addition to real time assessments by the treating clinical team, the Covance Medical Monitor will assess the available hematology data on a periodic basis to identify any pathologic trends or safety issues. Any apparent increase in the expected rate or severity of hematologic safety events will be discussed with the Principal Investigators and the Sponsor. In addition, the Data Monitoring Committee (DMC) will assess available hematology data on a periodic basis to independently assess any pathologic trends or safety issues. If the rate or severity of hematologic toxicities appears to be above the expected rate or the severity appears worse than that expected, the trial enrollment will be suspended and no further subjects will be treated while a comprehensive data review is conducted. Depending on the outcome of the safety review the study may be stopped, the design adjusted, or the study may continue as designed. Individual and Study stopping rules are provided in Section 8.4.

Safety laboratory results are to be initially assessed in real time by the Principal Investigator or designated person. Any study drug-related clinically significant out-of-range laboratories or study drug-related adverse events will be followed as needed until resolution or stable.

The in-clinic assessments and telemedicine/phone call visits will specifically ask about possible hematologic toxicity including any evidence of the list below. Subjects will be provided with a list of the following events in lay terms and will be instructed to call the research team if any of these events occur.

- Ecchymosis/purpura/petechiae
- Epistaxis
- Hemoptysis
- Hematuria
- Gingival bleeding
- Prolonged bleeding time from needle sticks, abrasions or lacerations
- Hematemesis
- Rectal bleeding
- Blood in stool
- Any other unusual bleeding noted by the subject or caregiver

Any of these symptoms considered clinically significant will be recorded as an adverse event and must be followed until resolved or stable.

10.9 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established to provide independent oversight to this trial. The primary responsibility of the DMC will be to review the progress and conduct of the trial in order to maintain scientific rigor and to ensure the wellbeing of subjects participating in the trial. The specific responsibilities of the DMC will be detailed in a separate DMC charter. The DMC will include at a minimum at least one statistician and two clinicians who will perform periodic data review to assess whether there are clinically significant differences between treatment arms that could affect participant safety. All adverse events will be reviewed by the DMC during their reviews. Following

such a review, the DMC Chair will advise the Sponsor that the study be stopped, the design changed, or that the study may continue per protocol.

10.9.1 DMC Safety Review Schedule

The DMC is to review adverse events and safety laboratory assessments after the first 20 subjects complete the Day 8 visit, and again after the first 40 subjects complete the Day 8 visit.

11 STATISTICAL CONSIDERATIONS

A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. All analyses will be descriptive in nature and presented by group.

Summaries for quantitative variables will include the mean, median, quartiles, standard error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and 95% confidence interval (CI), when appropriate. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.4 or higher).

Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. The following sections will briefly summarize of the planned statistical analyses and analysis sets for the primary and secondary endpoints.

11.1 Study Populations for Analysis

All safety analyses will be based on the ITT population, which is defined as all randomized subjects. As will be described in the SAP, efficacy analyses of changes in viral load will be based on the population of subjects with detectable viral load at baseline or similar qualification. Sample size may be adjusted if an inadequate number of subjects have detectable viral load at baseline.

11.2 Safety Analyses

Safety and tolerability will be assessed in terms of AEs, SAEs, WHO Assessments, and safety laboratory data.

Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of post-first dose (treatment-emergent) adverse events will be tabulated by MedDRA preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results and study assessments will be summarized using appropriate descriptive statistics.

11.3 Efficacy Analyses

Efficacy will primarily be assessed via viral load changes.

11.4 Sample Size Considerations

Formal sample size calculations are not applicable for this proof-of-concept study. The sample size of approximately 100 subjects planned to be entered in this trial is expected to be adequate to provide safety and efficacy information to advise future study design.

11.5 Randomization

A randomization scheme will be provided by an independent statistician to the drug packaging company to ensure subjects are randomly assigned to SOC + brequinar or SOC + placebo in a 1:1 ratio.

11.6 Pooling of Study Centers

Not applicable to this small, early phase study.

11.7 Interim Analysis

No interim analysis is planned for this trial.

12 INVESTIGATOR RESPONSIBILITIES

12.1 Investigator's Performance

The Investigator will ensure that all those concerned with conducting the trial are:

- provided with copies of the protocol and all safety information prior to the start of the trial;
- trained regarding the conduct of the study and the training has been documented.

The Investigator will sign the Investigator's Statement and Agreement found in Section 15.2 to indicate commitment to comply with the contents.

12.2 Confidentiality

The Investigator shall assure the subject that his/her identity will be protected and confidentiality will be maintained during all audits and inspections of the trial site and documentation. A unique number will be assigned to each subject at the start of the trial and this, with the subject's initials, will be used to identify the subject. In some cases, a further step may be taken to assign "fake initials" to the subject, per individual site requirements. The subject's number will be the site number followed by the number of this subject at this site and will be used as the unique identifier in the source records and on the eCRF, on all trial correspondence and in the trial database. The Investigator will keep a list of identification codes or initials used for each subject along with the unique number assigned.

All information provided to the Investigator relevant to the investigational product (IP), as well as information obtained during the course of the trial will be regarded as confidential. The Investigator and members of his/her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the Sponsor which will not be unreasonably withheld, except as required by law, or as permitted by the Publications section of this protocol, Section 12.7.

The Investigator will take all measures to ensure subject's confidentiality will be maintained at all times.

12.3 Source Documentation

Investigators are to maintain adequate source documentation of the original study data, for example medication records, laboratory reports and pharmacy records as appropriate. The Investigator will allow inspections of the trial site and documentation by clinical research and audit personnel from the Sponsor, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the eCRFs. In order to do this, direct access to the subjects' medical or clinic records is necessary. The Investigator will ensure that certain information is contained in the medical or clinic written or electronic records of the subject and that the entries are signed and dated, as follows:

- sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories;
- a note on the day the subject entered the trial describing the trial number, the IP being evaluated, the trial number assigned to that subject and a statement that consent was obtained;

- a note of each subsequent trial visit including any concerns about AEs and their resolution;
- notes of all concomitant medication taken by the subject, including start and stop dates;
- a note of when the subject terminated from the trial, the reason for termination and the subject's general condition at termination;
- a copy of the signed informed consent form should be kept in the medical records of each subject during the clinical phase of the study. A signed copy should also be filed in the investigator file.

12.4 Data Collection

Suitably qualified and trained personnel at the trial site will ensure compliance with the protocol, adherence to ICH GCP obligations, proper maintenance of trial records including IP accountability records, correct administration of IP including storage conditions and accurate reporting of AEs. In addition, suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. All queries and discrepancies relating to the data collection are to be resolved at the completion of the trial. Remote data capture is encouraged whenever possible.

12.5 Case Report Forms, Investigator's Site File and Record Retention

The Sponsor may provide the CRFs in paper, electronic (eCRF), or other media. The forms will be reviewed against source documentation at each monitoring visit. All CRFs and supporting source documentation must be completed and available to the Sponsor in a timely manner. Changes or corrections due to data clarification and resolutions will be tracked by paper or electronically with an audit trail.

Prior to review of the case report forms by the Sponsor's representative, they should be reviewed for completeness and accuracy by the Investigator or a member of the research team.

The Investigator must maintain an Investigator Site File which includes, but is not limited to, the IB, the protocol plus any amendments, all correspondence with the IRB including the approval for the trial to proceed, Regulatory Authority approval/ notification (if applicable) including a sample of an approved informed consent, IP accountability, Source Documents, investigator and staff curricula vitae (CVs,) trial documentation, and all trial correspondence. The original signed informed consent forms and the final report will be kept in the Investigator Site File.

The Investigator will archive all essential documents. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The Investigator has a responsibility to retain essential documents for as long as is required by the Sponsor and applicable regulatory authorities. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained. Investigators will be asked to contact the Sponsor prior to the destruction of any data or removal to another site if this occurs prior to the Sponsor notification that the documentation is no longer required. Any transfer of ownership of the data or of documents will be documented in writing. The new owner will assume responsibility for data retention and archiving.

Should the Investigator retire, relocate, or for other reasons withdraw from the responsibility of keeping the trial essential documents, custody must be transferred to a person who will accept that responsibility, and the Sponsor must be notified in writing of the name and address of said person.

12.6 Non-Protocol Research

No investigational procedures other than those outlined in this protocol may be undertaken on the subjects in this trial without the prior written permission of the subject, the Sponsor, the IRB and, when appropriate, the regulatory authority.

12.7 Publication

The Sponsor acknowledges the benefit of making widely available the results of all clinical trials and intends to publish the results of this trial. All publications resulting from the clinical trial must be in a form that does not reveal technical information that the Sponsor considers confidential or proprietary. A copy of any abstract, presentation or manuscript proposed for publication must be submitted to the Sponsor for review at least 30 days before its submission for any meeting or journal. In addition, if deemed necessary by the Sponsor for protection of proprietary information prior to patent filing, the Investigator agrees to a further delay of 60 days before any presentation or publication is submitted. The Sponsor reserves the right to include the report of this trial in any regulatory documentation or submission or in any informational materials prepared for the medical profession.

Authorship determination will be at the discretion of the Sponsor and will include evaluation of the following criteria: Investigator must participate in the review of and content of the protocol; review and comment on the study results; participate in the writing, reviewing and commenting of the manuscript; and approve the final manuscript for submission.

13 SPONSOR RESPONSIBILITIES

13.1 General

The Sponsor agrees to adhere to the ICH Note for Guidance on GCP (CPMP/ICH/135/95, Jan.97) and US FDA Regulations. It is the Sponsor's responsibility to obtain appropriate regulatory approval to perform the trial (if applicable). The Sponsor should notify promptly all concerned investigator(s), IRB(s) and the Regulatory Authority of findings that could adversely affect the health of the patients/ subjects, impact on the conduct of the trial or alter the Regulatory Authority's authorization to continue the trial. If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects the Sponsor will notify the relevant regulatory authority and relevant IRB of the new events, the measures taken and the plan for further action as soon as possible. This will be by telephone in the first instance followed by a written report.

On completion of the trial, the Sponsor will inform the regulatory authority that the trial has ended. If the study is terminated for any reason the Sponsor will provide a written statement to the relevant regulatory authority and the IRB with the reasons for termination of the trial. This will be conducted within 15 days of the decision to terminate the trial. The Sponsor will report in an expeditious manner all SUSARs to the relevant regulatory authority and IRBs.

13.2 Indemnity

The Sponsor will provide compensation insurance against any risk incurred by a subject as a result of participation in this trial. The Sponsor will indemnify the Investigators as detailed in a separate document.

13.3 Data Monitoring

Suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site or will access the electronic health record (EHR) or conduct remote monitoring visits at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. CRFs and source documentation will be available for review during monitoring visits to the trial site. The function of this monitoring is to ensure compliance with the protocol, adherence to regulatory and GCP obligations, proper maintenance of records including IP accountability records, correct administration of IP including storage conditions and accurate reporting of AEs. On-site visits are not required for any monitoring visits for this study.

Once the data from the case report forms have been entered onto the database, they will be reviewed, and the data verified against the subject's source data. Any discrepancies will be tracked by paper or electronically with an electronic audit trail.

13.4 Audit

The Sponsor has an obligation to audit a proportion of studies. A department other than the clinical department will undertake this obligation. Therefore, the Sponsor, an independent auditor or a regulatory authority may audit the trial site and trial documentation. These audits may take place while the trial is being conducted or up to several years later.

13.5 Confidentiality

The Sponsor will not keep any material on file bearing any subject's name, and subjects' confidentiality will be maintained at all times.

13.6 Finance

This will be the subject of a separate agreement between the Investigator/Institution and Sponsor.

14 REFERENCES

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15 APPENDICES

15.1 Appendix A: CCB-CRISIS-02 Schedule of Events

CCB-CRISIS-02 Schedule of Events **Windows are relative to first dose time** **Procedures**	**Screen (days -14 to -1) HH+TM[f]**	**D1 HH+ TM**	**D2, 3 (± 8 hrs) TC[f]**	**D4 (± 8 hrs) TM**	**D5,6, 7 (± 8 hrs) TC**	**D8 (± 1 day) HH+ TM**	**D12 (± 1 day) TM**	**D15 (± 1 day) HH+ TM**	**D22 (±1 day) TM**	**Final Visit D29 (± 2 days) HH+TM**
Informed Consent (note Date and Time)	X									
AE/Concomitant Medications (dose, route, duration or ongoing)	X	X	X	X	X	X	X	X	X	X
Medical history (relevant within one year or ongoing)/ History of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection)	X									
Demographics (subject reported height and weight, date of birth, gender, race, ethnicity)	X									
Check for Physical Exam abnormalities (subject self-reported)	X									
Pregnancy Test (WOCBP)	X (serum)									X (urine)
Hematology/Chemistry[a]	X	X				X		X		
Vital Signs[b]	X	X		X		X	X	X	X	X
Symptom Assessment[c]	X	X		X		X	X	X	X	X
SARS-CoV-2 RT-PCR/Viral load sample[d]	X	X		X		X	X	X	X	X
Hospital Status						X		X	X	X
WHO Ordinal Scale Assessment		X				X		X	X	X
Confirm Eligibility		X								
Randomize subject and dispense Study Medication		X								
Study drug administration[e]		X	X	X	X D5 Only					
Drug Accountability						X				

[a]Do not repeat if within 48h of Day 1 visit. Send to Covance Central Laboratory Services (CCLS) for analysis.
[b]Vital signs include heart rate, respiratory rate, body temperature, and SpO2. Subject will be provided with a thermometer and pulse oximeter with heart rate monitoring capability. Training will be provided during the first visit by the home health nurse. Vital signs parameters will be observed and recorded by study staff via telemedicine or during a visit by the home health nurse.
[c]Symptom Assessment will use a checklist provided to the subject with symptoms such as sore throat, cough, GI symptoms (vomiting, diarrhea), anosmia, dysgeusia, other (specify), etc. Severity None, Mild, Moderate, or Severe will be collected.
[d] RT-PCR at Screening may be performed by the site if the subject cannot provide documentation of a positive SARS-CoV-2 result. Samples collected after Screening will be saliva samples sent for viral load analysis. Day 1 sample must be obtained prior to dosing. Viral load specimens after Screening will be saliva samples self-collected by the subject using an Omnigene® collection system or similar. The home health nurse will train the subject and observe sample collection on Day 1. These samples are to be sent to CCLS for analysis. The viral load sample may also be used to perform viral cultures (sample can be split by the central laboratory, no additional sample required).
[e]Subject will self-administer study drug once daily Days 1 – 5 and record doses in a medication diary. Note that any visits/visit activities may be conducted via telephone, telemedicine, or digital media other than serum pregnancy test and chemistry/hematology sample collection. These labs may be collected at the clinical site or another designated out-patient facility/laboratory or collected via home visit. Arrangements for shipping viral load samples will be made by the study team.
[f]HH = Home Health in-person visit; TC = Telephone Call with site and subject; TM = Telemedicine with site and subject.

15.2 Appendix B: Investigator's Statement and Agreement

STUDY NUMBER: CCB-CRISIS-02

The CRISIS2 Study: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2.

INVESTIGATOR'S STATEMENT AND AGREEMENT

I (*the Investigator*) have read this protocol and hereby agree to conduct the trial in accord with all of its provisions. It is further agreed that the details of this trial and all information provided to me by Clear Creek Bio, Inc. (*the Sponsor*) will be held in the strictest confidence and will not be revealed for any reason without written authorization from Clear Creek Bio, Inc. except to those who are to participate in the conduct of the trial.

I agree that all data, the case report forms, and all materials provided for the conduct of the trial are the property of Clear Creek Bio, Inc. unless specified otherwise in writing. It is understood that Clear Creek Bio, Inc. will utilize the information derived from this trial in various ways, such as for submission to government regulatory agencies, required internal reports, and presentations without violating patient/ subject confidentiality in any way.

I further agree that Clear Creek Bio, Inc. or its representatives will be permitted access, in accordance with current Good Clinical Practice Guidelines, to all data generated by this trial and the source documents from which case report form data were generated.

PRINCIPAL INVESTIGATOR

Printed Name: _____

Signature: _____ **Date:** _____

15.3 Appendix C: WHO Ordinal Scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized: moderate disease	Hospitalized; no oxygen therapy*	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: severe disease	Hospitalized; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$	7
	Mechanical ventilation $pO_2/FiO_2 < 150$ ($SpO_2/FiO_2 < 200$) or vasopressors	8
	Mechanical ventilation $pO_2/FiO_2 < 150$ and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

WHO clinical progression scale

STUDY PROTOCOL

The CRISIS2 Study: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2

Study No: CCB-CRISIS-02

Version: 4.0

Version Date: 01 October 2020

Sponsor:

Clear Creek Bio, Inc.
585 Massachusetts Avenue, 4th Floor,
Cambridge MA 02139

Sponsor Telephone: (617) 765-2252

Sponsor Facsimile: (617) 863-2082

IND Number: 149291

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine amino transferase
AML	Acute myeloid leukemia
ARDS	Acute respiratory disease syndrome
AST	Aspartate amino transferase
BRQ	Brequinar
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus-19 infection
CRP	c-reactive protein
CTCAE	Common terminology criteria for adverse events
CTEP	Cancer Therapy Evaluation Program
CV	Curricula vitae
DHO	Dihydroorotate
DHODH	Dihydroorotate dehydrogenase
DHODHi	Dihydroorotate dehydrogenase inhibitor
DMC	Data Safety Monitoring Board
ECMO	Extra corporeal membrane oxygenation
EHR	Electronic health record
ESR	Erythrocyte Sedimentation Rate
EUA	Emergency Use Authorization
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council on Harmonization
ICU	Intensive care unit
IMP	Inosine-5’ phosphate
IP	Investigational product
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NEWS2	National Early Warning System (NEWS) 2 Score
RNA	Ribonucleic Acid
RdRp	RNA-dependent RNA polymerase
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	SARS Coronavirus 2
SOC	Standard of Care
SUSAR	Suspected unexpected serious adverse reaction
SpO_2	Peripheral capillary oxygen saturation

Abbreviation	Definition
UMP	Uridine 5'-monophosphatase
US	United States
XMP	Xanthosine-5' phosphate
WHO	World Health Organization
WOCBP	Women of childbearing potential

2 SYNOPSIS

CCB-CRISIS-02 SYNOPSIS	
IND	149291
Title	The CRISIS2 Study: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2
Protocol Number	CCB-CRISIS-02
Rationale	Brequinar is a potent DHODH inhibitor that has been previously studied in more than 1,000 cancer, psoriasis, and organ transplant patients. Brequinar has been found to have potent *in vitro* antiviral activity against many RNA viruses including SARS-CoV-2. The antiviral activity of brequinar against SARS-CoV-2 is likely due to DHODH inhibition and shows nanomolar potency and a high selectivity index in inhibiting viral replication in *in vitro* studies. The CRISIS2 trial will study out-patients (non-hospitalized patients) who have a positive SARS-CoV-2 test and are symptomatic. Subjects will be randomized to receive standard of care (SOC) + 5 days of brequinar or SOC + 5 days of placebo. The purpose of this study is to determine if the *in vitro* antiviral activity of brequinar can be duplicated in patients infected with SARS-CoV-2 by measuring the effect of brequinar on viral shedding. Importantly, the safety and tolerability of brequinar will also be determined in these patients. The results of this proof-of-concept study will inform future studies that will help determine if brequinar is a safe and effective drug for the treatment of SARS-CoV-2 infection.
Investigational Product and Dosage	Subjects will be randomized in a 1:1 ratio to either standard of care (SOC) + 5 days of brequinar 100 mg or SOC + 5 days of placebo. Investigational product will be supplied as either brequinar 100 mg oral capsules or placebo capsules. The subjects are to self-administer one capsule on Study Days 1 – 5. Treatment assignment will be randomized, double-blind.
Primary Objectives	● To demonstrate a change from baseline in quantitative SARS-CoV-2 viral load for brequinar-treated subjects compared to placebo-treated subjects through Day 29.
Secondary Objectives	Through Day 29: ● To characterize the safety and tolerability of brequinar in out-patient COVID-19 subjects as measured by frequencies of grade 3 and 4 AEs and SAEs; ● To demonstrate a shorter duration of viral shedding in subjects treated with brequinar compared to subjects who received placebo;

	● To reduce the percentage of subjects requiring hospital admission as an in-patient for > 24 hours for brequinar subjects compared to subjects who received placebo; ● To reduce all-cause mortality through Day 29 for brequinar subjects compared to subjects who received placebo.
Exploratory Objectives	Through Day 29: ● To determine time to viral clearance (two consecutive negative tests); ● To determine time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline; ● To determine time to clinical improvement as measured by a favorable shift in the WHO Ordinal Scale score measured for the subset of subjects with baseline WHO Ordinal Scale of 2 for brequinar subjects compared to subjects who received placebo.
Design	This will be a phase 2 randomized, double blind, multi-center study with approximately 100 subjects. All subjects will receive SOC per relevant guidelines for treatment of out-patients with COVID-19 infection. In addition to SOC, subjects will self-administer one capsule once daily for 5 days. Subjects will have a Screening Visit followed as soon as possible with Study Day 1. Study procedures are presented in detail in the Schedule of Events. Study visits (virtual or in person) will take place at Screening and on Study Days 1 - 8, 12, 15, 22, and 29. The visits that include bloodwork must be conducted at the study site or arrangements made for sample collection at the subject's home or other appropriate location. Other visits/visit activities for that visit may be conducted remotely using telephone, telemedicine or other remote technique. Subjects are to self-collect a viral load sample, obtain their respiratory rate, heart rate, body temperature and SpO2, and complete a symptom assessment with the site via telemedicine on Days 1, 4, 8, 12, 15, 22, and 29. The site will also have a telephone call with the subject on Study Days 2, 3, 5, 6, and 7 for changes in concomitant medications and assessment of adverse events, especially those that may indicate thrombocytopenia and mucositis. A home health nurse will visit the subject at Screening and on study Days 1, 8, 15, and 29. Telemedicine only visits will be conducted by site staff on study Days 4, 12, and 22.
Sample Size:	Approximately 100 subjects will be randomized to 5 days of either SOC + brequinar 100 mg or SOC + placebo in a 1:1 ratio (approximately 50 subjects assigned to brequinar 100 mg and 50 subjects to placebo).
Number of Sites:	Approximately 15
Study Period:	An enrollment period of 3 months is expected.

