CCB-CRISIS-01

STUDY PROTOCOL

The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)

NCT04425252

Original Protocol Date: 03/31/2020

Amendment 01 Date: 04/10/2020

Amendment 02 Date: 05/01/2020

Amendment 03 Date: 06/05/2020

Amendment 04 Date: 07/06/2020

Amendment 05 Date: 07/31/2020

Amendment 06 Date: 08/05/2020

Amendment 07 Date: 09/10/2020

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16.1.1 Protocol and protocol amendments

Protocol dated 31March 2020

Protocol dated 10 April 2020

Protocol dated 05 June 2020

Protocol dated 06 July 2020

Protocol dated 31 July 2020

Protocol dated 05 August 2020

Protocol dated 10 September 2020

PROTOCOL NUMBER: CCB-CRISIS-01
PROTOCOL VERSION: FINAL Ver.1.0
DATE: 31MAR2020

CCB-01 Approvals and Revision History

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Revision History/Amendments:

Version Number	Date
1.0	31 March 2020

STUDY PROTOCOL

The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of combined suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)

Study No: CCB-CRISIS-01

Version Date: 31 March 2020

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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
BID	Bis in die (two times a day)
BRQ	Brequinar
BUN	Blood urea nitrogen
C6min	Concentration at 6 minutes
CHO/HGPRT	Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase
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
HER	Electronic health record
ESR	Erythrocyte Sedimentation Rate
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
IMPDH	Inosine-5’-monophosphate
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
SARS	Severe Acute Respiratory Syndrome
SOC	Standard of Care

Abbreviation	Definition
SPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
UMP	Uridine 5'-monophosphatase
US	United States
XMP	Xanthosine-5' phosphate
WHO	World Health Organization
WOCBP	Women of childbearing potential

2 SYNOPSIS

CCB-CRISIS-01 SYNOPSIS	
IND	149291
Title	The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of combined suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)
Protocol	CCB-CRISIS-01
Investigational Product and Dosage	Brequinar is available as 100 and 250 mg oral capsules. One 500 mg/m^2 dose is to be administered on Study Day 1. Ribavirin is available as 200 mg capsules. A dose of 400 mg is to be administered BID x 5 days (Study Days 1 – 5). Subjects will be randomized in a 1:1:1 ratio to either standard of care (SOC) alone, SOC + brequinar, or SOC + brequinar + ribavirin. Treatment assignment will be randomized, open label.
Primary Objective	● To determine the safety and tolerability of SOC, SOC plus brequinar, and SOC plus brequinar plus ribavirin in hospitalized COVID-19 subjects.
Secondary Objectives	● To determine the rates of/changes in clinical status measures listed through Day 15: – Mortality (assessed through Day 29) – Hospitalization status – Duration of hospitalization – NEWS2 Score
Exploratory Objectives	• To determine the change in nasopharyngeal viral load (if nasopharyngeal kit available, otherwise oropharyngeal) through Day 15 ● To determine the change in plasma viral load through Day 15 ● To determine the change in inflammatory markers through Day 15
Design	This will be a phase 1a randomized, open label, multi-center study with approximately 72 subjects. All subjects will receive SOC per institutional guidelines for treatment of patients with COVID-19 infection. In addition to SOC, the brequinar alone group will receive 1 dose of brequinar 500 mg/m^2. In addition