Inclusion Criteria:	1. Willing and able to provide informed consent for the trial, written, electronic, verbal, or other method deemed acceptable by the institution and IRB. 2. 18 years of age or older. 3. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other FDA-approved commercial or public health assay within 14 days of first dose. 4. Out-patient (never hospitalized as an in-patient for COVID-19 or was evaluated/treated for COVID-19 only in the Emergency Room with a stay of < 24 hours). 5. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men and women treated or enrolled on this protocol must also agree to use adequate contraception for the duration of study participation, and for 90 days after completion of brequinar administration. 6. Male subjects must agree to refrain from sperm donation and female subjects must agree to refrain from ovum donation from initial study drug administration until 90 days after the last dose of brequinar. 7. Must have at least one COVID-19 symptom including but not limited to fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, shortness of breath, dyspnea, anosmia, dysgeusia, or other symptom commonly associated with COVID-19. 8. Able to swallow capsules.
Exclusion Criteria:	1. Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient 2. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test 3. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide) or other agents known to cause bone marrow suppression leading to thrombocytopenia 4. Platelets ≤150,000 cell/mm^3 5. Hemoglobin < 10 gm/dL 6. Absolute neutrophil count < 1500 cells/mm^3 7. Renal dysfunction, i.e., creatinine clearance < 30 mL/min

	8. AST and/or ALT > 2 x ULN, or total bilirubin > ULN. Gilbert's Syndrome is allowed. 9. Bleeding disorders or blood loss requiring transfusion in the six weeks preceding enrollment 10. Ongoing gastrointestinal ulcer, or gastrointestinal bleeding within 6 weeks of first dose. 11. Chronic hepatitis B infection, active hepatitis C infection, active liver disease and/or cirrhosis per subject report. 12. Heart failure, current uncontrolled cardiovascular disease, including unstable angina, uncontrolled arrhythmias, major adverse cardiac event within 6 months (e.g. stroke, myocardial infarction, hospitalization due to heart failure, or revascularization procedure).
Treatment	All subjects will receive standard of care (SOC) including symptomatic care. Subjects will be randomly assigned to SOC + brequinar 100 mg daily x 5 or SOC + placebo daily x 5. Study encounters will be conducted remotely whenever possible.
DMC	A Data Monitoring Committee (DMC) will meet periodically to review the safety and scientific conduct of the study. At a minimum, the DMC is to review adverse events and safety laboratory assessments after the first 20 subjects complete Day 8, and again after the first 40 subjects complete Day 8.
Procedures	Study procedures are outlined in the Schedule of Events. Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF.
Safety/ Tolerability	**Safety/Tolerability** Adverse events will be collected from the time of first dose through Day 29. After Day 29, collect/record only Serious Adverse Events (SAEs) or those judged by the Investigator or designated person to be related to study drug. Treatment-emergent adverse events will be those with an onset after the date and time of first treatment. Subjects who develop Grade 3 or 4 toxicities or SAEs are to be re-evaluated every 2 days, as feasible, until the toxicity returns to Grade ≤ 2 severity. During assessment for adverse events, investigators and site staff are to elicit from the subject any signs or symptoms of mucositis or thrombocytopenia, e.g.: • Ecchymosis/purpura/petechiae • Epistaxis • Hemoptysis • Hematuria • Gingival bleeding

	• Prolonged bleeding time from needle sticks, abrasions or lacerations • Hematemesis • Rectal bleeding • Blood in stool • Any other unusual bleeding noted by the subject or caregiver
Stopping Criteria	Individual Criteria: • Participants who develop a Grade 3 toxicity that is assessed by the investigator to be related to the study drug are to be permanently discontinued from study treatment. • Participants who develop a Grade 4 toxicity, regardless of relatedness to study drug, are to be permanently discontinued from study treatment. Study-Level Stopping Criteria: Study enrollment is to be paused if any of the below criteria are met: • If ≥ 3 subjects develop the same related Grade 4 (life-threatening) adverse event or laboratory abnormality; • If ≥ 5 subjects develop the same related Grade 3 or 4 adverse event or laboratory abnormality; • If ≥ 10 subjects develop any related Grade 3 or 4 adverse event or laboratory abnormality. All adverse events will be reviewed by the DMC during their reviews. Following assessment by the Data Monitoring Committee (DMC), the DMC will determine whether to stop the study, amend the protocol, or continue the study per protocol.
Statistical Analysis	A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. All analyses of safety and efficacy for this study will be descriptive in nature and presented by group. Subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. Summaries for quantitative variables will include the mean, median, quartiles, standard error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the 95% CI, when appropriate. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.4 or higher). Safety and tolerability will be assessed in terms of AEs, SAEs, and safety laboratory data. Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of treatment-emergent adverse events, defined as TEAEs occurring after first dose will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results and other clinical measures will be summarized using appropriate descriptive statistics.

CCB-CRISIS-02 Schedule of Events

CCB-CRISIS-02 Schedule of Events **Windows are relative to first dose time** **Procedures**	**Screen (days -14 to -1) HH+TM[f]**	**D1 HH + TM**	**D2, 3 (± 8 hrs) TC[f]**	**D4 (± 8 hrs) TM**	**D5,6, 7 (± 8 hrs) TC**	**D8 (± 1 day) HH+ TM**	**D12 (± 1 day) TM**	**D15 (± 1 day) HH+ TM**	**D22 (±1 day) TM**	**Final Visit D29 (± 2 days) HH+TM**
Informed Consent (note Date and Time)	X									
AE/Concomitant Medications (dose, route, duration or ongoing)	X	X	X	X	X	X	X	X	X	X
Medical history (relevant within one year or ongoing)/ History of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection)	X									
Demographics (subject reported height and weight, date of birth, gender, race, ethnicity)	X									
Check for Physical Exam abnormalities (subject self-reported)	X									
Pregnancy Test (WOCBP)	X (serum)									X (urine)
Hematology/Chemistry[a]	X	X				X		X		
Vital Signs[b]	X	X		X		X	X	X	X	X
Symptom Assessment[c]	X	X		X		X	X	X	X	X
SARS-CoV-2 RT-PCR/Viral load sample[d]	X	X		X		X	X	X	X	X
Hospital Status						X		X	X	X
WHO Ordinal Scale Assessment		X				X		X	X	X
Confirm Eligibility		X								
Randomize subject and dispense Study Medication		X								
Study drug administration[e]		X	X	X	X D5 only					
Drug Accountability						X				

[a]Do not repeat if within 48h of Day 1 visit. Send to Covance Central Laboratory Services (CCLS) for analysis.

[b]Vital signs include heart rate, respiratory rate, body temperature, SpO2. Subject will be provided with a thermometer and pulse oximeter with heart rate monitoring capability. Training will be provided during the first visit by the home health nurse. Vital signs parameters will be observed and recorded by study staff via telemedicine or during a visit by the home health nurse.

[c]Symptom Assessment will use a checklist provided to the subject with symptoms such as sore throat, cough, GI symptoms (vomiting, diarrhea), anosmia, dysgeusia, other (specify), etc. Severity None, Mild, Moderate, or Severe will be collected.

[d]RT-PCR at Screening may be performed by the site if the subject cannot provide documentation of a positive SARS-CoV-2 result. Samples collected after Screening will be saliva samples sent for viral load analysis. Day 1 sample must be obtained prior to dosing. Viral load specimens after Screening will be saliva samples self-collected by the subject using an Omnigene® collection system or similar. The home health nurse will train the subject and observe sample collection on Day 1. These samples are to be sent to CCLS for analysis. The viral load sample may also be used to perform viral cultures (sample can be split by the central laboratory, no additional sample required).

[e]Subject will self-administer study drug once daily Days 1 – 5 and record doses in a medication diary. Note that any visits/visit activities may be conducted via telephone, telemedicine, or digital media other than serum pregnancy test and chemistry/hematology sample collection. These labs may be collected at the clinical site or another designated out-patient facility/laboratory or collected via home visit. Arrangements for shipping viral load samples will be made by the study team.

[f]HH = Home Health in-person visit; TC = Telephone Call with site and subject; TM = Telemedicine with site and subject.

STUDY PERSONNEL

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3 INTRODUCTION

3.1 Coronavirus-19 (COVID-19)

Beginning in December 2019, Chinese scientists isolated a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from patients with virus-infected pneumonia which was later designated as coronavirus disease 2019 (COVID-19) by the World Health Organisation (WHO) (Zhou et al., 2020 [2]; Phelan et al., 2020 [3]).

Approximately 14% of those affected with this virus will develop severe disease requiring hospitalization and oxygen support; 5% will require admission to the intensive care unit (Handel et al., 2020 [4]). Severe cases may be complicated by acute respiratory disease syndrome (ARDS), sepsis and septic shock, and multi-organ failure, including acute kidney injury and cardiac injury. Risk factors for death include older age and co-morbid disease such as hypertension and diabetes (Zhou, et al., 2020 [2]). This means that most patients will be treated as out-patients. Reducing viral load in this environment is critically important for both the subjects themselves by preventing worsening of symptoms and possibly avoiding hospitalization, but also to reduce the transmission of the disease to others in the patients' households and their communities.

3.1.1 Coronavirus Biology

Coronaviruses, like other RNA-based viruses, do not have the machinery to synthesize their own nucleotides and thus depend upon the host intracellular pool of nucleotides for viral replication. In essence, viruses steal the host RNA building blocks, and without these building blocks they are unable to replicate. The SARS-CoV-2 is a single-stranded (positive sense) RNA virus with a genome that is 29,811 nucleotides long, quite a lot larger than other RNA-based viruses (e.g. the hepatitis C genome comprises only 9600 nucleotides). The nucleotide composition is broken down as: 29.9% adenosines, 18.4% cytosines, 19.6% guanines, and 32.1% uridines (Sah et al., 2020 [12]).

3.2 Host Nucleotide Synthesis

Host *de novo* pyrimidine synthesis generates uridine monophosphate (UMP) as the building block for all pyrimidine ribonucleotides and deoxyribonucleotides (**Error! Reference source not found.**). There exists no salvage pathway for the synthesis of UMP, the fundamental building block of pyrimidines. Inhibition of enzymatic steps upstream of UMP (Figure 3-1) leads to a rapid and profound depletion of intracellular pyrimidines.

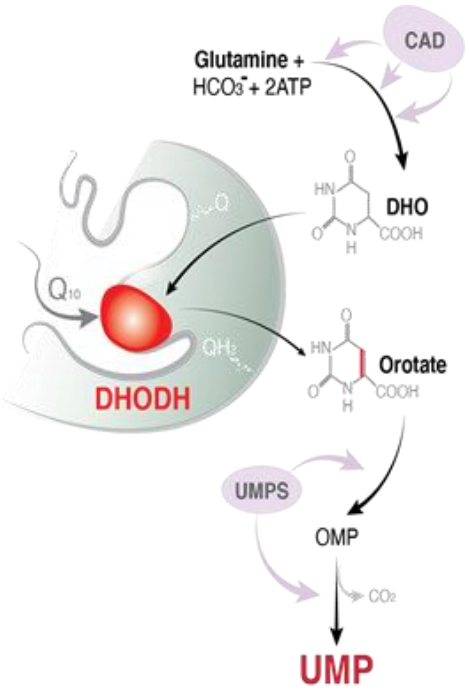

Figure 3-1. DHODH is a mitochondrial enzyme that catalyzes the 4th step of pyrimidine synthesis; it is completely essential for the generation of UMP.

3.3 Dihydroorotate dehydrogenase (DHODH)

The enzyme dihydroorotate dehydrogenase (DHODH) catalyzes the 4th step of *de novo* pyrimidine synthesis and inhibition of DHODH completely halts all pyrimidine production. As shown in Figure 3-1, DHODH is located on the inner mitochondrial membrane and transfers electrons between DHO and complex III of the electron-transport chain via the reduction of its ubiquinone (coenzyme Q10) cofactor.

DHODH is a clear therapeutic target for the inhibition of host pyrimidine synthesis. The chemical inhibition of DHODH *in vitro* or *in vivo* leads to the rapid depletion of UMP and subsequent depletion of downstream products thymine and cytosine. This forces a cell to rely on the salvage of extracellular pyrimidine nucleotides and this extracellular salvage is not capable of maintaining the cell's normal nucleotide pool (Sykes et al., 2016) [1]).

3.4 Brequinar

Brequinar is an orally available and potent inhibitor of DHODH. Brequinar is one of more than 300 quinoline-carboxylic acid derivatives prepared in an analog synthesis program in the 1980s, which was started after it was found that a compound of this class had antitumor activity. Brequinar was selected by DuPont for further development as a potential clinical drug because of its activity against experimental tumors and because its water solubility made it relatively straightforward to formulate.

In an indication such as treating SARS-CoV-2 infection, brequinar will act as a host-targeting antiviral. It is an orally available and potent inhibitor of dihydroorotate dehydrogenase (DHODH), the enzyme

that catalyzes the fourth step in pyrimidine synthesis, namely the conversion of dihydroorotate (DHO) to orotate. DHODH inhibitors, including brequinar, inhibit *de novo* pyrimidine synthesis thereby leading to a depletion of a cell's pool of uridine, cytidine and thymidine ribonucleotides and deoxyribonucleotides.

The antiviral activity of brequinar has been demonstrated in studies of rotavirus replication in human intestinal Caco-2 cells as well as in human primary intestinal organoids (Chen et al., 2019 [6]). Treatment with teriflunomide, another DHODHi, has been effective *in vitro* and *in vivo* in a murine model of foot and mouth disease virus (Mei-Jian et al., 2019 [7]). DHODH inhibition (DHODHi) also inhibited the growth of dengue virus *in vitro* (Wang et al., 2011 [8]). DHODHi also showed antiviral effects against RNA viruses including influenza A, Zika, Ebola and coronavirus SARS-CoV-2 (Xiong et al., 2020 [11]**).** Brequinar has also been shown to inhibit the replication of Ebola virus, vesicular stomatitis virus and Zika virus *in vitro* (Luthra et al., 2018 [9]). Brequinar inhibits the replication of human immunodeficiency virus (HIV) *in vitro* (Andersen et al., 2019 [10]). When considering brequinar as an antiviral for treatment of SARS-CoV-2, oral brequinar is highly bioavailable (>95%) and has good penetration of lung tissue with an average tissue:blood ratio of 0.5 following a single dose of brequinar in the rat. It is therefore expected to achieve a similar period of DHODH inhibition in lung tissue (Brequinar IB [5]).

3.5 Rationale for the Planned Trial

DHODH inhibition has been extensively studied as a potential therapeutic target in the treatment of RNA-based viruses. The inhibition of DHODH is effective in inhibiting viral replication in pre-clinical models involving many RNA-based viruses with nanomolar potency and a high selectivity index (see the Brequinar IB [5], Section 5). In these pre-clinical models, the benefit of DHODH inhibition can be reversed by the supplementation of exogenous nucleotides, confirming that the on-target effect of host pyrimidine depletion is key to the anti-viral activity.

The CCB-CRISIS-02 trial will study standard of care (SOC) with 5 days of brequinar (DHODH inhibition) compared to SOC with 5 days of placebo treatment. Clear Creek Bio hypothesizes that a defined 5-day course of brequinar will inhibit the enzyme DHODH to a degree sufficient to result in the transient depletion of host pyrimidine nucleotides, thereby inhibiting viral replication. A recent publication demonstrated that inhibitors of DHODH could potentiate the activity of inhibitors of RNA-dependent RNA polymerase (RdRp) in the treatment of dengue virus, another single-stranded RNA virus similar to SARS-CoV-2 (Liu et al., 2020 [13]). This inhibition of viral replication may restore the balance in favor of the host immune system for the clearance of SARS-CoV-2.

Marketed DHODHi medications are available, including leflunomide or teriflunomide, however these are very weak inhibitors of DHODH with cellular potency ~500 times lower than brequinar. These low potency inhibitors of DHODH are not expected to have the ability to acutely lower the pool of intracellular pyrimidines to the degree that is required for decreasing the viral load associated with SARS-CoV-2 infection, making brequinar the better choice for acute SARS-CoV-2 infection.

The CRISIS2 study is a proof-of-concept study in patients with SARS-Cov-2 infection and will serve as a basis for future studies to determine the safety and effectiveness of brequinar in COVID-19.

3.5.1 Brequinar Dose Selection

Safety data from previous oncology clinical studies of brequinar with 5 days of consecutive daily dosing suggest that 5 days of daily doses of 100 mg p.o. will be safe and well tolerated. A dose of brequinar 100 mg achieves plasma concentrations of approximately 1 uM (0.4 ug/ml) that should result in sufficient suppression of nucleotide synthesis. When given over 5 days, these plasma concentrations are achieved on a daily basis without accumulation, also assuring the safety of this regimen (see Brequinar IB [5]).

3.5.2 Risk/Benefit of Brequinar

As presented in the Brequinar IB [5], an extensive safety and pharmacokinetic database exists with more than 1,000 patients treated with brequinar. Cancer patients (N = 806) have been exposed to this compound for treatment of a variety of solid tumors at various treatment regimens, doses, and routes including a single dose, once weekly, twice weekly, single dose every 3 weeks, daily times 5 every 4 weeks, and daily times 21 days for multiple courses. Lower doses than used in the cancer studies have also been utilized for patients with psoriasis and organ transplant. The maximum intravenous dose given was 2,250 mg/m^2 every 3 weeks, and the maximum oral dose was 100 mg/m^2 daily for 21 days. There has been limited testing of DHODHi to date in the clinic for infection with SARS-CoV-2. DHODHi therapy at relatively high doses in the context of trials for patients with cancer has the expected safety side-effects of mucositis and bone marrow suppression. Importantly, however, the prior clinical experience in 39 subjects who received daily brequinar for 5 consecutive days at or lower than 100 mg/day show no cases of mucositis and only 1 (2.6%) episode of mild thrombocytopenia. Based on these data the 100 mg per day dose proposed for administration in this study should be within a safe and tolerable range as well as demonstrating the predicted antiviral effect.

The potential benefit in using brequinar to treat SARS-CoV-2 infection is the hypothesis that a 5-day period of brequinar dosing will suppress host *de novo* pyrimidine synthesis for this period thus decreasing viral load. Inhibition of DHODH is expected to reduce the ability of the virus to replicate and it is for this reason that brequinar will be administered to patients with COVID-19 in this study.

3.6 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration of high-dose brequinar in patients with refractory solid tumors, reversible myelosuppression, in particular thrombocytopenia, and mucositis have been the primary dose-limiting toxicities. In addition, skin rash, nausea/vomiting, fatigue, and leukopenia have been dose-limiting in trials utilizing other schedules of brequinar administration. However, these effects were self-limiting, transient, required treatment in few cases, and resolved following discontinuation of dosing. These adverse effects have been associated with higher doses of brequinar given via the intravenous route and for longer durations than the 100 mg dose and 5-day regimen proposed for this study.

In addition to studying a higher risk population with symptomatic COVID-19, a comprehensive safety monitoring plan will be utilized in this study to assess the ongoing safety and well-being of participants (see Section 10.8).

3.7 Possible Interactions with Concomitant Medical Treatments

Brequinar has been administered to subjects taking a variety of concomitant medications that are typical in severely ill cancer patients including antibiotics, antifungals and other critical care medications. No formal interaction studies have been conducted for these medications, however, there have not been any reports of interactions with any medications during the clinical trials with more than 800 cancer patients.

3.7.1 CYP Interactions

No formal clinical drug-drug interaction studies have been performed for brequinar with medications commonly used in treating hematologic malignancies. The nonclinical studies performed to date have demonstrated there is no first-pass metabolism and there have been no apparent hepatotoxic effects in the clinical studies. Brequinar itself does not appear to be a substrate for metabolism by cytochrome P450 enzymes when tested under a variety of conditions. (See Brequinar IB [5]; nonclinical data on file with Clear Creek).

3.8 Steps to be Taken to Control or Mitigate Risks

All subjects will be treated by highly experienced clinicians familiar with the treatment of viral infections and their complications.

4 TRIAL OBJECTIVES

4.1 Primary Objective

To demonstrate a change from baseline in quantitative SARS-CoV-2 viral load for brequinar-treated subjects compared to placebo-treated subjects through Day 29.

4.2 Secondary Objectives

The secondary objectives of this study are:

Through Day 29:

- To characterize the safety and tolerability of brequinar in out-patient COVID-19 subjects as measured by frequencies of grade 3 and 4 AEs and SAEs;
- To demonstrate a shorter duration of viral shedding in subjects treated with brequinar compared to subjects who received placebo;
- To reduce the percentage of subjects requiring hospital admission as an inpatient for >24 hours for brequinar subjects compared to subjects who received placebo;
- To reduce all-cause mortality through Day 29 for brequinar subjects compared to subjects who received placebo.

4.3 EXPLORATORY OBJECTIVES

Through Day 29:

- To determine time to viral clearance (two consecutive negative tests);
- To determine time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline;
- To determine time to clinical improvement as measured by a favorable shift in the WHO Ordinal Scale score for the subset of subjects with baseline WHO Ordinal Scale of 2 for brequinar subjects compared to subjects who received placebo.

5 TRIAL DESIGN

This will be a phase II randomized, placebo-controlled, double blind, multi-center study with approximately 100 subjects. All subjects will receive standard of care per (SOC) institutional guidelines for treatment of patients with COVID-19 infection. In addition to SOC, the subjects will self-administer one capsule once daily for 5 days.

Subjects will have a Screening Visit followed as soon as possible with Study Day 1. Study procedures are presented in detail in the Schedule of Events (Appendix 15.1). Study visits (virtual or in person) will take place at Screening and on Study Days 1 - 8, 12, 15, 22, and 29. The visits that include bloodwork must be conducted at the study site or arrangements made for sample collection at the subject's home or other appropriate location. Other visits/visit activities for that visit may be conducted remotely using telephone, telemedicine or other remote technique. Subjects are to self-collect a viral load sample, obtain their respiratory rate, heart rate, body temperature and SpO2, and complete a symptom assessment checklist with the site via telemedicine on Days 1, 4, 8, 12, 15, 22, and 29. The site will also have a telephone call with the subject on Study Days 2, 3, 5, 6, and 7 for changes in concomitant medications and assessment of adverse events, especially those that may indicate thrombocytopenia (see Section 10.8) and mucositis. A home health nurse will visit the subject at Screening and on study Days 1, 8, 15, and 29. Telemedicine only visits will be conducted by site staff on study Days 4, 12, and 22.

6 TRIAL ENDPOINTS

6.1 Primary Endpoint

Quantitative SARS-CoV-2 viral load through Day 29.

6.2 Secondary Endpoints

The secondary endpoints of this study are:

Through Day 29:

- Rates of AEs and SAEs including laboratory assessments;
- Duration of viral shedding;
- Percentage of subjects requiring admission as an inpatient for >24 hours.
- All-cause mortality.

6.3 Exploratory Endpoints

Through Day 29:

- Time to viral clearance (two consecutive negative tests);
- Time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline;
- Time to clinical improvement measured by a favorable shift in WHO Ordinal Scale score for the subset of subjects with baseline WHO Ordinal Scale of 2.

7 TRIAL POPULATION

7.1 Number of Subjects

Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 100 subjects have completed the study. Subjects will be randomized to either standard of care plus brequinar 100 mg or standard of care plus placebo in a 1:1 ratio (approximately 50 subjects assigned to standard of care plus brequinar 100 mg and approximately 50 subjects assigned to standard of care plus placebo).

7.2 Inclusion criteria

1. Willing and able to provide informed consent for the trial, written, electronic, verbal or other method deemed acceptable by the institution and IRB.
2. 18 years of age or older.
3. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other FDA-approved commercial or public health assay within 14 days of first dose.
4. Out-patient (never hospitalized as an in-patient for COVID-19 or was evaluated/treated for COVID-19 only in the Emergency Room with a stay of < 24 hours).
5. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men and women treated or enrolled on this protocol must also agree to use adequate contraception for the duration of study participation, and for 90 days after completion of brequinar administration.
6. Male subjects must agree to refrain from sperm donation and female subjects must agree to refrain from ovum donation from initial study drug administration until 90 days after the last dose of brequinar.
7. At least one COVID-19 symptom including but not limited to fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, shortness of breath, dyspnea, anosmia, dysgeusia, or other symptom commonly associated with COVID-19.
8. Able to swallow capsules.

7.3 Exclusion Criteria

1. Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient
2. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test
3. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide) or other agents known to cause bone marrow suppression leading to thrombocytopenia
4. Platelets $\leq$150,000 cell/mm^3

5. Hemoglobin < 10 gm/dL
6. Absolute neutrophil count < 1500 cells/mm^3
7. Renal dysfunction, i.e., creatinine clearance < 30 mL/min
8. AST and/or ALT > 2 x ULN, or total bilirubin > ULN. Gilbert's Syndrome is allowed.
9. Bleeding disorders or blood loss requiring transfusion in the six weeks preceding enrollment
10. Ongoing gastrointestinal ulcer, or gastrointestinal bleeding within 6 weeks of first dose.
11. Chronic hepatitis B infection, active hepatitis C infection, active liver disease and/or cirrhosis per subject report.
12. Heart failure, current uncontrolled cardiovascular disease, including unstable angina, uncontrolled arrhythmias, major adverse cardiac event within 6 months (e.g. stroke, myocardial infarction, hospitalization due to heart failure, or revascularization procedure).

8 STUDY TREATMENTS

8.1 Description of Study Medications

8.1.1 Brequinar

Brequinar and placebo will be supplied as 100 mg capsules. Dosing will be a single 5-day course of brequinar 100 mg capsules or placebo 100 mg capsules once daily for 5 doses.

8.2 Treatment Administration

This will be a phase 2 randomized, placebo-controlled, double blind, multi-center study with approximately 100 subjects. All subjects will receive standard of care (SOC) for COVID-19 infection. Subjects will be randomly assigned in a 1:1 ratio to standard of care plus brequinar or standard of care plus placebo.

8.2.1 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit. The *NIH Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria.

Adverse events (AEs) commonly observed in patients treated with brequinar are provided in the Investigator's Brochure (IB) and include thrombocytopenia, nausea, anemia, diarrhea, vomiting, leukopenia, stomatitis, rash, granulocytopenia, fatigue, and infection. In a study of 209 cancer subjects treated once-weekly (DuP 785-012, see Brequinar IB [5]), the deaths of three patients were attributed to study drug toxicity (two to hemorrhage, one following acute renal failure). Severe toxicities grades (Grades 3 to 4) which typically led to discontinuation in this study included hematologic toxicities (anemia, thrombocytopenia, leukopenia, granulocytopenia), digestive system toxicity (nausea, vomiting, stomatitis, others including gastric hemorrhage) and mucositis.

In three oncology studies with five consecutive days of intravenous (IV) brequinar dosing in 168 subjects (Study 785-001 [14], 785-003 [15], and 785-005 [16]) there were no toxic deaths. For subjects from these three studies who were treated with a daily dose of 100 mg or below (as will be dosed in CCB-CRISIS-02), AEs through 21 days showed that 2 of 39 subjects (5.1%) had a severe (Grades 3 or 4) AE related to study drug (1 subject each with hyperbilirubinemia and hyperglycemia), and no subjects discontinued from the study due to a study drug-related AE. The few study drug related AEs through 21 days at or below the 100 mg dose from these three studies included 2 subjects each with nausea, vomiting, and creatinine elevated and one subject each with thrombocytopenia and diarrhea. When only studies with oral dosing were considered at this dose level (Studies 785-022 [17], 785-031 [18] , and 785-034 [19]), the study drug related AEs through 21 days (each observed in one subject only) included diarrhea, headache, nausea, pruritus, abdominal pain, anorexia, chest pain, dry mouth, fatigue, keratosis, stomatitis, and vomiting. See brequinar IB [5].

In most instances, brequinar-related toxicities were transient, clinically manageable, and reversible upon discontinuation of brequinar treatment. Any of these events reported with brequinar use can be serious in nature and may result in death.

A 5-day course of oral brequinar administered once daily at a low level relative to those administered in the cancer studies is expected to be safe and well tolerated in the COVID-19 population.

8.3 Study Discontinuation

Subjects will remain in the study through at least Study Day 29 (or longer if needed to follow up study drug-related adverse events). Participants may discontinue from the study by withdrawing consent at any time or for any reason as presented in Section 9.7.

8.4 Stopping Criteria

8.4.1 Individual Stopping Criteria

- Participants who develop a Grade 3 toxicity that is assessed by the investigator to be related to the study drug are to be permanently discontinued from study treatment.
- Participants who develop a Grade 4 toxicity, regardless of relatedness to study drug, are to be permanently discontinued from study treatment.
- Subjects who develop Grade 3 or 4 toxicities are to be followed by re-evaluation every 2 days, as feasible, until the toxicity returns to ≤ Grade 2 severity.

8.4.2 Study-Level Stopping Criteria

Study enrollment is to be paused if any of the below criteria are met:

- If ≥ 3 subjects develop the same related Grade 4 (life-threatening) adverse event or laboratory abnormality;
- If ≥ 5 subjects develop the same related Grade 3 or 4 adverse event or laboratory abnormality;
- If ≥ 10 subjects develop any related Grade 3 or 4 adverse event or laboratory abnormality.

Following assessment by the Data Monitoring Committee (DMC, see Section 10.9), the DMC will determine whether to stop the study, amend the protocol, or continue the study per protocol.

8.5 Concomitant Medication/Treatment

Record the name, dose, start/stop date, indication for use, route, and whether ongoing or stopped for medications/treatments taken within two weeks prior to study entry as well as any medications taken during the study are to be recorded. Prohibited medications are identified in Section 8.8.

8.6 Treatment Compliance

Compliance will be assessed by reviewing the subject's medication diary and study records as appropriate.

8.7 Storage, Stability, Labeling and Packaging

8.7.1 Storage and Stability

The study drug is stored at room temperature. Stability testing is ongoing.

8.7.2 Labeling and Packaging

The bulk drug and unit-dose containers will be labeled in accordance with national laws and regulations.

8.7.3 Blinding and Randomization

The trial will be conducted in double blinded, randomized manner with random assignment to standard of care plus brequinar or standard of care plus placebo. The brequinar and placebo capsules will be provided to each participating institution in pre-numbered bottles intended for individual subjects to be dispensed by the institution's pharmacist or designated person. Randomization assignments will be provided by an independent statistician to the drug packaging company. The pharmacist/designated person will dispense the next number in sequence to the next patient who qualifies for the study at an individual site.

8.7.4 Unblinding/Expectedness

Contact the Covance Medical Monitor if it is necessary to break the blind for this blinded study due to an adverse event (AE). Each site will be provided with a sealed envelope containing individual sealed envelopes for subject numbers assigned to that site. Each individual subject number sealed envelope will have the treatment (brequinar or placebo) randomly assigned to that subject number. Do not open the outer envelope or the individual sealed envelope unless it has been agreed with the Medical Monitor and the Sponsor that unblinding is necessary for that particular AE. Unblinding must be documented in the study records. Envelope seals are to be checked to ensure they remain intact during drug accountability monitoring.

If after a discussion with the Medical Monitor, the investigator or treating clinician believes the AE leading to unblinding to be related to the study drug, no further doses of drug should be administered to that subject.

Expectedness will be determined by establishing whether an adverse event is among those identified in the protocol and the brequinar IB or are commonly associated with COVID-19 or similar severe viral illnesses and their complications.

8.7.5 Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator must keep a record of all study medication received, administered, and discarded. It must be clear from the records whether the subject received study medication and what subject number was assigned to which subject. Adequate drug is to be dispensed for the number of subjects expected to be treated at each institution.

The pharmacist/staff member responsible for drug accountability is to document the date and time of dispensing and for what subject the study drug was intended (i.e., record subject initials and birth date or other unique identifier). A pharmacy manual will be provided by the Sponsor.

At the end of the study any unused study drug will be returned to the Sponsor for destruction or may be destroyed locally; disposition of study drug will be documented.

The Sponsor will be permitted access to the trial supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation. Records may be electronic or paper and may be accessed remotely for monitoring/drug accountability purposes.

Each subject will be provided with one bottle with five brequinar or five placebo capsules for the five days of dosing.

8.8 Prohibited Medications

Treatment is prohibited with another DHODH inhibitor (e.g., leflunomide and teriflunomide). Treatment is prohibited with agents known to cause bone marrow suppression leading to thrombocytopenia.

8.9 Study Adjustments Due to COVID-19

Due to the highly contagious nature of COVID-19, multiple adjustments and revised procedures are rapidly evolving regarding clinical trial management and study conduct. Reasonable procedures implemented by study staff to avoid spreading this disease are acceptable to Clear Creek with written permission. Examples include but are not limited to e-consent, telephone consent and study visits conducted by telemedicine, telephone or other digital media.

Background standard of care is to be maintained in both treatment arms. The standard of care is expected to change as additional information, such as that from randomized controlled trials, emerges, and the Sponsor and the treating clinicians will need to address anticipated off-label use of any other drugs, devices, or interventions that might be used to manage COVID-19 (e.g. anticoagulants).

The Sponsor and treating clinicians are to consider changes in SOC over time, for example, overlapping toxicities of brequinar and a SOC treatment expected to be widely used is to be considered. The availability of new standard of care treatment may change over time and vary from one clinical trial site to another. The Sponsor will discuss these issues with FDA should the need arise.

9 CONDUCT OF THE TRIAL

9.1 Ethical and Regulatory Considerations

The trial will be performed in accordance with the Declaration of Helsinki (1964) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Scotland (2000, Note of Clarification 2002 & 2004) and Seoul 2008 (Appendix A), and Fortaleza (Brazil) (2013), and with the International Council on Harmonization (ICH) Tripartite Guideline on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and United States (US) FDA Regulations.

9.2 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki must be implemented in each clinical study before protocol-specified procedures are carried out. Informed consent must be obtained in accordance with US Code of Federal Regulations (21 CFR Part 50), the FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency (March 2020, Updated April 16, 2020) [20], as well as local and national regulations. Information should be given in both oral and written form whenever possible and deemed appropriate by the Institutional Review Board (IRB). Subjects and their relatives, if necessary, must be given ample opportunity to inquire about details of the study.

The Investigator or qualified designated person will verbally inform subjects as to the nature, expected duration and purpose of the trial, the administration of the Investigational Product (IP), and the hazards involved, as well as the potential benefits that may come from treatment with this IP. The trial procedures will be explained in lay language and any questions will be answered. The subjects will be given an IRB-approved consent form. The subjects will be given appropriate time to consider their participation in the trial and have any questions answered prior to signing the consent form. If a subject agrees to participate, he/she will sign and date an informed consent form and be provided with a copy of the signed consent. All subjects who sign an informed consent form are to be recorded on the applicable screening log. If the subject is unable to consent for any reason, a designated family member or healthcare power of attorney or other person may consent per institutional policy.

The subject will be informed that his/her medical records will be subject to review by the Sponsor, Sponsor's representatives, and possibly by a representative of the FDA and other relevant regulatory authorities. Subjects will be informed that they are free to refuse participation in this clinical investigation, and if they should participate, it will be made clear to them that they may withdraw from the trial at any time without prejudicing further medical care they may require. The subject will receive a copy of the consent form as well as an information sheet about the trial.

Informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to completing the informed consent process but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. Documentation of consent will be subject to review by the Sponsor; if in writing, a copy will be given to the subject and a copy will be filed with the subject's medical notes. Verbal consents will be documented by the study team as appropriate and agreed by the IRB.

Note that informed consent procedures have been affected by COVID-19, and the study staff may use any consent method that has been approved by the IRB (e.g., phone consent, verbal consent with

witness, e-consent, etc.) of the local institution. In-person consent, written consent signatures and providing hard copies to the subject are examples of procedures that may be foregone under these circumstances.

The study should be discussed with the potential participant only after an initial review of his/her clinical status and appropriateness for participation have been evaluated to determine if he/she meets the subject selection criteria.

A sample subject information sheet and consent form are available from Clear Creek. The final version at each institution may differ depending on institutional requirements and standard formats. This protocol will not be amended for site specific changes as such changes are to be made to the site's consent when required.

9.3 Institutional Review Board

It is the responsibility of the Investigator to submit the protocol, consent form and information sheet to the IRB. An IB will be available for review by the IRB. The protocol and informed consent form (ICF) must be approved by the IRB prior to the recruitment of the first subject. The template consent form may be revised in accordance with site-specific requirements with Sponsor review and approval. A copy of the IRB written approval must be provided to the Sponsor and investigator before the trial may start at that institution. Written approval from the IRB is also required for substantial protocol amendments prior to their implementation.

A substantial amendment may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments are "substantial" when they are likely to have an impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any IP used in the trial.

If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects, the Investigator will notify the Sponsor and the IRB of the new events and the measures taken as soon as possible.

The Investigator will report promptly to the Sponsor and IRB any new information that may adversely affect the safety of the subjects or the conduct of the trial. On completion of the trial, the Investigator will inform the applicable IRB as per local IRB requirements that the trial has ended. If the study is terminated for any reason, the investigator will return all clinical supplies and study-related equipment supplied by the Sponsor to the Sponsor unless otherwise specified.

9.4 Schedule of Events

Study activities will be conducted or supervised by experienced personnel throughout the study based on the Schedule of Events. The subjects may collect the saliva sample for viral load testing and perform other study activities such as body temperature, heart rate, respiratory rate, SpO2, and symptom

assessments themselves with appropriate training. Equipment will be provided to the subject for study purposes including a pulse oximeter with heart rate monitoring capability and a thermometer. Telemedicine visits such as phone calls or other remote media are to be utilized as much as possible. Subjects may need to come to an out-patient facility or be visited by a home health professional for some study assessments.

See 15.1 Schedule of Events in Appendix A for the full list of study assessments and timings.

Blood chemistry tests include blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALK), alanine amino transferase (ALT), aspartate amino transferase (AST), total bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, calcium, lactate dehydrogenase (LDH), and C-reactive protein (CRP). Chemistry samples may be banked for future analyses.

Hematology tests include hemoglobin, hematocrit, complete blood count with full differential, and platelet count.

Viral load sampling is to be carried out on Days 1, 4, 8, 12, 15, 22, and 29. The subject is to self-collect saliva samples with appropriate training for this analysis. Samples may be banked for future analyses. If the subject cannot provide documentation of the previous positive COVID-19 test, the site may perform an additional RT-PCR test as part of the Screening visit. The subject must have a documented positive result to be eligible for the study.

Safety laboratory results (chemistry and hematology) are to be reviewed by investigator or designated site personnel within 48 hours of receipt of results.

Hospitalization status after enrollment is to be recorded as not hospitalized or admitted to hospital as an in-patient with admission > 24 hours.

As much of the study as possible will be conducted via telemedicine remote from the site (e.g., consent, medical history, concomitant medications may be collected remotely). Subjects will be visited at home (or place of residence) by a home health nurse at Screening and on study Days 1, 8, 15, and 29. On study Days 4, 12, and 22 the vital signs and saliva collections will be observed via telemedicine by the study site staff. Site staff will have a telephone call with subjects on study days 2, 3, 5, 6, and 7 to assess changes in concomitant medications and to assess adverse events, especially those that may indicate thrombocytopenia, e.g., unusual bruising, epistaxis, gingival bleeding, etc., and mucositis. Subjects will be provided with a pulse oximeter and thermometer during the Screening in-home visit, as well as being trained on the use of these devices during that visit. Training will also be provided by the home health nurse for the saliva collection required for viral load testing. Assessments will be recorded by the home nurse during home visits and by the site staff during telemedicine visits. These data will be entered in the eCRF by the site staff or as determined by the study team.

9.5 Study Conduct

The study visits are to be conducted as shown in the Schedule of Events, Appendix 15.1.

Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF.

9.5.1 Unscheduled Visits

Unscheduled visits and tests are permitted as needed to assess AEs/SAEs throughout the study. Unscheduled visits and tests are also permitted as needed to assess AEs/ SAEs with onset within two (2) weeks after the final study visit providing the AE is considered related to study drug

9.6 Compliance with Study Procedures

The time at which study procedures are conducted should follow the protocol timelines as closely as possible. However, it is recognized in a clinical setting that protocol-specified timings may not occur exactly as specified in the protocol, particularly when conducted remotely by the subject. Provided that activities are carried out within the identified windows it will not be necessary to file a protocol deviation. Remote visits such as a telemedicine visit may be conducted to collect as much information as possible remotely. A home visit or return to the clinical site or an out-patient laboratory may be arranged for safety labs or other assessments, when required. Telemedicine or other remote technique is to be utilized to ensure subject compliance when subject is performing self-collection of study assessments.