	to SOC, the brequinar plus ribavirin group will receive brequinar 500 mg/m^2 on Day 1 plus ribavirin 400 mg BID on Days 1 through 5. There are no restrictions on concomitant medications or treatments other than those contraindicated for use with ribavirin. Additional subjects may be enrolled following data review. Subjects will have a Screening Visit followed as soon as possible with Study Day 1 (Day 1 may take place on the same day if entry criteria data are available). Study procedures are presented in detail in the procedures section, see below. Subjects will be followed through Day 15 with mortality assessed at Day 29. If discharge occurs prior to Day 5 for subjects in the brequinar plus ribavirin treatment group, the subject will be provided with sufficient ribavirin to take at home to complete the treatment course. In this case, the subject is to return to the clinic for Day 7 and Day 15 visits. Study information such as vital signs is to be collected using the available EHR data when possible.
Sample Size:	Approximately 72 subjects will be randomized to either brequinar or brequinar plus ribavirin or standard of care in a 1:1:1 ratio (approximately 24 subjects on brequinar, 24 subjects on the brequinar plus ribavirin combination, and 24 assigned to standard of care). Additional subjects may be enrolled following data review.
Number of Sites:	1 - 5
Study Period:	An enrollment period of 3 months is expected.
Inclusion Criteria:	1. Willing and able to provide written informed consent for the trial (or designated care giver/healthcare power of attorney may consent if subject unable per institutional guidelines). 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-cleared commercial or public health assay. 4. Life expectancy > 48h in the opinion of the investigator. 5. Hospitalized (in patient with expected duration ≥ 24 hours) 6. The effects of brequinar on the developing human fetus are unknown and ribavirin is contraindicated in women who are pregnant as well as in the male partners of women who are pregnant. 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 treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study. participation, and for 90 days after completion of brequinar administration and for 6 months after completion of ribavirin administration. 7. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of brequinar and for 6 months after completion of ribavirin administration.
Exclusion Criteria:	1 In intensive care unit (ICU) or equivalent level of care or expected to require ICU level of care within next 24 hours. 2 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 3 Active malignancy other than squamous cell carcinoma; anticancer treatment such as chemotherapy or radiation therapy within the past month. 4 Estimated creatinine clearance < 50 mL/min. 5 Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test. 6 Treatment with ribavirin, mycophenolate, leflunomide or teriflunomide, didanosine, azathioprine, tacrolimus, sirolimus, or pre-existing prednisone at higher than 20 mg daily (ongoing or within 2 weeks of study entry). 7 Stevens-Johnson Syndrome or other hypersensitivity reactions to ribavirin or any component of the product.
Treatment	All subjects will receive standard of care (SOC) per institutional guidelines. Subjects will be randomly assigned to SOC alone or SOC plus brequinar alone (1 dose of brequinar 500 mg/m^2) or SOC plus brequinar plus ribavirin (brequinar 500 mg/m^2 on Day 1 plus ribavirin 400 mg BID on Days 1 through 5).
Procedures	**Screening Visit (Study Day -1)** These procedures must be completed within 24h prior to starting dosing. Obtain the subject's written informed consent (be sure to note time of consent), then collect baseline information.

	• Demographics (height, weight, date of birth, gender, race, ethnicity); body weight. • Pertinent medical/surgical history and concomitant medications. • History of current illness (date of first symptom, what symptoms is subject experiencing (e.g. fever, sore throat, cough, fatigue, short of breath) • Physical examination (including weight). • Pregnancy test for women of childbearing potential (WOCBP). • Hematology/chemistry including inflammatory markers as specified in the Laboratory Manual. • Vital Signs including pO_2 • Polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay for SARS-CoV-2 infection (may utilize test results from external laboratory to meet entry criteria provided such results are accurately documented and can be confirmed). • Samples for nasopharyngeal viral load (if nasopharyngeal available, otherwise oropharyngeal) and plasma viral load. • Serum sample for research purposes. • NEWS2 Criteria. • Confirm subject meets all inclusion and no exclusion criteria. **Treatment** The treatment period is up to 5 days: standard of care alone (SOC); or SOC + brequinar 500 mg/m^2 on Day 1 only; or SOC + brequinar 500 mg/m^2 only on Day 1 plus ribavirin 400 mg given twice daily on Days 1 – 5 (a total of 10 doses). Data points such as Vital Signs and safety labs are to be collected from the EHR when possible, a separate visit by study staff is not required. If subject is admitted and enrolled in the study between 12:00 PM and 8 AM, the first dose of brequinar is to be given as soon as possible. If assigned to the brequinar + ribavirin group, administer the brequinar as soon as possible and give the first ribavirin dose at the next occurring 8 AM or PM ± 4 h dosing time. If a subject's first ribavirin dose occurs in the PM, the subject will receive the final ribavirin dose on Day 6 in the AM.