9.7 Early Withdrawal from the Study

A subject may withdraw from the study at any time for any reason or for one of the reasons listed below. The Sponsor or Investigator may also terminate a subject's study participation after discussion with the other party if it is believed it would be unsafe for the subject to continue in the study.

Subjects must discontinue study medication if any of the following events occur:

- Significant protocol violation or non-compliance, either on the part of the subject or the investigator or other site personnel;
- Decision of the Investigator or Sponsor that removal is in the subject's best interest;
- Severe unrelated medical illness or complication;
- Safety reasons/ significant adverse event;
- Subject request (withdrawal of consent);
- Sponsor decision.

Collect/conduct all scheduled evaluations even for subjects who discontinue study medication prior to completing the treatment period unless consent is withdrawn.

9.8 Early Termination of the Study

If the Sponsor or an Investigator believes it would be unsafe to continue the study, or for any reason at the Sponsor's request, the study may be terminated at that site or the entire study terminated after discussion with the other parties.

The Sponsor will provide a written statement to the IRB and the relevant regulatory authority with the reasons for termination of the study. This will be conducted within 15 days of the decision to terminate the study.

If the study is terminated, a close out monitoring visit will be performed and applicable procedures will be carried out to close the trial site(s).

9.9 Non-Childbearing Potential

Women of non-childbearing potential are defined as those who have no uterus, ligation of the fallopian tubes, or permanent cessation of ovarian function due to ovarian failure or surgical removal of the ovaries. Documentation of surgical procedure or physical examination is required for subjects who have had a hysterectomy or tubal ligation. A woman is also presumed to be infertile due to natural causes if she has been amenorrheic for greater than 12 months and has an FSH greater than 40 IU/L. In the absence of such documentation, a negative serum pregnancy test is required for inclusion into the study.

10 ADVERSE EVENT REPORTING

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

Events that occur prior to first dose will be entered as medical history; events that occur after first dose will be entered as adverse events (AEs) on the AE form.

Subjects will be questioned and observed for evidence of AEs, whether or not judged by the Investigator or designated person to be related to study drug. All AEs will be documented in the subject's medical record and CRF. For any pre-existing condition or abnormal laboratory finding that changes in severity after dosing, this change should be recorded as an AE. New abnormal laboratory findings that are clinically significant are considered AEs. Investigators and site staff are to elicit from the subject and note any signs or symptoms of mucositis and thrombocytopenia (see Section 10.8).

Adverse events will be collected from the time of first dose through Day 29. After Day 29, collect/record only Serious Adverse Events (SAEs) which are assessed by the Investigator or designated person to be related to study drug and have an onset within 14 days of study completion (Day 29 or earlier if discontinue prior to Day 29). AE details are to be documented including start and stop date and times, whether continuous or intermittent, severity, any intervention utilized to correct the event (e.g., medication, surgery, or other therapy), outcome and the relationship to the study drug.

AEs identified in the protocol as critical to the evaluation of safety must be reported to the Sponsor by the Investigator according to the reporting requirements within the time periods specified in the protocol.

AEs determined by the Investigator to be related to study drug must be followed until resolution or until they are considered stable or for at least 30 days after discontinuation of study drug.

Abnormal laboratory values or test results occurring after study enrollment constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, are Grades 3 or 4, or require therapy.

If a death occurs during the SAE reporting period, the cause of death such as pneumonia, ARDS, or respiratory failure, is considered as the AE and the death is considered its outcome. Death should be considered an outcome, not an event. The event or condition leading to death should be recorded and reported as a single medical concept on the AE eCRF. Generally, only one such event should be reported. “Fatal” will be recorded as the outcome of this respective event; death due to an outcome of an AE will not be recorded as separate event. If the primary cause of death is disease progression, the cause of death should be clearly identified as COVID-19.

In cases of surgical or diagnostic procedures, the condition leading to the procedure is considered as the AE instead of the procedure itself. Each AE will be coded by the Sponsor from the verbatim text to a preferred term using a thesaurus based on the Medical Dictionary for Regulatory Activities (MedDRA). For example, record appendicitis, not appendectomy.

The following guidelines will be followed for the recording and reporting of adverse and serious adverse events.

1. The medical history section of the case report form will serve as the source document for baseline events.

    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed.

        i. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.

2. Adverse events occurring after first dose are to be recorded in the eCRF using the AE form.

3. Serious adverse events will be reported to the local IRB according to institutional policy.

The *NIH Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf) will be used for adverse event reporting.

10.1 Follow Up of Grade 3 or 4 Toxicities

Grade 3 or 4 toxicities are to be followed by re-evaluation every 2 days, as feasible, until the toxicity returns to Grade ≤ 2 severity.

10.2 Infection Follow Up

Any new infection that occurs on study regardless of infecting agent (i.e., viral or non-viral) should be captured. Additionally, the site of infection and source of culture (BAL, tracheal aspirate, sputum, blood, urine, etc.) should also be recorded.

10.3 Classification of Causality

Attribution is the relationship between an adverse event or serious adverse event

and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment

Guidance for assessing causality:

The Investigator will need to determine whether an AE is considered related to ("caused by"') the study drug rather than some underlying condition, for example, COVID-19.

For the purposes of this study, 'drug related' shall mean 'Definite', 'Probable' and 'Possible' relationship to drug as determined by the Investigator.

10.4 Classification of Severity

The NIH Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017) will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria.

AEs that are expected are subject to expedited reporting only if the adverse event varies in nature, intensity or frequency from the expected toxicity information that is provided in the Investigator Brochure.

10.5 Serious Adverse Event (SAE) Reporting

The regulatory definition of an SAE is any untoward medical occurrence or effect that at any dose fulfills one or more of these criteria:

- results in death;
- is life threatening (at the time of the event);
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability / incapacity
- is a congenital anomaly / birth defect;
- or is an event considered medically serious by the Investigator.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

A life-threatening adverse event is one that places the patient/subject, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.

An unexpected adverse event is any adverse drug event, the nature or severity of which is not consistent with the applicable product information (e.g. IB for an unauthorized investigational product or summary of product characteristics for an authorized product).

Enter only one event as the reason for the SAE on the SAE form. Other non-serious events which did not directly result in the SAE should be detailed in the description section on the SAE form and listed separately as AEs if necessary. For fatal SAEs, report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term.

Note that hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of COVID-19 infection, not associated with any deterioration in condition;
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent;
- Social reasons and respite care in the absence of any deterioration in the subject's general condition;
- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above.

ANY SERIOUS ADVERSE EVENT MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) BY EMAIL TO THE SAE REPORTING EMAIL USING THE FORM PROVIDED. ENTER THE SUBJECT'S AVAILABLE INFORMATION INTO THE eCRF WITHIN 48 HOURS.

The subjects are to be identified in the immediate and follow-up reports by unique code numbers supplied by the sponsor. The email address for reporting SAEs can be found below and at the front of this protocol.

Reports relating to the subject's subsequent medical course following an SAE must be submitted to Covance Patient Safety until the event has subsided or, in case of permanent impairment, it stabilizes, and the overall clinical outcome has been ascertained.

SAE REPORTING EMAIL: SAEIntake@covance.com

Medical Monitor:

Norberto Soto, MD	Telephone:	(609) 212-7892
Covance Physician/Medical Monitor	Email:	Norberto.Soto@Covance.com

Sponsor Representative:

Barbara Powers, MSN, Ph.D.	Telephone:	M: (484) 686-0545
VP, Clinical Operations	Email:	bpowers@clearcreekbio.com

All SAEs will be reported to the IRB periodically, at the end of the study, or per local institutional guidelines.

10.6 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected, unexpected, serious adverse reactions (SUSARs) are SAEs that are both related to the study drug (Relationship = Related) and unexpected (not previously described in the investigator's brochure). All SUSARs will be reported in an expedited manner to the Sponsor or designee and IRB by the Investigators and to all relevant regulatory authorities by the Sponsor. Expectedness will be judged by the Covance Physician and site Investigator. It is critical that all SAEs are reported within the 24-hour guideline so that the expectedness determination can be made. SUSARs require immediate attention and expedited reporting to relevant regulatory authorities.

The Sponsor will ensure that all relevant information about **fatal or life-threatening** SUSARs are appropriately recorded and reported to the concerned Regulatory Authority and to the concerned

IRB(s) within seven (7) calendar days of the date of first report to Covance Patient Safety / Sponsor. Follow-up information will be communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs will be reported to the Regulatory Authority and to the IRB(s) concerned as soon as possible within a maximum of fifteen calendar days of first notification to Covance Patient Safety / Sponsor.

The Sponsor or designee will also inform all Investigators studying the investigational medicinal product about SUSARs and ensure that all IRBs have been notified.

For reported deaths of a subject, the Investigator shall supply the Sponsor and the IRB(s) with requested additional information on an expedited basis.

10.7 Pregnancies

Pregnancy occurring in a female subject or a subject's partner during the study period will be documented in the subject's source documents and reported to Covance Patient Safety (by email to SAEIntake@covance.com) and to the IRB by the investigational staff within 1 working day of their knowledge of the event. The collection period for a pregnancy occurring in a subject or a subject's partner will begin at the first dose of study drug and will continue through 90 days after the last dose of study drug. Monitoring of the subject or partner should continue until the conclusion of the pregnancy, if the subject or subject's partner has consented to this. Monitoring of the baby should continue for 3 months after birth, if the subject or subject's partner has consented to this.

Pregnancy itself is not an AE; it should be reported for tracking purposes. The Investigator or designee will discontinue the pregnant subject from the treatment aspects of the study, continue to follow her per protocol for safety outcomes only, and advise her to seek prenatal care and counseling from her primary care provider. Data on fetal outcome and breast-feeding will be collected for regulatory reporting and drug safety evaluation, if the subject has consented to this.

If the pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as (S)AEs.

The site clinical staff will request the pregnant subject to notify the site of the outcome of the pregnancy (i.e., birth, loss, or termination). To help ensure this, the site clinical staff will follow the subject until the end of pregnancy, with the subject's consent. This request and the subject's response will be documented in the subject's source document.

10.8 Safety Monitoring for Hematologic Toxicities

Myelosuppression is a known effect of DHODH inhibition that is associated with prolonged exposure and high doses. To reduce the risk of this effect with brequinar in COVID-19 subjects, the extensive brequinar safety database with over 1,000 patients has been evaluated to select a dose level expected to be safe and well tolerated with regard to hematologic toxicity. In addition to enhancing safety by

selecting a relatively brief 5-day exposure and a low brequinar dose, all subjects in the clinical trial will be under the care of highly qualified medical personnel. Clinically significant out-of-range laboratory results will be reported as adverse events.

In addition to real time assessments by the treating clinical team, the Covance Medical Monitor will assess the available hematology data on a periodic basis to identify any pathologic trends or safety issues. Any apparent increase in the expected rate or severity of hematologic safety events will be discussed with the Principal Investigators and the Sponsor. In addition, the Data Monitoring Committee (DMC) will assess available hematology data on a periodic basis to independently assess any pathologic trends or safety issues. If the rate or severity of hematologic toxicities appears to be above the expected rate or the severity appears worse than that expected, the trial enrollment will be suspended and no further subjects will be treated while a comprehensive data review is conducted. Depending on the outcome of the safety review the study may be stopped, the design adjusted, or the study may continue as designed. Individual and Study stopping rules are provided in Section 8.4.

Safety laboratory results are to be initially assessed in real time by the Principal Investigator or designated person. Any study drug-related clinically significant out-of-range laboratories or study drug-related adverse events will be followed as needed until resolution or stable.

The in-clinic assessments and telemedicine/phone call visits will specifically ask about possible hematologic toxicity including any evidence of the list below. Subjects will be provided with a list of the following events in lay terms and will be instructed to call the research team if any of these events occur.

- Ecchymosis/purpura/petechiae
- Epistaxis
- Hemoptysis
- Hematuria
- Gingival bleeding
- Prolonged bleeding time from needle sticks, abrasions or lacerations
- Hematemesis
- Rectal bleeding
- Blood in stool
- Any other unusual bleeding noted by the subject or caregiver

Any of these symptoms considered clinically significant will be recorded as an adverse event and must be followed until resolved or stable.

10.9 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established to provide independent oversight to this trial. The primary responsibility of the DMC will be to review the progress and conduct of the trial in order to maintain scientific rigor and to ensure the wellbeing of subjects participating in the trial. The specific responsibilities of the DMC will be detailed in a separate DMC charter. The DMC will include at a minimum at least one statistician and two clinicians who will perform periodic data review to assess whether there are clinically significant differences between treatment arms that could affect participant safety. All adverse events will be reviewed by the DMC during their reviews. Following

such a review, the DMC Chair will advise the Sponsor that the study be stopped, the design changed, or that the study may continue per protocol.

10.9.1 DMC Safety Review Schedule

The DMC is to review adverse events and safety laboratory assessments after the first 20 subjects complete the Day 8 visit, and again after the first 40 subjects complete the Day 8 visit.

11 STATISTICAL CONSIDERATIONS

A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. All analyses will be descriptive in nature and presented by group.

Summaries for quantitative variables will include the mean, median, quartiles, standard error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and 95% confidence interval (CI), when appropriate. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.4 or higher).

Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. The following sections will briefly summarize of the planned statistical analyses and analysis sets for the primary and secondary endpoints.

11.1 Study Populations for Analysis

All safety analyses will be based on the ITT population, which is defined as all randomized subjects. As will be described in the SAP, efficacy analyses of changes in viral load will be based on the population of subjects with detectable viral load at baseline or similar qualification. Sample size may be adjusted if an inadequate number of subjects have detectable viral load at baseline.

11.2 Safety Analyses

Safety and tolerability will be assessed in terms of AEs, SAEs, WHO Assessments, and safety laboratory data.

Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of post-first dose (treatment-emergent) adverse events will be tabulated by MedDRA preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results and study assessments will be summarized using appropriate descriptive statistics.

11.3 Efficacy Analyses

Efficacy will primarily be assessed via viral load changes.

11.4 Sample Size Considerations

Formal sample size calculations are not applicable for this proof-of-concept study. The sample size of approximately 100 subjects planned to be entered in this trial is expected to be adequate to provide safety and efficacy information to advise future study design.

11.5 Randomization

A randomization scheme will be provided by an independent statistician to the drug packaging company to ensure subjects are randomly assigned to SOC + brequinar or SOC + placebo in a 1:1 ratio.

11.6 Pooling of Study Centers

Not applicable to this small, early phase study.

11.7 Interim Analysis

No interim analysis is planned for this trial.

12 INVESTIGATOR RESPONSIBILITIES

12.1 Investigator's Performance

The Investigator will ensure that all those concerned with conducting the trial are:

- provided with copies of the protocol and all safety information prior to the start of the trial;
- trained regarding the conduct of the study and the training has been documented.

The Investigator will sign the Investigator's Statement and Agreement found in Section 15.2 to indicate commitment to comply with the contents.

12.2 Confidentiality

The Investigator shall assure the subject that his/her identity will be protected and confidentiality will be maintained during all audits and inspections of the trial site and documentation. A unique number will be assigned to each subject at the start of the trial and this, with the subject's initials, will be used to identify the subject. In some cases, a further step may be taken to assign "fake initials" to the subject, per individual site requirements. The subject's number will be the site number followed by the number of this subject at this site and will be used as the unique identifier in the source records and on the eCRF, on all trial correspondence and in the trial database. The Investigator will keep a list of identification codes or initials used for each subject along with the unique number assigned.

All information provided to the Investigator relevant to the investigational product (IP), as well as information obtained during the course of the trial will be regarded as confidential. The Investigator and members of his/her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the Sponsor which will not be unreasonably withheld, except as required by law, or as permitted by the Publications section of this protocol, Section 12.7.

The Investigator will take all measures to ensure subject's confidentiality will be maintained at all times.

12.3 Source Documentation

Investigators are to maintain adequate source documentation of the original study data, for example medication records, laboratory reports and pharmacy records as appropriate. The Investigator will allow inspections of the trial site and documentation by clinical research and audit personnel from the Sponsor, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the eCRFs. In order to do this, direct access to the subjects' medical or clinic records is necessary. The Investigator will ensure that certain information is contained in the medical or clinic written or electronic records of the subject and that the entries are signed and dated, as follows:

- sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories;
- a note on the day the subject entered the trial describing the trial number, the IP being evaluated, the trial number assigned to that subject and a statement that consent was obtained;

- a note of each subsequent trial visit including any concerns about AEs and their resolution;
- notes of all concomitant medication taken by the subject, including start and stop dates;
- a note of when the subject terminated from the trial, the reason for termination and the subject's general condition at termination;
- a copy of the signed informed consent form should be kept in the medical records of each subject during the clinical phase of the study. A signed copy should also be filed in the investigator file.

12.4 Data Collection

Suitably qualified and trained personnel at the trial site will ensure compliance with the protocol, adherence to ICH GCP obligations, proper maintenance of trial records including IP accountability records, correct administration of IP including storage conditions and accurate reporting of AEs. In addition, suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. All queries and discrepancies relating to the data collection are to be resolved at the completion of the trial. Remote data capture is encouraged whenever possible.

12.5 Case Report Forms, Investigator's Site File and Record Retention

The Sponsor may provide the CRFs in paper, electronic (eCRF), or other media. The forms will be reviewed against source documentation at each monitoring visit. All CRFs and supporting source documentation must be completed and available to the Sponsor in a timely manner. Changes or corrections due to data clarification and resolutions will be tracked by paper or electronically with an audit trail.

Prior to review of the case report forms by the Sponsor's representative, they should be reviewed for completeness and accuracy by the Investigator or a member of the research team.

The Investigator must maintain an Investigator Site File which includes, but is not limited to, the IB, the protocol plus any amendments, all correspondence with the IRB including the approval for the trial to proceed, Regulatory Authority approval/ notification (if applicable) including a sample of an approved informed consent, IP accountability, Source Documents, investigator and staff curricula vitae (CVs,) trial documentation, and all trial correspondence. The original signed informed consent forms and the final report will be kept in the Investigator Site File.

The Investigator will archive all essential documents. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The Investigator has a responsibility to retain essential documents for as long as is required by the Sponsor and applicable regulatory authorities. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained. Investigators will be asked to contact the Sponsor prior to the destruction of any data or removal to another site if this occurs prior to the Sponsor notification that the documentation is no longer required. Any transfer of ownership of the data or of documents will be documented in writing. The new owner will assume responsibility for data retention and archiving.

Should the Investigator retire, relocate, or for other reasons withdraw from the responsibility of keeping the trial essential documents, custody must be transferred to a person who will accept that responsibility, and the Sponsor must be notified in writing of the name and address of said person.

12.6 Non-Protocol Research

No investigational procedures other than those outlined in this protocol may be undertaken on the subjects in this trial without the prior written permission of the subject, the Sponsor, the IRB and, when appropriate, the regulatory authority.

12.7 Publication

The Sponsor acknowledges the benefit of making widely available the results of all clinical trials and intends to publish the results of this trial. All publications resulting from the clinical trial must be in a form that does not reveal technical information that the Sponsor considers confidential or proprietary. A copy of any abstract, presentation or manuscript proposed for publication must be submitted to the Sponsor for review at least 30 days before its submission for any meeting or journal. In addition, if deemed necessary by the Sponsor for protection of proprietary information prior to patent filing, the Investigator agrees to a further delay of 60 days before any presentation or publication is submitted. The Sponsor reserves the right to include the report of this trial in any regulatory documentation or submission or in any informational materials prepared for the medical profession.

Authorship determination will be at the discretion of the Sponsor and will include evaluation of the following criteria: Investigator must participate in the review of and content of the protocol; review and comment on the study results; participate in the writing, reviewing and commenting of the manuscript; and approve the final manuscript for submission.

13 SPONSOR RESPONSIBILITIES

13.1 General

The Sponsor agrees to adhere to the ICH Note for Guidance on GCP (CPMP/ICH/135/95, Jan.97) and US FDA Regulations. It is the Sponsor's responsibility to obtain appropriate regulatory approval to perform the trial (if applicable). The Sponsor should notify promptly all concerned investigator(s), IRB(s) and the Regulatory Authority of findings that could adversely affect the health of the patients/ subjects, impact on the conduct of the trial or alter the Regulatory Authority's authorization to continue the trial. If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects the Sponsor will notify the relevant regulatory authority and relevant IRB of the new events, the measures taken and the plan for further action as soon as possible. This will be by telephone in the first instance followed by a written report.

On completion of the trial, the Sponsor will inform the regulatory authority that the trial has ended. If the study is terminated for any reason the Sponsor will provide a written statement to the relevant regulatory authority and the IRB with the reasons for termination of the trial. This will be conducted within 15 days of the decision to terminate the trial. The Sponsor will report in an expeditious manner all SUSARs to the relevant regulatory authority and IRBs.

13.2 Indemnity

The Sponsor will provide compensation insurance against any risk incurred by a subject as a result of participation in this trial. The Sponsor will indemnify the Investigators as detailed in a separate document.

13.3 Data Monitoring

Suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site or will access the electronic health record (EHR) or conduct remote monitoring visits at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. CRFs and source documentation will be available for review during monitoring visits to the trial site. The function of this monitoring is to ensure compliance with the protocol, adherence to regulatory and GCP obligations, proper maintenance of records including IP accountability records, correct administration of IP including storage conditions and accurate reporting of AEs. On-site visits are not required for any monitoring visits for this study.

Once the data from the case report forms have been entered onto the database, they will be reviewed, and the data verified against the subject's source data. Any discrepancies will be tracked by paper or electronically with an electronic audit trail.

13.4 Audit

The Sponsor has an obligation to audit a proportion of studies. A department other than the clinical department will undertake this obligation. Therefore, the Sponsor, an independent auditor or a regulatory authority may audit the trial site and trial documentation. These audits may take place while the trial is being conducted or up to several years later.

13.5 Confidentiality

The Sponsor will not keep any material on file bearing any subject's name, and subjects' confidentiality will be maintained at all times.

13.6 Finance

This will be the subject of a separate agreement between the Investigator/Institution and Sponsor.

14 REFERENCES

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15. Study DUP 785-003 Clinical Study Report (on file with Clear Creek)
16. Study DUP 785-005 Clinical Study Report (on file with Clear Creek)
17. Study DUP 785-022 Clinical Study Report (on file with Clear Creek)
18. Study DUP 785-031 Clinical Study Report (on file with Clear Creek)
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20. FDA Guidance "COVID-19: Developing Drugs and Biological Products for the Treatment or Prevention (https://www.fda.gov/media/137926/download)

15 APPENDICES

15.1 Appendix A: CCB-CRISIS-02 Schedule of Events

CCB-CRISIS-02 Schedule of Events **Windows are relative to first dose time** **Procedures**	**Screen (days -14 to -1) HH+TM[f]**	**D1 HH+ TM**	**D2, 3 (± 8 hrs) TC[f]**	**D4 (± 8 hrs) TM**	**D5,6, 7 (± 8 hrs) TC**	**D8 (± 1 day) HH+ TM**	**D12 (± 1 day) TM**	**D15 (± 1 day) HH+ TM**	**D22 (±1 day) TM**	**Final Visit D29 (± 2 days) HH+TM**
Informed Consent (note Date and Time)	X									
AE/Concomitant Medications (dose, route, duration or ongoing)	X	X	X	X	X	X	X	X	X	X
Medical history (relevant within one year or ongoing)/ History of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection)	X									
Demographics (subject reported height and weight, date of birth, gender, race, ethnicity)	X									
Check for Physical Exam abnormalities (subject self-reported)	X									
Pregnancy Test (WOCBP)	X (serum)									X (urine)
Hematology/Chemistry[a]	X	X				X		X		
Vital Signs[b]	X	X		X		X	X	X	X	X
Symptom Assessment[c]	X	X		X		X	X	X	X	X
SARS-CoV-2 RT-PCR/Viral load sample[d]	X	X		X		X	X	X	X	X
Hospital Status						X		X	X	X
WHO Ordinal Scale Assessment		X				X		X	X	X
Confirm Eligibility		X								
Randomize subject and dispense Study Medication		X								
Study drug administration[e]		X	X	X	X D5 Only					
Drug Accountability						X				

[a]Do not repeat if within 48h of Day 1 visit. Send to Covance Central Laboratory Services (CCLS) for analysis.
[b]Vital signs include heart rate, respiratory rate, body temperature, and SpO2. Subject will be provided with a thermometer and pulse oximeter with heart rate monitoring capability. Training will be provided during the first visit by the home health nurse. Vital signs parameters will be observed and recorded by study staff via telemedicine or during a visit by the home health nurse.
[c]Symptom Assessment will use a checklist provided to the subject with symptoms such as sore throat, cough, GI symptoms (vomiting, diarrhea), anosmia, dysgeusia, other (specify), etc. Severity None, Mild, Moderate, or Severe will be collected.
[d] RT-PCR at Screening may be performed by the site if the subject cannot provide documentation of a positive SARS-CoV-2 result. Samples collected after Screening will be saliva samples sent for viral load analysis. Day 1 sample must be obtained prior to dosing. Viral load specimens after Screening will be saliva samples self-collected by the subject using an Omnigene® collection system or similar. The home health nurse will train the subject and observe sample collection on Day 1. These samples are to be sent to CCLS for analysis. The viral load sample may also be used to perform viral cultures (sample can be split by the central laboratory, no additional sample required).
[e]Subject will self-administer study drug once daily Days 1 – 5 and record doses in a medication diary. Note that any visits/visit activities may be conducted via telephone, telemedicine, or digital media other than serum pregnancy test and chemistry/hematology sample collection. These labs may be collected at the clinical site or another designated out-patient facility/laboratory or collected via home visit. Arrangements for shipping viral load samples will be made by the study team.
[f]HH = Home Health in-person visit; TC = Telephone Call with site and subject; TM = Telemedicine with site and subject.

15.2 Appendix B: Investigator's Statement and Agreement

STUDY NUMBER: CCB-CRISIS-02

The CRISIS2 Study: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2.

INVESTIGATOR'S STATEMENT AND AGREEMENT

I (*the Investigator*) have read this protocol and hereby agree to conduct the trial in accord with all of its provisions. It is further agreed that the details of this trial and all information provided to me by Clear Creek Bio, Inc. (*the Sponsor*) will be held in the strictest confidence and will not be revealed for any reason without written authorization from Clear Creek Bio, Inc. except to those who are to participate in the conduct of the trial.

I agree that all data, the case report forms, and all materials provided for the conduct of the trial are the property of Clear Creek Bio, Inc. unless specified otherwise in writing. It is understood that Clear Creek Bio, Inc. will utilize the information derived from this trial in various ways, such as for submission to government regulatory agencies, required internal reports, and presentations without violating patient/ subject confidentiality in any way.

I further agree that Clear Creek Bio, Inc. or its representatives will be permitted access, in accordance with current Good Clinical Practice Guidelines, to all data generated by this trial and the source documents from which case report form data were generated.

PRINCIPAL INVESTIGATOR

Printed Name: _____

Signature: _____ Date: _____

15.3 Appendix C: WHO Ordinal Scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized: moderate disease	Hospitalized; no oxygen therapy*	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: severe disease	Hospitalized; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥ 200	7
	Mechanical ventilation pO_2/FiO_2 <150 (SpO_2/FiO_2 < 200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

WHO clinical progression scale

STUDY PROTOCOL

The CRISIS2 Study: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2

Study No: CCB-CRISIS-02

Version: 5.0

Version Date: 19 November 2020

Sponsor:

Clear Creek Bio, Inc.
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IND Number: 149291

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine amino transferase
AML	Acute myeloid leukemia
ARDS	Acute respiratory disease syndrome
AST	Aspartate amino transferase
BRQ	Brequinar
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CI	Confidence interval
COVID-19	Coronavirus-19 infection
CRP	c-reactive protein
CTCAE	Common terminology criteria for adverse events
CTEP	Cancer Therapy Evaluation Program
CV	Curricula vitae
DHO	Dihydroorotate
DHODH	Dihydroorotate dehydrogenase
DHODHi	Dihydroorotate dehydrogenase inhibitor
DMC	Data Safety Monitoring Board
ECMO	Extra corporeal membrane oxygenation
EHR	Electronic health record
ESR	Erythrocyte Sedimentation Rate
EUA	Emergency Use Authorization
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Council on Harmonization
ICU	Intensive care unit
IMP	Inosine-5’ phosphate
IP	Investigational product
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NEWS2	National Early Warning System (NEWS) 2 Score
RNA	Ribonucleic Acid
RdRp	RNA-dependent RNA polymerase
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	SARS Coronavirus 2
SOC	Standard of Care
SUSAR	Suspected unexpected serious adverse reaction
SpO_2	Peripheral capillary oxygen saturation

Abbreviation	Definition
UMP	Uridine 5'-monophosphatase
US	United States
XMP	Xanthosine-5' phosphate
WHO	World Health Organization
WOCBP	Women of childbearing potential

2 SYNOPSIS

CCB-CRISIS-02 SYNOPSIS	
IND	149291
Title	The CRISIS2 Study: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2
Protocol Number	CCB-CRISIS-02
Rationale	Brequinar is a potent DHODH inhibitor that has been previously studied in more than 1,000 cancer, psoriasis, and organ transplant patients. Brequinar has been found to have potent *in vitro* antiviral activity against many RNA viruses including SARS-CoV-2. The antiviral activity of brequinar against SARS-CoV-2 is likely due to DHODH inhibition and shows nanomolar potency and a high selectivity index in inhibiting viral replication in *in vitro* studies. The CRISIS2 trial will study out-patients (non-hospitalized patients) who have a positive SARS-CoV-2 test and are symptomatic. Subjects will be randomized to receive standard of care (SOC) + 5 days of brequinar or SOC + 5 days of placebo. The purpose of this study is to determine if the *in vitro* antiviral activity of brequinar can be duplicated in patients infected with SARS-CoV-2 by measuring the effect of brequinar on viral shedding. Importantly, the safety and tolerability of brequinar will also be determined in these patients. The results of this proof-of-concept study will inform future studies that will help determine if brequinar is a safe and effective drug for the treatment of SARS-CoV-2 infection.
Investigational Product and Dosage	Subjects will be randomized in a 1:1 ratio to either standard of care (SOC) + 5 days of brequinar 100 mg or SOC + 5 days of placebo. Investigational product will be supplied as either brequinar 100 mg oral capsules or placebo capsules. The subjects are to self-administer one capsule on Study Days 1 – 5. Treatment assignment will be randomized, double-blind.
Primary Objectives	● To demonstrate a change from baseline in quantitative SARS-CoV-2 viral load for brequinar-treated subjects compared to placebo-treated subjects through Day 29.
Secondary Objectives	Through Day 29: ● To characterize the safety and tolerability of brequinar in out-patient COVID-19 subjects as measured by frequencies of grade 3 and 4 AEs and SAEs; ● To demonstrate a shorter duration of viral shedding in subjects treated with brequinar compared to subjects who received placebo;

	● To reduce the percentage of subjects requiring hospital admission as an in-patient for > 24 hours for brequinar subjects compared to subjects who received placebo; ● To reduce all-cause mortality through Day 29 for brequinar subjects compared to subjects who received placebo.
Exploratory Objectives	Through Day 29: ● To determine time to viral clearance (two consecutive negative tests); ● To determine time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline; ● To determine time to clinical improvement as measured by a favorable shift in the WHO Ordinal Scale score measured for the subset of subjects with baseline WHO Ordinal Scale of 2 or 3 for brequinar subjects compared to subjects who received placebo.
Design	This will be a phase 2 randomized, double blind, multi-center study with approximately 100 subjects. All subjects will receive SOC per relevant guidelines for treatment of out-patients with COVID-19 infection. In addition to SOC, subjects will self-administer one capsule once daily for 5 days. To be eligible for screening, subjects must have a documented positive SARs-CoV-2 test result and have at least one symptom consistent with SARS-CoV-2 infection in the opinion of the investigator. Subjects will have a Screening Visit followed as soon as possible with randomization on Study Day 1. First dose of study drug must take place ≤ 7 days from onset of first symptom. Study procedures are presented in detail in the Schedule of Events. Study visits (virtual or in person) will take place at Screening and on Study Days 1 - 8, 12, 15, 22, and 29. The visits that include bloodwork must be conducted at the study site or arrangements made for sample collection at the subject's home or other appropriate location. Other visits/visit activities for that visit may be conducted remotely using telephone, telemedicine or other remote technique. Subjects are to self-collect a viral load sample, obtain their respiratory rate, heart rate, body temperature and SpO2, and complete a symptom assessment with the site via telemedicine on Days 1, 4, 8, 12, 15, 22, and 29. The site will also have a telephone call with the subject on Study Days 2, 3, 5, 6, and 7 for changes in concomitant medications and assessment of adverse events, especially those that may indicate thrombocytopenia and mucositis. Screening and study Day 1 are to be conducted at the site unless the site is unable to accommodate in-person visits. If the site is unable to accommodate in-person visits, a home visit may be arranged as long as first dose can be achieved within 7 days of symptom onset. Days 8, 15, and 29 require in-person visits and will be conducted via home visit. Any in-person visit may also have telemedicine or telephone components if all study activities cannot be completed in person. Telemedicine only visits will be conducted by site staff on study Days 4, 12, and 22.

Sample Size:	Approximately 100 subjects will be randomized to 5 days of either SOC + brequinar 100 mg or SOC + placebo in a 1:1 ratio (approximately 50 subjects assigned to brequinar 100 mg and 50 subjects to placebo).
Number of Sites:	Approximately 15
Study Period:	An enrollment period of 3 months is expected.
Inclusion Criteria:	1. Willing and able to provide informed consent for the trial, written, electronic, verbal, or other method deemed acceptable by the institution and IRB. 2. 18 years of age or older. 3. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other FDA-approved commercial or public health assay. 4. Out-patient (never hospitalized as an in-patient for COVID-19 or was evaluated/treated for COVID-19 only in the Emergency Room with a stay of < 24 hours). 5. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men and women treated or enrolled on this protocol must also agree to use adequate contraception for the duration of study participation, and for 90 days after completion of brequinar administration. 6. Male subjects must agree to refrain from sperm donation and female subjects must agree to refrain from ovum donation from initial study drug administration until 90 days after the last dose of brequinar. 7. Must have at least one COVID-19 symptom including but not limited to fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, shortness of breath, dyspnea, anosmia, dysgeusia, or other symptom commonly associated with COVID-19 in the opinion of the investigator. Symptom onset must be ≤7 days prior to first dose. Subject must have one or more symptoms at first dose. 8. Able to swallow capsules.
Exclusion Criteria:	1. Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient

	2. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test 3. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide) or other agents known to cause bone marrow suppression leading to thrombocytopenia 4. Platelets ≤150,000 cell/mm^3 5. Hemoglobin < 10 gm/dL 6. Absolute neutrophil count < 1500 cells/mm^3 7. Renal dysfunction, i.e., creatinine clearance < 30 mL/min 8. AST or ALT > 2 x ULN, or total bilirubin > ULN. Gilbert's Syndrome is allowed. 9. Bleeding disorders or blood loss requiring transfusion in the six weeks preceding enrollment 10. Ongoing gastrointestinal ulcer, or gastrointestinal bleeding within 6 weeks of first dose. 11. Chronic hepatitis B infection, active hepatitis C infection, active liver disease and/or cirrhosis per subject report. 12. Heart failure, current uncontrolled cardiovascular disease, including unstable angina, uncontrolled arrhythmias, major adverse cardiac event within 6 months (e.g. stroke, myocardial infarction, hospitalization due to heart failure, or revascularization procedure).
Treatment	All subjects will receive standard of care (SOC) including symptomatic care. Subjects will be randomly assigned to SOC + brequinar 100 mg daily x 5 or SOC + placebo daily x 5. Study encounters will be conducted remotely whenever possible.
DMC	A Data Monitoring Committee (DMC) will meet periodically to review the safety and scientific conduct of the study. At a minimum, the DMC is to review adverse events and safety laboratory assessments after the first 20 subjects complete Day 8, and again after the first 40 subjects complete Day 8.
Procedures	Study procedures are outlined in the Schedule of Events. Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF.
Safety/ Tolerability	**Safety/Tolerability** Adverse events will be collected from the time of first dose through Day 29. After Day 29, collect/record only Serious Adverse Events (SAEs) or those judged by the

	Investigator or designated person to be related to study drug. Treatment-emergent adverse events will be those with an onset after the date and time of first treatment. Subjects who develop Grade 3 or 4 toxicities or SAEs are to be re-evaluated every 2 days, as feasible, until the toxicity returns to Grade ≤ 2 severity. During assessment for adverse events, investigators and site staff are to elicit from the subject any signs or symptoms of mucositis or thrombocytopenia, e.g.: • Ecchymosis/purpura/petechiae • Epistaxis • Hemoptysis • Hematuria • Gingival bleeding • Prolonged bleeding time from needle sticks, abrasions or lacerations • Hematemesis • Rectal bleeding • Blood in stool • Any other unusual bleeding noted by the subject or caregiver
Stopping Criteria	Individual Criteria: • Participants who develop a Grade 3 toxicity that is assessed by the investigator to be related to the study drug are to be permanently discontinued from study treatment. • Participants who develop a Grade 4 toxicity, regardless of relatedness to study drug, are to be permanently discontinued from study treatment. Study-Level Stopping Criteria: Study enrollment is to be paused if any of the below criteria are met: • If ≥ 3 subjects develop the same related Grade 4 (life-threatening) adverse event or laboratory abnormality; • If ≥ 5 subjects develop the same related Grade 3 or 4 adverse event or laboratory abnormality; • If ≥ 10 subjects develop any related Grade 3 or 4 adverse event or laboratory abnormality. All adverse events will be reviewed by the DMC during their reviews. Following assessment by the Data Monitoring Committee (DMC), the DMC will determine whether to stop the study, amend the protocol, or continue the study per protocol.
Statistical Analysis	A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. All analyses of safety and efficacy for this study will be descriptive in nature and presented by group. Subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. Summaries for quantitative variables will include the mean, median, quartiles,

	standard error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the 95% CI, when appropriate. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.4 or higher). Safety and tolerability will be assessed in terms of AEs, SAEs, and safety laboratory data. Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of treatment-emergent adverse events, defined as TEAEs occurring after first dose will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results and other clinical measures will be summarized using appropriate descriptive statistics.

CCB-CRISIS-02 **Schedule of Events** **Windows are relative to first dose time** **Procedures**	**Screen (D -7 to -1) IPV[f]**	**D1 IPV**	**D2, 3 (± 8 hrs) TC[f]**	**D4 (± 8 hrs) TM**	**D5, 6, 7 (± 8 hrs) TC**	**D8 (± 8 hrs) IPV+TM**	**D12 (± 1 day) TM**	**D15 (± 1 day) IPV+TM**	**D22 (±1 day) TM**	**Final Visit D29 (± 2 days) IPV+TM**
Informed Consent (note Date and Time)	X									
AE/Concomitant Medications (dose, route, duration or ongoing)	X	X	X	X	X	X	X	X	X	X
Medical history (relevant within one year or ongoing)/ History of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection)	X									
Demographics (subject reported height and weight, date of birth, gender, race, ethnicity)	X									
Check for Physical Exam abnormalities (subject self-reported)	X									
Pregnancy Test (WOCBP) (serum at Screen and urine at D29)	X									X
Hematology/Chemistry[a]	X	X				X		X		
Vital Signs[b]	X	X		X		X	X	X	X	X
Symptom Assessment[c]	X	X		X		X	X	X	X	X
SARS-CoV-2 RT-PCR[d]	X									
Viral load sample (Day 1 pre-dose)[e]		X		X		X	X	X	X	X
Hospital Status						X		X	X	X
WHO Ordinal Scale Assessment		X				X		X	X	X
Confirm Eligibility		X								
Randomize subject and dispense Study Medication		X								
Study drug administration (Days 1 – 5 only)[f]		X	X	X	X					
Drug Accountability						X				

[a]Do not repeat if within 48h of Day 1 visit. Send to Covance Central Laboratory Services (CCLS) for analysis.

[b]Vital signs include heart rate, respiratory rate, body temperature, SpO2. Subject will be provided with a thermometer and pulse oximeter with heart rate monitoring capability. Training will be provided during the first visit. Vital signs parameters will be observed and recorded by study staff via telemedicine or in-person visit (IPV) (at the study site or home visit by the home health nurse).

[c]Symptom Assessment will capture symptoms such as sore throat, cough, GI symptoms (vomiting, diarrhea), anosmia, dysgeusia, other (specify), etc. Severity None, Mild, Moderate, or Severe will be collected. Symptom(s) onset date must be within 7 days of first dose.

[d]Documentation of a positive SARS-CoV-2 result from RT-PCR or other FDA-approved test is required to qualify for Screening.

[e]Samples collected after Screening will be saliva samples sent for viral load analysis. Day 1 sample must be obtained prior to dosing. Viral load specimens after Screening will be saliva samples self-collected by the subject using an Omnigene® collection system or similar. The site staff or home health nurse will train the subject and observe sample collection on Day 1. These samples are to be sent to CCLS for analysis. The viral load sample may also be used to perform viral cultures (sample can be split by the central laboratory, no additional sample required).