	Days 1 – 7 (8 AM ± 4 hours): • Collect any adverse events or new concomitant medications since previous visit (may be omitted on Day 1 if Screening visit was conducted on same day as Study Day 1). • Collect daily samples for hematology/chemistry including inflammatory markers (may be omitted if Screening visit conducted on same day as Study Day 1). Ensure that Day 1 samples are obtained prior to first dose of study drug, if applicable. Collect serum sample for research purposes. • Collect Vital Signs including pO_2. • Collect NEWS2 Criteria. • Collect nasopharyngeal viral load samples (oropharyngeal may be substituted if not available) Days 1, 3, 5, 7. • Collect plasma viral load samples Days 1 – 7. • Record hospitalization status (hospitalized, hospitalized in ICU, discharged). • Dispense study medication (Day 1 only if in brequinar only group, brequinar + ribavirin Days 1 – 5 if assigned to this group and dispense ribavirin at 8 PM ± 4 hours on these days. **Final Visit Day 15** (8 AM ± 4 hours) • Collect information for any adverse events or new concomitant medications since Day 7. • Collect samples for hematology/chemistry including inflammatory markers and serum sample for research purposes. • Collect Vital Signs including pO_2. • Collect NEWS2 Criteria. • Collect nasopharyngeal viral load sample (oropharyngeal may be substituted if not available). • Collect plasma viral load samples • Collect hospital status (hospitalized, hospitalized in ICU, discharged). • Determine survival status (also at Day 29). Note: If discharge occurs prior to Day 5 for subjects in the brequinar plus ribavirin treatment group, the subject will be provided with sufficient ribavirin to take at

	home to complete the treatment course. In this case, the subject is to return to the clinic for Day 7 and Day 15 visits.
Safety/ Tolerability	**Safety/Tolerability** Adverse events will be collected beginning from the time of informed consent through at least 14 days after the final dose of study medication.
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 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). Subject demographics and baseline characteristics will be summarized. Subject data listings will also be provided. Safety and tolerability will be assessed in terms of AEs, SAEs, safety laboratory data, and vital signs. Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of treatment-emergent adverse events (TEAEs), defined as AEs 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, vital sign measurements, and other clinical measures will be summarized using appropriate descriptive statistics.

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3 INTRODUCTION

3.1 Background

3.2 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]).

3.2.1 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 [22]).

3.3 Host Nucleotide Synthesis

Host *de novo* nucleotide synthesis is divided into two arms: purine synthesis (A, G) and pyrimidine synthesis (U, T, C). Host *de novo* pyrimidine synthesis generates uridine monophosphate (UMP) as the building block for all pyrimidine ribonucleotides and deoxyribonucleotides (Figure 3-1). Host *de novo* purine synthesis has more redundancy with parallel paths of adenosine and guanosine synthesis.

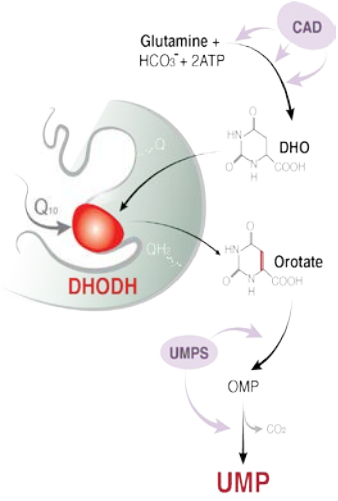

Figure 3-1. DHODH is a mitochondrial enzyme that catalyzes the 4th step of pyrimidine synthesis; it is completely essential for the generation of UMP.

These pathways of pyrimidine and purine synthesis are non-overlapping and differ in two salient aspects: [1] the pool of intracellular purines (A, G) tends to be larger than the pool of pyrimidines (U, T, C) and [2] there exists no salvage pathway for the synthesis of UMP, the fundamental building block of

pyrimidines. For these reasons, inhibition of enzymatic steps upstream of UMP (Figure 3-1) leads to a more rapid and more profound depletion of intracellular pyrimidines than inhibition of enzymatic steps upstream of GMP (Figure 3-2).

3.4 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.

3.5 Inosine monophosphate dehydrogenase (IMPDH)

Inosine monophosphate dehydrogenase (IMPDH) catalyzes the conversion of IMP to XMP en route to the *de novo* synthesis of GMP (Figure 3-2). Inhibition of IMPDH results in a depletion of intracellular guanosine monophosphate.

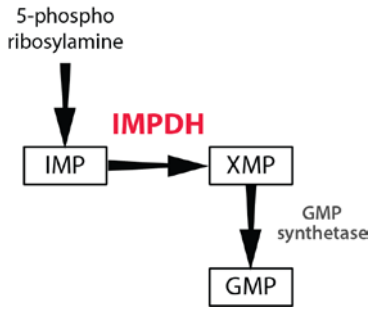

Figure 3-2. IMPDH catalyzes the conversion of IMP to XMP in the synthesis of guanosine monophosphate.