[f]Subject will self-administer study drug once daily Days 1 – 5 and record doses in a medication diary. Note that any visits/visit activities may be conducted via telephone, telemedicine, or digital media other than serum pregnancy test and chemistry/hematology sample collection. These labs may be collected at the clinical site or another designated out-patient facility/laboratory or collected via home visit. Arrangements for shipping viral load samples will be made by the study team.

[f]IPV= in-person visit (subject's home or at clinical site, may also include TM or TC if all study visit activities cannot be completed by the in-person personnel); TC = Telephone Call with site and subject; TM = Telemedicine with site and subject.

STUDY PERSONNEL

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3 INTRODUCTION

3.1 Coronavirus-19 (COVID-19)

Beginning in December 2019, Chinese scientists isolated a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from patients with virus-infected pneumonia which was later designated as coronavirus disease 2019 (COVID-19) by the World Health Organisation (WHO) (Zhou et al., 2020 [2]; Phelan et al., 2020 [3]).

Approximately 14% of those affected with this virus will develop severe disease requiring hospitalization and oxygen support; 5% will require admission to the intensive care unit (Handel et al., 2020 [4]). Severe cases may be complicated by acute respiratory disease syndrome (ARDS), sepsis and septic shock, and multi-organ failure, including acute kidney injury and cardiac injury. Risk factors for death include older age and co-morbid disease such as hypertension and diabetes (Zhou, et al., 2020 [2]). This means that most patients will be treated as out-patients. Reducing viral load in this environment is critically important for both the subjects themselves by preventing worsening of symptoms and possibly avoiding hospitalization, but also to reduce the transmission of the disease to others in the patients' households and their communities.

3.1.1 Coronavirus Biology

Coronaviruses, like other RNA-based viruses, do not have the machinery to synthesize their own nucleotides and thus depend upon the host intracellular pool of nucleotides for viral replication. In essence, viruses steal the host RNA building blocks, and without these building blocks they are unable to replicate. The SARS-CoV-2 is a single-stranded (positive sense) RNA virus with a genome that is 29,811 nucleotides long, quite a lot larger than other RNA-based viruses (e.g. the hepatitis C genome comprises only 9600 nucleotides). The nucleotide composition is broken down as: 29.9% adenosines, 18.4% cytosines, 19.6% guanines, and 32.1% uridines (Sah et al., 2020 [12]).

3.2 Host Nucleotide Synthesis

Host *de novo* pyrimidine synthesis generates uridine monophosphate (UMP) as the building block for all pyrimidine ribonucleotides and deoxyribonucleotides (**Error! Reference source not found.**). There exists no salvage pathway for the synthesis of UMP, the fundamental building block of pyrimidines. Inhibition of enzymatic steps upstream of UMP (Figure 3-1) leads to a rapid and profound depletion of intracellular pyrimidines.

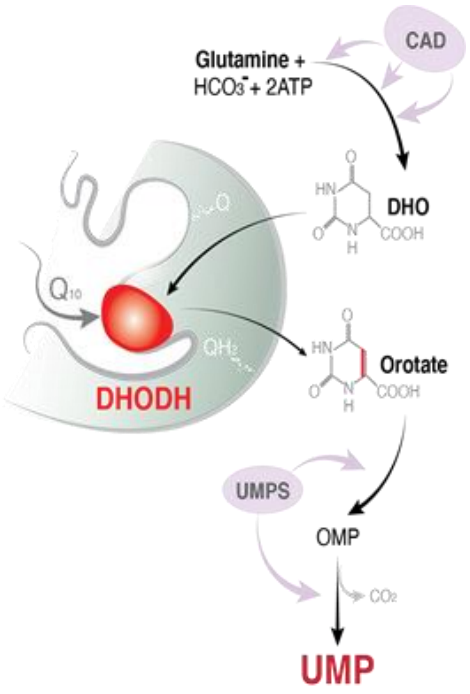

Figure 3-1. DHODH is a mitochondrial enzyme that catalyzes the 4th step of pyrimidine synthesis; it is completely essential for the generation of UMP.

3.3 Dihydroorotate dehydrogenase (DHODH)

The enzyme dihydroorotate dehydrogenase (DHODH) catalyzes the 4th step of *de novo* pyrimidine synthesis and inhibition of DHODH completely halts all pyrimidine production. As shown in Figure 3-1, DHODH is located on the inner mitochondrial membrane and transfers electrons between DHO and complex III of the electron-transport chain via the reduction of its ubiquinone (coenzyme Q10) cofactor.

DHODH is a clear therapeutic target for the inhibition of host pyrimidine synthesis. The chemical inhibition of DHODH *in vitro* or *in vivo* leads to the rapid depletion of UMP and subsequent depletion of downstream products thymine and cytosine. This forces a cell to rely on the salvage of extracellular pyrimidine nucleotides and this extracellular salvage is not capable of maintaining the cell's normal nucleotide pool (Sykes et al., 2016) [1]).

3.4 Brequinar

Brequinar is an orally available and potent inhibitor of DHODH. Brequinar is one of more than 300 quinoline-carboxylic acid derivatives prepared in an analog synthesis program in the 1980s, which was started after it was found that a compound of this class had antitumor activity. Brequinar was selected by DuPont for further development as a potential clinical drug because of its activity against experimental tumors and because its water solubility made it relatively straightforward to formulate.

In an indication such as treating SARS-CoV-2 infection, brequinar will act as a host-targeting antiviral. It is an orally available and potent inhibitor of dihydroorotate dehydrogenase (DHODH), the enzyme

that catalyzes the fourth step in pyrimidine synthesis, namely the conversion of dihydroorotate (DHO) to orotate. DHODH inhibitors, including brequinar, inhibit *de novo* pyrimidine synthesis thereby leading to a depletion of a cell's pool of uridine, cytidine and thymidine ribonucleotides and deoxyribonucleotides.

The antiviral activity of brequinar has been demonstrated in studies of rotavirus replication in human intestinal Caco-2 cells as well as in human primary intestinal organoids (Chen et al., 2019 [6]). Treatment with teriflunomide, another DHODHi, has been effective *in vitro* and *in vivo* in a murine model of foot and mouth disease virus (Mei-Jian et al., 2019 [7]). DHODH inhibition (DHODHi) also inhibited the growth of dengue virus *in vitro* (Wang et al., 2011 [8]). DHODHi also showed antiviral effects against RNA viruses including influenza A, Zika, Ebola and coronavirus SARS-CoV-2 (Xiong et al., 2020 [11]**).** Brequinar has also been shown to inhibit the replication of Ebola virus, vesicular stomatitis virus and Zika virus *in vitro* (Luthra et al., 2018 [9]). Brequinar inhibits the replication of human immunodeficiency virus (HIV) *in vitro* (Andersen et al., 2019 [10]). When considering brequinar as an antiviral for treatment of SARS-CoV-2, oral brequinar is highly bioavailable (>95%) and has good penetration of lung tissue with an average tissue:blood ratio of 0.5 following a single dose of brequinar in the rat. It is therefore expected to achieve a similar period of DHODH inhibition in lung tissue (Brequinar IB [5]).

3.5 Rationale for the Planned Trial

DHODH inhibition has been extensively studied as a potential therapeutic target in the treatment of RNA-based viruses. The inhibition of DHODH is effective in inhibiting viral replication in pre-clinical models involving many RNA-based viruses with nanomolar potency and a high selectivity index (see the Brequinar IB [5], Section 5). In these pre-clinical models, the benefit of DHODH inhibition can be reversed by the supplementation of exogenous nucleotides, confirming that the on-target effect of host pyrimidine depletion is key to the anti-viral activity.

The CCB-CRISIS-02 trial will study standard of care (SOC) with 5 days of brequinar (DHODH inhibition) compared to SOC with 5 days of placebo treatment. Clear Creek Bio hypothesizes that a defined 5-day course of brequinar will inhibit the enzyme DHODH to a degree sufficient to result in the transient depletion of host pyrimidine nucleotides, thereby inhibiting viral replication. A recent publication demonstrated that inhibitors of DHODH could potentiate the activity of inhibitors of RNA-dependent RNA polymerase (RdRp) in the treatment of dengue virus, another single-stranded RNA virus similar to SARS-CoV-2 (Liu et al., 2020 [13]). This inhibition of viral replication may restore the balance in favor of the host immune system for the clearance of SARS-CoV-2.

Marketed DHODHi medications are available, including leflunomide or teriflunomide, however these are very weak inhibitors of DHODH with cellular potency ~500 times lower than brequinar. These low potency inhibitors of DHODH are not expected to have the ability to acutely lower the pool of intracellular pyrimidines to the degree that is required for decreasing the viral load associated with SARS-CoV-2 infection, making brequinar the better choice for acute SARS-CoV-2 infection.

The CRISIS2 study is a proof-of-concept study in patients with SARS-Cov-2 infection and will serve as a basis for future studies to determine the safety and effectiveness of brequinar in COVID-19.

3.5.1 Brequinar Dose Selection

Safety data from previous oncology clinical studies of brequinar with 5 days of consecutive daily dosing suggest that 5 days of daily doses of 100 mg p.o. will be safe and well tolerated. A dose of brequinar 100 mg achieves plasma concentrations of approximately 1 uM (0.4 ug/ml) that should result in sufficient suppression of nucleotide synthesis. When given over 5 days, these plasma concentrations are achieved on a daily basis without accumulation, also assuring the safety of this regimen (see Brequinar IB [5]).

3.5.2 Risk/Benefit of Brequinar

As presented in the Brequinar IB [5], an extensive safety and pharmacokinetic database exists with more than 1,000 patients treated with brequinar. Cancer patients (N = 806) have been exposed to this compound for treatment of a variety of solid tumors at various treatment regimens, doses, and routes including a single dose, once weekly, twice weekly, single dose every 3 weeks, daily times 5 every 4 weeks, and daily times 21 days for multiple courses. Lower doses than used in the cancer studies have also been utilized for patients with psoriasis and organ transplant. The maximum intravenous dose given was 2,250 mg/m^2 every 3 weeks, and the maximum oral dose was 100 mg/m^2 daily for 21 days. There has been limited testing of DHODHi to date in the clinic for infection with SARS-CoV-2. DHODHi therapy at relatively high doses in the context of trials for patients with cancer has the expected safety side-effects of mucositis and bone marrow suppression. Importantly, however, the prior clinical experience in 39 subjects who received daily brequinar for 5 consecutive days at or lower than 100 mg/day show no cases of mucositis and only 1 (2.6%) episode of mild thrombocytopenia. Based on these data the 100 mg per day dose proposed for administration in this study should be within a safe and tolerable range as well as demonstrating the predicted antiviral effect.

The potential benefit in using brequinar to treat SARS-CoV-2 infection is the hypothesis that a 5-day period of brequinar dosing will suppress host *de novo* pyrimidine synthesis for this period thus decreasing viral load. Inhibition of DHODH is expected to reduce the ability of the virus to replicate and it is for this reason that brequinar will be administered to patients with COVID-19 in this study.

3.6 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration of high-dose brequinar in patients with refractory solid tumors, reversible myelosuppression, in particular thrombocytopenia, and mucositis have been the primary dose-limiting toxicities. In addition, skin rash, nausea/vomiting, fatigue, and leukopenia have been dose-limiting in trials utilizing other schedules of brequinar administration. However, these effects were self-limiting, transient, required treatment in few cases, and resolved following discontinuation of dosing. These adverse effects have been associated with higher doses of brequinar given via the intravenous route and for longer durations than the 100 mg dose and 5-day regimen proposed for this study.

In addition to studying a higher risk population with symptomatic COVID-19, a comprehensive safety monitoring plan will be utilized in this study to assess the ongoing safety and well-being of participants (see Section 10.8).

3.7 Possible Interactions with Concomitant Medical Treatments

Brequinar has been administered to subjects taking a variety of concomitant medications that are typical in severely ill cancer patients including antibiotics, antifungals and other critical care medications. No formal interaction studies have been conducted for these medications, however, there have not been any reports of interactions with any medications during the clinical trials with more than 800 cancer patients.

3.7.1 CYP Interactions

No formal clinical drug-drug interaction studies have been performed for brequinar with medications commonly used in treating hematologic malignancies. The nonclinical studies performed to date have demonstrated there is no first-pass metabolism and there have been no apparent hepatotoxic effects in the clinical studies. Brequinar itself does not appear to be a substrate for metabolism by cytochrome P450 enzymes when tested under a variety of conditions. (See Brequinar IB [5]; nonclinical data on file with Clear Creek).

3.8 Steps to be Taken to Control or Mitigate Risks

All subjects will be treated by highly experienced clinicians familiar with the treatment of viral infections and their complications.

4 TRIAL OBJECTIVES

4.1 Primary Objective

To demonstrate a change from baseline in quantitative SARS-CoV-2 viral load for brequinar-treated subjects compared to placebo-treated subjects through Day 29.

4.2 Secondary Objectives

The secondary objectives of this study are:

Through Day 29:

- To characterize the safety and tolerability of brequinar in out-patient COVID-19 subjects as measured by frequencies of grade 3 and 4 AEs and SAEs;
- To demonstrate a shorter duration of viral shedding in subjects treated with brequinar compared to subjects who received placebo;
- To reduce the percentage of subjects requiring hospital admission as an inpatient for >24 hours for brequinar subjects compared to subjects who received placebo;
- To reduce all-cause mortality through Day 29 for brequinar subjects compared to subjects who received placebo.

4.3 EXPLORATORY OBJECTIVES

Through Day 29:

- To determine time to viral clearance (two consecutive negative tests);
- To determine time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline;
- To determine time to clinical improvement as measured by a favorable shift in the WHO Ordinal Scale score for the subset of subjects with baseline WHO Ordinal Scale of 2 or 3 for brequinar subjects compared to subjects who received placebo.

5 TRIAL DESIGN

This will be a phase II randomized, placebo-controlled, double blind, multi-center study with approximately 100 subjects. All subjects will receive standard of care per (SOC) institutional guidelines for treatment of patients with COVID-19 infection. In addition to SOC, the subjects will self-administer one capsule once daily for 5 days.

Subjects must have at least one symptom consistent with SARS-CoV-2 infection according to the investigator and first symptom onset must be ≤7 days prior to first dose. Subjects will have a Screening Visit followed as soon as possible with Study Day 1. Study procedures are presented in detail in the Schedule of Events (Appendix 15.1). Study visits (virtual or in person) will take place at Screening and on Study Days 1 - 8, 12, 15, 22, and 29. The visits that include bloodwork must be conducted at the study site or arrangements made for sample collection at the subject's home or other appropriate location. Other visits/visit activities for that visit may be conducted remotely using telephone, telemedicine or other remote technique. Subjects are to self-collect a viral load sample. Subjects will obtain their own respiratory rate, heart rate, body temperature and SpO2 during telemedicine visits or study staff will collect these parameters during an in-person visit at the clinic or subject's home. The symptom assessment can be conducted with the study staff via telemedicine or in the clinic on Days 1, 4, 8, 12, 15, 22, and 29. The site will also have a telephone call with the subject on Study Days 2, 3, 5, 6, and 7 for changes in concomitant medications and assessment of adverse events, especially those that may indicate thrombocytopenia (see Section 10.8) and mucositis. An in-person visit will be conducted (at the clinic or home visit) at Screening and on study Days 1, 8, 15, and 29; in-person visits may be combined with telemedicine or telephone visits if all required study visit activities cannot be completed by the in-person personnel. Telemedicine only visits will be conducted by site staff on study Days 4, 12, and 22.

6 TRIAL ENDPOINTS

6.1 Primary Endpoint

Quantitative SARS-CoV-2 viral load through Day 29.

6.2 Secondary Endpoints

The secondary endpoints of this study are:

Through Day 29:

- Rates of AEs and SAEs including laboratory assessments;
- Duration of viral shedding;
- Percentage of subjects requiring admission as an inpatient for >24 hours.
- All-cause mortality.

6.3 Exploratory Endpoints

Through Day 29:

- Time to viral clearance (two consecutive negative tests);
- Time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline;
- Time to clinical improvement measured by a favorable shift in WHO Ordinal Scale score for the subset of subjects with baseline WHO Ordinal Scale of 2.

7 TRIAL POPULATION

7.1 Number of Subjects

Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 100 subjects have completed the study. Subjects will be randomized to either standard of care plus brequinar 100 mg or standard of care plus placebo in a 1:1 ratio (approximately 50 subjects assigned to standard of care plus brequinar 100 mg and approximately 50 subjects assigned to standard of care plus placebo).

7.2 Inclusion criteria

1. Willing and able to provide informed consent for the trial, written, electronic, verbal or other method deemed acceptable by the institution and IRB.
2. 18 years of age or older.
3. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other FDA-approved commercial or public health assay.
4. Out-patient (never hospitalized as an in-patient for COVID-19 or was evaluated/treated for COVID-19 only in the Emergency Room with a stay of < 24 hours).
5. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men and women treated or enrolled on this protocol must also agree to use adequate contraception for the duration of study participation, and for 90 days after completion of brequinar administration.
6. Male subjects must agree to refrain from sperm donation and female subjects must agree to refrain from ovum donation from initial study drug administration until 90 days after the last dose of brequinar.
7. At least one COVID-19 symptom including but not limited to fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, shortness of breath, dyspnea, anosmia, dysgeusia, or other symptom commonly associated with COVID-19 in the opinion of the investigator. Symptom onset must be ≤7 days prior to first dose. Subject must have one or more symptoms at first dose.
8. Able to swallow capsules.

7.3 Exclusion Criteria

1. Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient
2. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test
3. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide) or other agents known to cause bone marrow suppression leading to thrombocytopenia

4. Platelets ≤150,000 cell/mm^3
5. Hemoglobin < 10 gm/dL
6. Absolute neutrophil count < 1500 cells/mm^3
7. Renal dysfunction, i.e., creatinine clearance < 30 mL/min
8. AST or ALT > 2 x ULN, or total bilirubin > ULN. Gilbert's Syndrome is allowed.
9. Bleeding disorders or blood loss requiring transfusion in the six weeks preceding enrollment
10. Ongoing gastrointestinal ulcer, or gastrointestinal bleeding within 6 weeks of first dose.
11. Chronic hepatitis B infection, active hepatitis C infection, active liver disease and/or cirrhosis per subject report.
12. Heart failure, current uncontrolled cardiovascular disease, including unstable angina, uncontrolled arrhythmias, major adverse cardiac event within 6 months (e.g. stroke, myocardial infarction, hospitalization due to heart failure, or revascularization procedure).

8 STUDY TREATMENTS

8.1 Description of Study Medications

8.1.1 Brequinar

Brequinar and placebo will be supplied as 100 mg capsules. Dosing will be a single 5-day course of brequinar 100 mg capsules or placebo 100 mg capsules once daily for 5 doses.

8.2 Treatment Administration

This will be a phase 2 randomized, placebo-controlled, double blind, multi-center study with approximately 100 subjects. All subjects will receive standard of care (SOC) for COVID-19 infection. Subjects will be randomly assigned in a 1:1 ratio to standard of care plus brequinar or standard of care plus placebo.

8.2.1 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit. The *NIH Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria.

Adverse events (AEs) commonly observed in patients treated with brequinar are provided in the Investigator's Brochure (IB) and include thrombocytopenia, nausea, anemia, diarrhea, vomiting, leukopenia, stomatitis, rash, granulocytopenia, fatigue, and infection. In a study of 209 cancer subjects treated once-weekly (DuP 785-012, see Brequinar IB [5]), the deaths of three patients were attributed to study drug toxicity (two to hemorrhage, one following acute renal failure). Severe toxicities grades (Grades 3 to 4) which typically led to discontinuation in this study included hematologic toxicities (anemia, thrombocytopenia, leukopenia, granulocytopenia), digestive system toxicity (nausea, vomiting, stomatitis, others including gastric hemorrhage) and mucositis.

In three oncology studies with five consecutive days of intravenous (IV) brequinar dosing in 168 subjects (Study 785-001 [14], 785-003 [15], and 785-005 [16]) there were no toxic deaths. For subjects from these three studies who were treated with a daily dose of 100 mg or below (as will be dosed in CCB-CRISIS-02), AEs through 21 days showed that 2 of 39 subjects (5.1%) had a severe (Grades 3 or 4) AE related to study drug (1 subject each with hyperbilirubinemia and hyperglycemia), and no subjects discontinued from the study due to a study drug-related AE. The few study drug related AEs through 21 days at or below the 100 mg dose from these three studies included 2 subjects each with nausea, vomiting, and creatinine elevated and one subject each with thrombocytopenia and diarrhea. When only studies with oral dosing were considered at this dose level (Studies 785-022 [17], 785-031 [18] , and 785-034 [19]), the study drug related AEs through 21 days (each observed in one subject only) included diarrhea, headache, nausea, pruritus, abdominal pain, anorexia, chest pain, dry mouth, fatigue, keratosis, stomatitis, and vomiting. See brequinar IB [5].

In most instances, brequinar-related toxicities were transient, clinically manageable, and reversible upon discontinuation of brequinar treatment. Any of these events reported with brequinar use can be serious in nature and may result in death.

A 5-day course of oral brequinar administered once daily at a low level relative to those administered in the cancer studies is expected to be safe and well tolerated in the COVID-19 population.

8.3 Study Discontinuation

Subjects will remain in the study through at least Study Day 29 (or longer if needed to follow up study drug-related adverse events). Participants may discontinue from the study by withdrawing consent at any time or for any reason as presented in Section 9.7.

8.4 Stopping Criteria

8.4.1 Individual Stopping Criteria

- Participants who develop a Grade 3 toxicity that is assessed by the investigator to be related to the study drug are to be permanently discontinued from study treatment.
- Participants who develop a Grade 4 toxicity, regardless of relatedness to study drug, are to be permanently discontinued from study treatment.
- Subjects who develop Grade 3 or 4 toxicities are to be followed by re-evaluation every 2 days, as feasible, until the toxicity returns to ≤ Grade 2 severity.

8.4.2 Study-Level Stopping Criteria

Study enrollment is to be paused if any of the below criteria are met:

- If ≥ 3 subjects develop the same related Grade 4 (life-threatening) adverse event or laboratory abnormality;
- If ≥ 5 subjects develop the same related Grade 3 or 4 adverse event or laboratory abnormality;
- If ≥ 10 subjects develop any related Grade 3 or 4 adverse event or laboratory abnormality.

Following assessment by the Data Monitoring Committee (DMC, see Section 10.9), the DMC will determine whether to stop the study, amend the protocol, or continue the study per protocol.

8.5 Concomitant Medication/Treatment

Record the name, dose, start/stop date, indication for use, route, and whether ongoing or stopped for medications/treatments taken within two weeks prior to study entry as well as any medications taken during the study are to be recorded. Prohibited medications are identified in Section 8.8.

8.6 Treatment Compliance

Compliance will be assessed by reviewing the subject's medication diary and study records as appropriate.

8.7 Storage, Stability, Labeling and Packaging

8.7.1 Storage and Stability

The study drug is stored at room temperature. Stability testing is ongoing.

8.7.2 Labeling and Packaging

The bulk drug and unit-dose containers will be labeled in accordance with national laws and regulations.

8.7.3 Blinding and Randomization

The trial will be conducted in double blinded, randomized manner with random assignment to standard of care plus brequinar or standard of care plus placebo. The brequinar and placebo capsules will be provided to each participating institution in pre-numbered bottles intended for individual subjects to be dispensed by the institution's pharmacist or designated person. Randomization assignments will be provided by an independent statistician to the drug packaging company. The pharmacist/designated person will dispense the next number in sequence to the next patient who qualifies for the study at an individual site.

8.7.4 Unblinding/Expectedness

Contact the Covance Medical Monitor if it is necessary to break the blind for this blinded study due to an adverse event (AE). Each site will be provided with a sealed envelope containing individual sealed envelopes for subject numbers assigned to that site. Each individual subject number sealed envelope will have the treatment (brequinar or placebo) randomly assigned to that subject number. Do not open the outer envelope or the individual sealed envelope unless it has been agreed with the Medical Monitor and the Sponsor that unblinding is necessary for that particular AE. Unblinding must be documented in the study records. Envelope seals are to be checked to ensure they remain intact during drug accountability monitoring.

If after a discussion with the Medical Monitor, the investigator or treating clinician believes the AE leading to unblinding to be related to the study drug, no further doses of drug should be administered to that subject.

Expectedness will be determined by establishing whether an adverse event is among those identified in the protocol and the brequinar IB or are commonly associated with COVID-19 or similar severe viral illnesses and their complications.

8.7.5 Study Drug Accountability

The study drug provided is for use only as directed in this protocol.

The Investigator must keep a record of all study medication received, administered, and discarded. It must be clear from the records whether the subject received study medication and what subject number was assigned to which subject. Adequate drug is to be dispensed for the number of subjects expected to be treated at each institution.

The pharmacist/staff member responsible for drug accountability is to document the date and time of dispensing and for what subject the study drug was intended (i.e., record subject initials and birth date or other unique identifier). A pharmacy manual will be provided by the Sponsor.

At the end of the study any unused study drug will be returned to the Sponsor for destruction or may be destroyed locally; disposition of study drug will be documented.

The Sponsor will be permitted access to the trial supplies at any time within usual business hours and with appropriate notice during or after completion of the study to perform drug accountability reconciliation. Records may be electronic or paper and may be accessed remotely for monitoring/drug accountability purposes.

Each subject will be provided with one bottle with five brequinar or five placebo capsules for the five days of dosing.

8.8 Prohibited Medications

Treatment is prohibited with another DHODH inhibitor (e.g., leflunomide and teriflunomide). Treatment is prohibited with agents known to cause bone marrow suppression leading to thrombocytopenia.

8.9 Study Adjustments Due to COVID-19

Due to the highly contagious nature of COVID-19, multiple adjustments and revised procedures are rapidly evolving regarding clinical trial management and study conduct. Reasonable procedures implemented by study staff to avoid spreading this disease are acceptable to Clear Creek with written permission. Examples include but are not limited to e-consent, telephone consent and study visits conducted by telemedicine, telephone or other digital media.

Background standard of care is to be maintained in both treatment arms. The standard of care is expected to change as additional information, such as that from randomized controlled trials, emerges, and the Sponsor and the treating clinicians will need to address anticipated off-label use of any other drugs, devices, or interventions that might be used to manage COVID-19 (e.g. anticoagulants).

The Sponsor and treating clinicians are to consider changes in SOC over time, for example, overlapping toxicities of brequinar and a SOC treatment expected to be widely used is to be considered. The availability of new standard of care treatment may change over time and vary from one clinical trial site to another. The Sponsor will discuss these issues with FDA should the need arise.

9 CONDUCT OF THE TRIAL

9.1 Ethical and Regulatory Considerations

The trial will be performed in accordance with the Declaration of Helsinki (1964) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Scotland (2000, Note of Clarification 2002 & 2004) and Seoul 2008 (Appendix A), and Fortaleza (Brazil) (2013), and with the International Council on Harmonization (ICH) Tripartite Guideline on Good Clinical Practice (CPMP/ICH/135/95, Jan.97) and United States (US) FDA Regulations.

9.2 Informed Consent

The principles of informed consent in the current edition of the Declaration of Helsinki must be implemented in each clinical study before protocol-specified procedures are carried out. Informed consent must be obtained in accordance with US Code of Federal Regulations (21 CFR Part 50), the FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency (March 2020, Updated April 16, 2020) [20], as well as local and national regulations. Information should be given in both oral and written form whenever possible and deemed appropriate by the Institutional Review Board (IRB). Subjects and their relatives, if necessary, must be given ample opportunity to inquire about details of the study.

The Investigator or qualified designated person will verbally inform subjects as to the nature, expected duration and purpose of the trial, the administration of the Investigational Product (IP), and the hazards involved, as well as the potential benefits that may come from treatment with this IP. The trial procedures will be explained in lay language and any questions will be answered. The subjects will be given an IRB-approved consent form. The subjects will be given appropriate time to consider their participation in the trial and have any questions answered prior to signing the consent form. If a subject agrees to participate, he/she will sign and date an informed consent form and be provided with a copy of the signed consent. All subjects who sign an informed consent form are to be recorded on the applicable screening log. If the subject is unable to consent for any reason, a designated family member or healthcare power of attorney or other person may consent per institutional policy.

The subject will be informed that his/her medical records will be subject to review by the Sponsor, Sponsor's representatives, and possibly by a representative of the FDA and other relevant regulatory authorities. Subjects will be informed that they are free to refuse participation in this clinical investigation, and if they should participate, it will be made clear to them that they may withdraw from the trial at any time without prejudicing further medical care they may require. The subject will receive a copy of the consent form as well as an information sheet about the trial.

Informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to completing the informed consent process but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. Documentation of consent will be subject to review by the Sponsor; if in writing, a copy will be given to the subject and a copy will be filed with the subject's medical notes. Verbal consents will be documented by the study team as appropriate and agreed by the IRB.

Note that informed consent procedures have been affected by COVID-19, and the study staff may use any consent method that has been approved by the IRB (e.g., phone consent, verbal consent with

witness, e-consent, etc.) of the local institution. In-person consent, written consent signatures and providing hard copies to the subject are examples of procedures that may be foregone under these circumstances.

The study should be discussed with the potential participant only after an initial review of his/her clinical status and appropriateness for participation have been evaluated to determine if he/she meets the subject selection criteria.

A sample subject information sheet and consent form are available from Clear Creek. The final version at each institution may differ depending on institutional requirements and standard formats. This protocol will not be amended for site specific changes as such changes are to be made to the site's consent when required.

9.3 Institutional Review Board

It is the responsibility of the Investigator to submit the protocol, consent form and information sheet to the IRB. An IB will be available for review by the IRB. The protocol and informed consent form (ICF) must be approved by the IRB prior to the recruitment of the first subject. The template consent form may be revised in accordance with site-specific requirements with Sponsor review and approval. A copy of the IRB written approval must be provided to the Sponsor and investigator before the trial may start at that institution. Written approval from the IRB is also required for substantial protocol amendments prior to their implementation.

A substantial amendment may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments are "substantial" when they are likely to have an impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any IP used in the trial.

If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects, the Investigator will notify the Sponsor and the IRB of the new events and the measures taken as soon as possible.

The Investigator will report promptly to the Sponsor and IRB any new information that may adversely affect the safety of the subjects or the conduct of the trial. On completion of the trial, the Investigator will inform the applicable IRB as per local IRB requirements that the trial has ended. If the study is terminated for any reason, the investigator will return all clinical supplies and study-related equipment supplied by the Sponsor to the Sponsor unless otherwise specified.

9.4 Schedule of Events

Study activities will be conducted or supervised by experienced personnel throughout the study based on the Schedule of Events. The subjects may self-collect the saliva sample for viral load testing and perform other study activities such as body temperature, heart rate, respiratory rate, SpO2, and

symptom assessments themselves with appropriate training. Equipment will be provided to the subject for study purposes including a pulse oximeter with heart rate monitoring capability and a thermometer. Telemedicine visits such as phone calls or other remote media are to be utilized as much as possible. Subjects may need to come to an out-patient facility or be visited by a home health professional for some study assessments.

See 15.1 Schedule of Events in Appendix A for the full list of study assessments and timings.

Blood chemistry tests include blood urea nitrogen (BUN), creatinine, alkaline phosphatase (ALK), alanine amino transferase (ALT), aspartate amino transferase (AST), total bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, calcium, lactate dehydrogenase (LDH), and C-reactive protein (CRP). Chemistry samples may be banked for future analyses.

Hematology tests include hemoglobin, hematocrit, complete blood count with full differential, and platelet count.

Viral load sampling is to be carried out on Days 1, 4, 8, 12, 15, 22, and 29. The subject is to self-collect saliva samples with appropriate training for this analysis. Samples may be banked for future analyses. The subject must have a documented positive SARS-C0V-2 result to be eligible for Screening. Eligible subjects must have symptom(s) consistent with SARS-CoV-2 infection at time of randomization in the opinion of the investigator and onset of first COVID-19 symptom must be ≤ 7 days prior to first dose.

Safety laboratory results (chemistry and hematology) are to be reviewed by investigator or designated site personnel within 48 hours of receipt of results.

Hospitalization status after enrollment is to be recorded as not hospitalized or admitted to hospital as an in-patient with admission > 24 hours.

As much of the study as possible will be conducted via telemedicine remote from the site (e.g., consent, medical history, concomitant medications may be collected remotely). Subjects will be visited at home (or place of residence) by a home health nurse or come to the site for an in-person visit at Screening and on study Day 1. The subjects will be visited at home for Study Days 8, 15, and 29. On study Days 4, 12, and 22 the vital signs and saliva collections will be observed via telemedicine by the study site staff. Site staff will have a telephone call with subjects on study days 2, 3, 5, 6, and 7 to assess changes in concomitant medications and to assess adverse events, especially those that may indicate thrombocytopenia, e.g., unusual bruising, epistaxis, gingival bleeding, etc., and mucositis. Subjects will be provided with a pulse oximeter and thermometer during the Screening or Day 1 visit, as well as being trained on the use of these devices during the visit. Training will also be provided for the saliva collection required for viral load testing. Assessments will be recorded by the study staff during home and clinic visits and by the site staff during telemedicine visits. These data will be entered in the eCRF by the site staff or as determined by the study team.

9.5 Study Conduct

The study visits are to be conducted as shown in the Schedule of Events, Appendix 15.1.

Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF.

9.5.1 Unscheduled Visits

Unscheduled visits and tests are permitted as needed to assess AEs/SAEs throughout the study. Unscheduled visits and tests are also permitted as needed to assess AEs/ SAEs with onset within two (2) weeks after the final study visit providing the AE is considered related to study drug

9.6 Compliance with Study Procedures

The time at which study procedures are conducted should follow the protocol timelines as closely as possible. However, it is recognized in a clinical setting that protocol-specified timings may not occur exactly as specified in the protocol, particularly when conducted remotely by the subject. Provided that activities are carried out within the identified windows it will not be necessary to file a protocol deviation. Remote visits such as a telemedicine visit may be conducted to collect as much information as possible remotely. A home visit or return to the clinical site or an out-patient laboratory may be arranged for safety labs or other assessments, when required. Telemedicine or other remote technique is to be utilized to ensure subject compliance when subject is performing self-collection of study assessments.

9.7 Early Withdrawal from the Study

A subject may withdraw from the study at any time for any reason or for one of the reasons listed below. The Sponsor or Investigator may also terminate a subject's study participation after discussion with the other party if it is believed it would be unsafe for the subject to continue in the study.

Subjects must discontinue study medication if any of the following events occur:

- Significant protocol violation or non-compliance, either on the part of the subject or the investigator or other site personnel;
- Decision of the Investigator or Sponsor that removal is in the subject's best interest;
- Severe unrelated medical illness or complication;
- Safety reasons/ significant adverse event;
- Subject request (withdrawal of consent);
- Sponsor decision.

Collect/conduct all scheduled evaluations even for subjects who discontinue study medication prior to completing the treatment period unless consent is withdrawn.

9.8 Early Termination of the Study

If the Sponsor or an Investigator believes it would be unsafe to continue the study, or for any reason at the Sponsor's request, the study may be terminated at that site or the entire study terminated after discussion with the other parties.

The Sponsor will provide a written statement to the IRB and the relevant regulatory authority with the reasons for termination of the study. This will be conducted within 15 days of the decision to terminate the study.

If the study is terminated, a close out monitoring visit will be performed and applicable procedures will be carried out to close the trial site(s).

9.9 Non-Childbearing Potential

Women of non-childbearing potential are defined as those who have no uterus, ligation of the fallopian tubes, or permanent cessation of ovarian function due to ovarian failure or surgical removal of the ovaries. Documentation of surgical procedure or physical examination is required for subjects who have had a hysterectomy or tubal ligation. A woman is also presumed to be infertile due to natural causes if she has been amenorrheic for greater than 12 months and has an FSH greater than 40 IU/L. In the absence of such documentation, a negative serum pregnancy test is required for inclusion into the study.

10 ADVERSE EVENT REPORTING

An adverse event is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

Events that occur prior to first dose will be entered as medical history; events that occur after first dose will be entered as adverse events (AEs) on the AE form.

Subjects will be questioned and observed for evidence of AEs, whether or not judged by the Investigator or designated person to be related to study drug. All AEs will be documented in the subject's medical record and CRF. For any pre-existing condition or abnormal laboratory finding that changes in severity after dosing, this change should be recorded as an AE. New abnormal laboratory findings that are clinically significant are considered AEs. Investigators and site staff are to elicit from the subject and note any signs or symptoms of mucositis and thrombocytopenia (see Section 10.8).

Adverse events will be collected from the time of first dose through Day 29. After Day 29, collect/record only Serious Adverse Events (SAEs) which are assessed by the Investigator or designated person to be related to study drug and have an onset within 14 days of study completion (Day 29 or earlier if discontinue prior to Day 29). AE details are to be documented including start and stop date and times, whether continuous or intermittent, severity, any intervention utilized to correct the event (e.g., medication, surgery, or other therapy), outcome and the relationship to the study drug.

AEs identified in the protocol as critical to the evaluation of safety must be reported to the Sponsor by the Investigator according to the reporting requirements within the time periods specified in the protocol.

AEs determined by the Investigator to be related to study drug must be followed until resolution or until they are considered stable or for at least 30 days after discontinuation of study drug.

Abnormal laboratory values or test results occurring after study enrollment constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, are Grades 3 or 4, or require therapy.

If a death occurs during the SAE reporting period, the cause of death such as pneumonia, ARDS, or respiratory failure, is considered as the AE and the death is considered its outcome. Death should be considered an outcome, not an event. The event or condition leading to death should be recorded and reported as a single medical concept on the AE eCRF. Generally, only one such event should be reported. “Fatal” will be recorded as the outcome of this respective event; death due to an outcome of an AE will not be recorded as separate event. If the primary cause of death is disease progression, the cause of death should be clearly identified as COVID-19.

In cases of surgical or diagnostic procedures, the condition leading to the procedure is considered as the AE instead of the procedure itself. Each AE will be coded by the Sponsor from the verbatim text to a preferred term using a thesaurus based on the Medical Dictionary for Regulatory Activities (MedDRA). For example, record appendicitis, not appendectomy.

The following guidelines will be followed for the recording and reporting of adverse and serious adverse events.

1. The medical history section of the case report form will serve as the source document for baseline events.

    a. Baseline events are any medical condition, symptom, or clinically significant lab abnormality present before the informed consent is signed.

        i. If exact start date is unknown, month and year or year may be used as the start date of the baseline event.

2. Adverse events occurring after first dose are to be recorded in the eCRF using the AE form.

3. Serious adverse events will be reported to the local IRB according to institutional policy.

The *NIH Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017)* (https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf) will be used for adverse event reporting.

10.1 Follow Up of Grade 3 or 4 Toxicities

Grade 3 or 4 toxicities are to be followed by re-evaluation every 2 days, as feasible, until the toxicity returns to Grade ≤ 2 severity.

10.2 Infection Follow Up

Any new infection that occurs on study regardless of infecting agent (i.e., viral or non-viral) should be captured. Additionally, the site of infection and source of culture (BAL, tracheal aspirate, sputum, blood, urine, etc.) should also be recorded.

10.3 Classification of Causality

Attribution is the relationship between an adverse event or serious adverse event

and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment

Guidance for assessing causality:

The Investigator will need to determine whether an AE is considered related to ("caused by"') the study drug rather than some underlying condition, for example, COVID-19.

For the purposes of this study, 'drug related' shall mean 'Definite', 'Probable' and 'Possible' relationship to drug as determined by the Investigator.

10.4 Classification of Severity

The NIH Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017) will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria.

AEs that are expected are subject to expedited reporting only if the adverse event varies in nature, intensity or frequency from the expected toxicity information that is provided in the Investigator Brochure.

10.5 Serious Adverse Event (SAE) Reporting

The regulatory definition of an SAE is any untoward medical occurrence or effect that at any dose fulfills one or more of these criteria:

- results in death;
- is life threatening (at the time of the event);
- requires in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability / incapacity
- is a congenital anomaly / birth defect;
- or is an event considered medically serious by the Investigator.

Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

A life-threatening adverse event is one that places the patient/subject, in the view of the Investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.

An unexpected adverse event is any adverse drug event, the nature or severity of which is not consistent with the applicable product information (e.g. IB for an unauthorized investigational product or summary of product characteristics for an authorized product).

Enter only one event as the reason for the SAE on the SAE form. Other non-serious events which did not directly result in the SAE should be detailed in the description section on the SAE form and listed separately as AEs if necessary. For fatal SAEs, report the cause of death as an SAE with a fatal outcome rather than reporting death as the SAE term.

Note that hospitalizations for the following reasons should not be reported as SAEs:

- Routine treatment or monitoring of COVID-19 infection, not associated with any deterioration in condition;
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent;
- Social reasons and respite care in the absence of any deterioration in the subject's general condition;
- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of an SAE given above.

ANY SERIOUS ADVERSE EVENT MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS) BY EMAIL TO THE SAE REPORTING EMAIL USING THE FORM PROVIDED. ENTER THE SUBJECT'S AVAILABLE INFORMATION INTO THE eCRF WITHIN 48 HOURS.

The subjects are to be identified in the immediate and follow-up reports by unique code numbers supplied by the sponsor. The email address for reporting SAEs can be found below and at the front of this protocol.

Reports relating to the subject's subsequent medical course following an SAE must be submitted to Covance Patient Safety until the event has subsided or, in case of permanent impairment, it stabilizes, and the overall clinical outcome has been ascertained.

SAE REPORTING EMAIL: SAEIntake@covance.com

Medical Monitor:

Norberto Soto, MD	Telephone:	(609) 212-7892
Covance Physician/Medical Monitor	Email:	Norberto.Soto@Covance.com

Sponsor Representative:

Barbara Powers, MSN, Ph.D.	Telephone:	M: (484) 686-0545
VP, Clinical Operations	Email:	bpowers@clearcreekbio.com

All SAEs will be reported to the IRB periodically, at the end of the study, or per local institutional guidelines.