3.6 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.

The antiviral activity of brequinar has been demonstrated in studies of rotavirus replication in human intestinal Caco2 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 [13])**.** 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]).

3.7 Ribavirin

Ribavirin is an FDA-approved anti-viral agent and is marketed in combination with interferon alfa-2b for the treatment of chronic hepatitis C (ribavirin generic SPC, Appendix D, Section 15.4).

Ribavirin is a purine nucleoside analog with multiple mechanisms of action. It is known to inhibit the host enzyme inosine-5'-monophosphate dehydrogenase (IMPDH), the enzyme that catalyzes the conversion of inosine 5'-phosphate (IMP) to xanthosine 5'-phosphate (XMP), the first committed and rate-limiting step in the *de novo* synthesis of guanine nucleotides. In addition, ribavirin binds to and inhibits the SARS-CoV-2 viral enzyme – the RNA dependent RNA polymerase (RdRp) (Elfiky et al., 2020 [26]). And finally, another important mechanism of action that may contribute to ribavirin's antiviral effect is the ability to act as a ribonucleotide analog which can be incorporated into the viral RNA genome and lead to detrimental mutations in a process termed hypermutagenesis (Ortega-Prieto et al., 2013 [24]).

In pre-clinical studies, ribavirin has a demonstrated broad spectrum *in vitro* anti-viral activity and acts as an immunomodulator in a mouse hepatitis coronavirus model (Ning et al, 1998 [21]).

Ribavirin and mycophenolate mofetil (a more potent IMPDH inhibitor) were proposed for the treatment of MERS CoV infection with hints of clinical activity in small case studies (Ghamdi et al., 2016 [11]; Chong et al., 2015 [12]). Ribavirin as a single agent showed hints of activity in the previous SARS outbreak (Poutanen et al., 2003 [25]). Ribavirin and other IMPDH inhibitors are currently being proposed as possible treatments for the current COVID-19 pandemic (Gordon et al., 2020 [26]). Ribavirin as a single-agent may not be highly-effective based on the clinical progression of patients with SARS who were treated only with ribavirin (Peiris et al., 2003 [18]). There is currently an active combination trial of lopinavir/ritonavir, ribavirin and IFN-beta in Hong Kong for COVID-19 (NCT04276688).

3.8 Rationale for the Planned Trial

The CRISIS trial studies standard of care (SOC), SOC with DHODH inhibition, and SOC with DHODH inhibition and IMPDH inhibition. SOC is evolving rapidly for COVID-19 and at institutions includes approved FDA drugs such as lopinavir/ritonavir that have shown activity in coronaviruses. These may be combined into this trial.

In particular this trial combines brequinar – an inhibitor of host pyrimidine synthesis (DHODH) – with the anti-viral ribavirin, a nucleoside analog that acts as an inhibitor of host IMPDH and an inhibitor of the viral RNA dependent RNA polymerase (RdRp). In addition, the misincorporation of ribavirin as a nucleoside analog into the replicating viral genome will be accentuated because the dose of ribavirin will be diluted into a smaller pool of host nucleotides, thereby increasing its effective intracellular concentration (Liu et al., 2020 [27]).

The temporary depletion of the host pyrimidine and purine pools in combination with the ribavirin effect on viral RdRp is hypothesized to lead to a significant reduction in virus replication at a critical point in the COVID-19 disease, restoring the balance in favor of the host immune system for ultimate clearance of SARS-CoV-2. This combination has been recently been shown to be effective in a pre-clinical model of disease where the authors demonstrated that inhibitors of DHODH could potentiate the activity of inhibitors of RdRp in the treatment of dengue virus, another single-stranded RNA virus (Liu et al., 2020 [27]).

DHODH is already considered a potential therapeutic target in antiviral, oncology and autoimmune indications. Multiple doses of high-potency DHODH inhibitors are under investigation in the treatment of patients with hematologic malignancies. In addition to an anticancer effect when delivered in multiple high-doses, DHODHi may also prove effective in inhibiting viral replication by starving the host cell - and thus the replicating virus - of nucleotides, thereby acutely reducing the viral load in diseases such as COVID-19.