10.6 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected, unexpected, serious adverse reactions (SUSARs) are SAEs that are both related to the study drug (Relationship = Related) and unexpected (not previously described in the investigator's brochure). All SUSARs will be reported in an expedited manner to the Sponsor or designee and IRB by the Investigators and to all relevant regulatory authorities by the Sponsor. Expectedness will be judged by the Covance Physician and site Investigator. It is critical that all SAEs are reported within the 24-hour guideline so that the expectedness determination can be made. SUSARs require immediate attention and expedited reporting to relevant regulatory authorities.

The Sponsor will ensure that all relevant information about **fatal or life-threatening** SUSARs are appropriately recorded and reported to the concerned Regulatory Authority and to the concerned

IRB(s) within seven (7) calendar days of the date of first report to Covance Patient Safety / Sponsor. Follow-up information will be communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs will be reported to the Regulatory Authority and to the IRB(s) concerned as soon as possible within a maximum of fifteen calendar days of first notification to Covance Patient Safety / Sponsor.

The Sponsor or designee will also inform all Investigators studying the investigational medicinal product about SUSARs and ensure that all IRBs have been notified.

For reported deaths of a subject, the Investigator shall supply the Sponsor and the IRB(s) with requested additional information on an expedited basis.

10.7 Pregnancies

Pregnancy occurring in a female subject or a subject's partner during the study period will be documented in the subject's source documents and reported to Covance Patient Safety (by email to SAEIntake@covance.com) and to the IRB by the investigational staff within 1 working day of their knowledge of the event. The collection period for a pregnancy occurring in a subject or a subject's partner will begin at the first dose of study drug and will continue through 90 days after the last dose of study drug. Monitoring of the subject or partner should continue until the conclusion of the pregnancy, if the subject or subject's partner has consented to this. Monitoring of the baby should continue for 3 months after birth, if the subject or subject's partner has consented to this.

Pregnancy itself is not an AE; it should be reported for tracking purposes. The Investigator or designee will discontinue the pregnant subject from the treatment aspects of the study, continue to follow her per protocol for safety outcomes only, and advise her to seek prenatal care and counseling from her primary care provider. Data on fetal outcome and breast-feeding will be collected for regulatory reporting and drug safety evaluation, if the subject has consented to this.

If the pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as (S)AEs.

The site clinical staff will request the pregnant subject to notify the site of the outcome of the pregnancy (i.e., birth, loss, or termination). To help ensure this, the site clinical staff will follow the subject until the end of pregnancy, with the subject's consent. This request and the subject's response will be documented in the subject's source document.

10.8 Safety Monitoring for Hematologic Toxicities

Myelosuppression is a known effect of DHODH inhibition that is associated with prolonged exposure and high doses. To reduce the risk of this effect with brequinar in COVID-19 subjects, the extensive brequinar safety database with over 1,000 patients has been evaluated to select a dose level expected to be safe and well tolerated with regard to hematologic toxicity. In addition to enhancing safety by

selecting a relatively brief 5-day exposure and a low brequinar dose, all subjects in the clinical trial will be under the care of highly qualified medical personnel. Clinically significant out-of-range laboratory results will be reported as adverse events.

In addition to real time assessments by the treating clinical team, the Covance Medical Monitor will assess the available hematology data on a periodic basis to identify any pathologic trends or safety issues. Any apparent increase in the expected rate or severity of hematologic safety events will be discussed with the Principal Investigators and the Sponsor. In addition, the Data Monitoring Committee (DMC) will assess available hematology data on a periodic basis to independently assess any pathologic trends or safety issues. If the rate or severity of hematologic toxicities appears to be above the expected rate or the severity appears worse than that expected, the trial enrollment will be suspended and no further subjects will be treated while a comprehensive data review is conducted. Depending on the outcome of the safety review the study may be stopped, the design adjusted, or the study may continue as designed. Individual and Study stopping rules are provided in Section 8.4.

Safety laboratory results are to be initially assessed in real time by the Principal Investigator or designated person. Any study drug-related clinically significant out-of-range laboratories or study drug-related adverse events will be followed as needed until resolution or stable.

The in-clinic assessments and telemedicine/phone call visits will specifically ask about possible hematologic toxicity including any evidence of the list below. Subjects will be provided with a list of the following events in lay terms and will be instructed to call the research team if any of these events occur.

- Ecchymosis/purpura/petechiae
- Epistaxis
- Hemoptysis
- Hematuria
- Gingival bleeding
- Prolonged bleeding time from needle sticks, abrasions or lacerations
- Hematemesis
- Rectal bleeding
- Blood in stool
- Any other unusual bleeding noted by the subject or caregiver

Any of these symptoms considered clinically significant will be recorded as an adverse event and must be followed until resolved or stable.

10.9 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established to provide independent oversight to this trial. The primary responsibility of the DMC will be to review the progress and conduct of the trial in order to maintain scientific rigor and to ensure the wellbeing of subjects participating in the trial. The specific responsibilities of the DMC will be detailed in a separate DMC charter. The DMC will include at a minimum at least one statistician and two clinicians who will perform periodic data review to assess whether there are clinically significant differences between treatment arms that could affect participant safety. All adverse events will be reviewed by the DMC during their reviews. Following

such a review, the DMC Chair will advise the Sponsor that the study be stopped, the design changed, or that the study may continue per protocol.

10.9.1 DMC Safety Review Schedule

The DMC is to review adverse events and safety laboratory assessments after the first 20 subjects complete the Day 8 visit, and again after the first 40 subjects complete the Day 8 visit.

11 STATISTICAL CONSIDERATIONS

A separate, detailed statistical analysis plan (SAP) will be finalized prior to locking the database. All analyses will be descriptive in nature and presented by group.

Summaries for quantitative variables will include the mean, median, quartiles, standard error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and 95% confidence interval (CI), when appropriate. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.4 or higher).

Subject disposition, subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. The following sections will briefly summarize of the planned statistical analyses and analysis sets for the primary and secondary endpoints.

11.1 Study Populations for Analysis

All safety analyses will be based on the ITT population, which is defined as all randomized subjects. As will be described in the SAP, efficacy analyses of changes in viral load will be based on the population of subjects with detectable viral load at baseline or similar qualification. Sample size may be adjusted if an inadequate number of subjects have detectable viral load at baseline.

11.2 Safety Analyses

Safety and tolerability will be assessed in terms of AEs, SAEs, WHO Assessments, and safety laboratory data.

Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of post-first dose (treatment-emergent) adverse events will be tabulated by MedDRA preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results and study assessments will be summarized using appropriate descriptive statistics.

11.3 Efficacy Analyses

Efficacy will primarily be assessed via viral load changes.

11.4 Sample Size Considerations

Formal sample size calculations are not applicable for this proof-of-concept study. The sample size of approximately 100 subjects planned to be entered in this trial is expected to be adequate to provide safety and efficacy information to advise future study design.

11.5 Randomization

A randomization scheme will be provided by an independent statistician to the drug packaging company to ensure subjects are randomly assigned to SOC + brequinar or SOC + placebo in a 1:1 ratio.

11.6 Pooling of Study Centers

Not applicable to this small, early phase study.

11.7 Interim Analysis

No interim analysis is planned for this trial.

12 INVESTIGATOR RESPONSIBILITIES

12.1 Investigator's Performance

The Investigator will ensure that all those concerned with conducting the trial are:

- provided with copies of the protocol and all safety information prior to the start of the trial;
- trained regarding the conduct of the study and the training has been documented.

The Investigator will sign the Investigator's Statement and Agreement found in Section 15.2 to indicate commitment to comply with the contents.

12.2 Confidentiality

The Investigator shall assure the subject that his/her identity will be protected and confidentiality will be maintained during all audits and inspections of the trial site and documentation. A unique number will be assigned to each subject at the start of the trial and this, with the subject's initials, will be used to identify the subject. In some cases, a further step may be taken to assign "fake initials" to the subject, per individual site requirements. The subject's number will be the site number followed by the number of this subject at this site and will be used as the unique identifier in the source records and on the eCRF, on all trial correspondence and in the trial database. The Investigator will keep a list of identification codes or initials used for each subject along with the unique number assigned.

All information provided to the Investigator relevant to the investigational product (IP), as well as information obtained during the course of the trial will be regarded as confidential. The Investigator and members of his/her research team agree not to disclose or publish such information in any way to any third-party without prior written permission from the Sponsor which will not be unreasonably withheld, except as required by law, or as permitted by the Publications section of this protocol, Section 12.7.

The Investigator will take all measures to ensure subject's confidentiality will be maintained at all times.

12.3 Source Documentation

Investigators are to maintain adequate source documentation of the original study data, for example medication records, laboratory reports and pharmacy records as appropriate. The Investigator will allow inspections of the trial site and documentation by clinical research and audit personnel from the Sponsor, external auditors or representatives of regulatory authorities. The purpose of these inspections is to verify and corroborate the data collected on the eCRFs. In order to do this, direct access to the subjects' medical or clinic records is necessary. The Investigator will ensure that certain information is contained in the medical or clinic written or electronic records of the subject and that the entries are signed and dated, as follows:

- sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories;
- a note on the day the subject entered the trial describing the trial number, the IP being evaluated, the trial number assigned to that subject and a statement that consent was obtained;

- a note of each subsequent trial visit including any concerns about AEs and their resolution;
- notes of all concomitant medication taken by the subject, including start and stop dates;
- a note of when the subject terminated from the trial, the reason for termination and the subject's general condition at termination;
- a copy of the signed informed consent form should be kept in the medical records of each subject during the clinical phase of the study. A signed copy should also be filed in the investigator file.

12.4 Data Collection

Suitably qualified and trained personnel at the trial site will ensure compliance with the protocol, adherence to ICH GCP obligations, proper maintenance of trial records including IP accountability records, correct administration of IP including storage conditions and accurate reporting of AEs. In addition, suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. All queries and discrepancies relating to the data collection are to be resolved at the completion of the trial. Remote data capture is encouraged whenever possible.

12.5 Case Report Forms, Investigator's Site File and Record Retention

The Sponsor may provide the CRFs in paper, electronic (eCRF), or other media. The forms will be reviewed against source documentation at each monitoring visit. All CRFs and supporting source documentation must be completed and available to the Sponsor in a timely manner. Changes or corrections due to data clarification and resolutions will be tracked by paper or electronically with an audit trail.

Prior to review of the case report forms by the Sponsor's representative, they should be reviewed for completeness and accuracy by the Investigator or a member of the research team.

The Investigator must maintain an Investigator Site File which includes, but is not limited to, the IB, the protocol plus any amendments, all correspondence with the IRB including the approval for the trial to proceed, Regulatory Authority approval/ notification (if applicable) including a sample of an approved informed consent, IP accountability, Source Documents, investigator and staff curricula vitae (CVs,) trial documentation, and all trial correspondence. The original signed informed consent forms and the final report will be kept in the Investigator Site File.

The Investigator will archive all essential documents. The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. The Investigator has a responsibility to retain essential documents for as long as is required by the Sponsor and applicable regulatory authorities. It is the responsibility of the Sponsor to inform the Investigator as to when these documents no longer need to be retained. Investigators will be asked to contact the Sponsor prior to the destruction of any data or removal to another site if this occurs prior to the Sponsor notification that the documentation is no longer required. Any transfer of ownership of the data or of documents will be documented in writing. The new owner will assume responsibility for data retention and archiving.

Should the Investigator retire, relocate, or for other reasons withdraw from the responsibility of keeping the trial essential documents, custody must be transferred to a person who will accept that responsibility, and the Sponsor must be notified in writing of the name and address of said person.

12.6 Non-Protocol Research

No investigational procedures other than those outlined in this protocol may be undertaken on the subjects in this trial without the prior written permission of the subject, the Sponsor, the IRB and, when appropriate, the regulatory authority.

12.7 Publication

The Sponsor acknowledges the benefit of making widely available the results of all clinical trials and intends to publish the results of this trial. All publications resulting from the clinical trial must be in a form that does not reveal technical information that the Sponsor considers confidential or proprietary. A copy of any abstract, presentation or manuscript proposed for publication must be submitted to the Sponsor for review at least 30 days before its submission for any meeting or journal. In addition, if deemed necessary by the Sponsor for protection of proprietary information prior to patent filing, the Investigator agrees to a further delay of 60 days before any presentation or publication is submitted. The Sponsor reserves the right to include the report of this trial in any regulatory documentation or submission or in any informational materials prepared for the medical profession.

Authorship determination will be at the discretion of the Sponsor and will include evaluation of the following criteria: Investigator must participate in the review of and content of the protocol; review and comment on the study results; participate in the writing, reviewing and commenting of the manuscript; and approve the final manuscript for submission.

13 SPONSOR RESPONSIBILITIES

13.1 General

The Sponsor agrees to adhere to the ICH Note for Guidance on GCP (CPMP/ICH/135/95, Jan.97) and US FDA Regulations. It is the Sponsor's responsibility to obtain appropriate regulatory approval to perform the trial (if applicable). The Sponsor should notify promptly all concerned investigator(s), IRB(s) and the Regulatory Authority of findings that could adversely affect the health of the patients/ subjects, impact on the conduct of the trial or alter the Regulatory Authority's authorization to continue the trial. If it is necessary to change or deviate from the protocol to eliminate an immediate hazard to the subjects the Sponsor will notify the relevant regulatory authority and relevant IRB of the new events, the measures taken and the plan for further action as soon as possible. This will be by telephone in the first instance followed by a written report.

On completion of the trial, the Sponsor will inform the regulatory authority that the trial has ended. If the study is terminated for any reason the Sponsor will provide a written statement to the relevant regulatory authority and the IRB with the reasons for termination of the trial. This will be conducted within 15 days of the decision to terminate the trial. The Sponsor will report in an expeditious manner all SUSARs to the relevant regulatory authority and IRBs.

13.2 Indemnity

The Sponsor will provide compensation insurance against any risk incurred by a subject as a result of participation in this trial. The Sponsor will indemnify the Investigators as detailed in a separate document.

13.3 Data Monitoring

Suitably qualified and trained clinical research personnel of the Sponsor will visit the trial site or will access the electronic health record (EHR) or conduct remote monitoring visits at regular intervals during the trial for monitoring purposes and to assist the research staff with any queries. CRFs and source documentation will be available for review during monitoring visits to the trial site. The function of this monitoring is to ensure compliance with the protocol, adherence to regulatory and GCP obligations, proper maintenance of records including IP accountability records, correct administration of IP including storage conditions and accurate reporting of AEs. On-site visits are not required for any monitoring visits for this study.

Once the data from the case report forms have been entered onto the database, they will be reviewed, and the data verified against the subject's source data. Any discrepancies will be tracked by paper or electronically with an electronic audit trail.

13.4 Audit

The Sponsor has an obligation to audit a proportion of studies. A department other than the clinical department will undertake this obligation. Therefore, the Sponsor, an independent auditor or a regulatory authority may audit the trial site and trial documentation. These audits may take place while the trial is being conducted or up to several years later.

13.5 Confidentiality

The Sponsor will not keep any material on file bearing any subject's name, and subjects' confidentiality will be maintained at all times.

13.6 Finance

This will be the subject of a separate agreement between the Investigator/Institution and Sponsor.

14 REFERENCES

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14. Study DUP 785-001 Clinical Study Report (on file with Clear Creek)
15. Study DUP 785-003 Clinical Study Report (on file with Clear Creek)
16. Study DUP 785-005 Clinical Study Report (on file with Clear Creek)
17. Study DUP 785-022 Clinical Study Report (on file with Clear Creek)
18. Study DUP 785-031 Clinical Study Report (on file with Clear Creek)
19. Study DUP 785-034 Clinical Study Report (on file with Clear Creek)
20. FDA Guidance "COVID-19: Developing Drugs and Biological Products for the Treatment or Prevention (https://www.fda.gov/media/137926/download)

15 APPENDICES

15.1 Appendix A: CCB-CRISIS-02 Schedule of Events

CCB-CRISIS-02 Schedule of Events **Windows are relative to first dose time Procedures**	**Screen (D -7 to -1) IPV[f]**	**D1 IPV**	**D2, 3 (± 8 hrs) TC[f]**	**D4 (± 8 hrs) TM**	**D5,6,7 (± 8 hrs) TC**	**D8 (± 8 hrs) IPV+TM**	**D12 (± 1 day) TM**	**D15 (± 1 day) IPV+TM**	**D22 (±1 day) TM**	**Final Visit D29 (± 2 days) IPV+TM**
Informed Consent (note Date and Time)	X									
AE/Concomitant Medications (dose, route, duration or ongoing)	X	X	X	X	X	X	X	X	X	X
Medical history (relevant within one year or ongoing)/ History of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection)	X									
Demographics (subject reported height and weight, date of birth, gender, race, ethnicity)	X									
Check for Physical Exam abnormalities (subject self-reported)	X									
Pregnancy Test (WOCBP)	X (serum)									X (urine)
Hematology/Chemistry[a]	X	X				X		X		
Vital Signs[b]	X	X		X		X	X	X	X	X
Symptom Assessment[c]	X	X		X		X	X	X	X	X
SARS-CoV-2 RT-PCR[d]	X									
Viral load sample (pre-dose Day 1)[e]		X		X		X	X	X	X	X
Hospital Status						X		X	X	X
WHO Ordinal Scale Assessment		X				X		X	X	X
Confirm Eligibility		X								
Randomize subject and dispense Study Medication		X								
Study drug administration[f]		X	X	X	X D5 Only					
Drug Accountability						X				

[a]Do not repeat if within 48h of Day 1 visit. Send to Covance Central Laboratory Services (CCLS) for analysis.
[b]Vital signs include heart rate, respiratory rate, body temperature, and SpO2. Subject will be provided with a thermometer and pulse oximeter with heart rate monitoring capability. Training will be provided during the first visit. Vital signs parameters will be observed and recorded by study staff via telemedicine or in person (IPV) (at the study site or home visit).
[c]Symptom Assessment will capture symptoms such as sore throat, cough, GI symptoms (vomiting, diarrhea), anosmia, dysgeusia, other (specify), etc. Severity None, Mild, Moderate, or Severe will be collected. Symptom(s) onset date must be within 7 days of first dose.
[d]Documentation of a positive SARS-CoV-2 result from RT-PCR or other FDA-approved test is required to qualify for Screening.
[e]Samples collected after Screening will be saliva samples sent for viral load analysis. Day 1 sample must be obtained prior to dosing. Viral load specimens after Screening will be saliva samples self-collected by the subject using an Omnigene® collection system or similar. The site staff or home health nurse will train the subject and observe sample collection on Day 1. These samples are to be sent to CCLS for analysis. The viral load sample may also be used to perform viral cultures (sample can be split by the central laboratory, no additional sample required).
[e]Subject will self-administer study drug once daily Days 1 – 5 and record doses in a medication diary. Note that any visits/visit activities may be conducted via telephone, telemedicine, or digital media other than serum pregnancy test and chemistry/hematology sample collection. These labs may be collected at the clinical site or another designated out-patient facility/laboratory or collected via home visit. Arrangements for shipping viral load samples will be made by the study team.
[f]IPV = in-person visit (subject's home or at clinical site; may also include TM or TC if all study visit activities cannot be completed by the in-person personnel); TC = Telephone Call with site and subject; TM = Telemedicine with site and subject.

15.2 Appendix B: Investigator's Statement and Agreement

STUDY NUMBER: CCB-CRISIS-02

The CRISIS2 Study: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2.

INVESTIGATOR'S STATEMENT AND AGREEMENT

I (*the Investigator*) have read this protocol and hereby agree to conduct the trial in accord with all of its provisions. It is further agreed that the details of this trial and all information provided to me by Clear Creek Bio, Inc. (*the Sponsor*) will be held in the strictest confidence and will not be revealed for any reason without written authorization from Clear Creek Bio, Inc. except to those who are to participate in the conduct of the trial.

I agree that all data, the case report forms, and all materials provided for the conduct of the trial are the property of Clear Creek Bio, Inc. unless specified otherwise in writing. It is understood that Clear Creek Bio, Inc. will utilize the information derived from this trial in various ways, such as for submission to government regulatory agencies, required internal reports, and presentations without violating patient/ subject confidentiality in any way.

I further agree that Clear Creek Bio, Inc. or its representatives will be permitted access, in accordance with current Good Clinical Practice Guidelines, to all data generated by this trial and the source documents from which case report form data were generated.

PRINCIPAL INVESTIGATOR

Printed Name: _____

Signature: _____ Date: _____

15.3 Appendix C: WHO Ordinal Scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized: moderate disease	Hospitalized; no oxygen therapy*	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: severe disease	Hospitalized; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥ 200	7
	Mechanical ventilation pO_2/FiO_2 <150 (SpO_2/FiO_2 < 200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

WHO clinical progression scale