Emerging data from SARS-CoV-2 infections show peaks of viral load 5 to 6 days after the onset of symptoms; the viremia then resolves within 10-14 days. This may be distinct from previous coronavirus infections where viral loads peaked approximately 10 days after the start of symptoms (Peiris et al., 2003 [18]). The timed and transient inhibition of DHODH and depletion of host pyrimidine nucleotides during the early period of the disease is expected to suppress viral replication during its peak and decrease viral load, leading to a rapid resolution of clinical symptoms.

Due to the relatively short course of active viral replication in COVID-19, a single dose of brequinar administered at the right time may provide clinical benefit in patients requiring hospitalization due to the coronavirus infection. See Figure 3-3 for changes in viral load versus day of symptom onset in two patients with SARS-CoV-2 (Pan et al., 2020 [19]).

Clear Creek hypothesizes that the timed inhibition of DHODHi or DHODHi + IMPDHi and depletion of host pyrimidine and purine nucleotides during the period of increased viral load will suppress viral replication leading to a more rapid resolution of clinical symptoms.

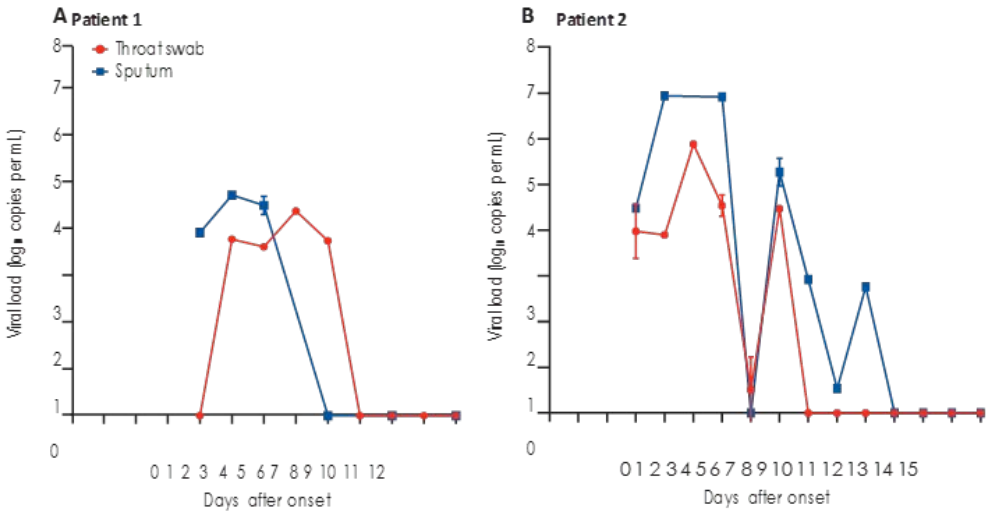

Figure 3-3. Changes in viral load versus day of symptom onset – COVID-19

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.

It is also hypothesized that the suppression of host nucleotide synthesis and therefore viral replication would be most effective early in the course of disease while there is still ongoing viral replication.

3.8.1 Brequinar Dose Selection

Safety data from previous oncology clinical studies of brequinar with maximum tolerated doses as high as 2250 mg/m^2 repeated every 3 weeks and from the active brequinar study in acute myeloid leukemia (AML) patients suggest that a single dose of 500 mg/m^2 p.o. will be safe and well tolerated. Brequinar has *in vitro* antiviral EC50s that range from 0.04-1.0 µM that equal 0.016-0.40 µg/mL of brequinar. If the effective concentration to inhibit 90% of virus replication (EC90) is assumed to be one log great, then a plasma concentration of 0.1-4 µg/mL would be needed. A single oral dose of 500 mg/m^2 maintains a plasma level of at least 4 µg/mL for 48-72 hours (see Brequinar IB [5]).

3.8.2 Ribavirin Dose Selection

Ribavirin is marketed in combination with interferon-alpha for treatment of chronic hepatitis caused by the RNA virus hepatitis C. The proposed dose for the COVID-19 study is based on the

ribavirin generic Summary of Product Characteristics (SPC) found in Section 15.4. In chronic hepatitis C patients, ribavirin at 400 mg BID has shown 13% anemia when combined with interferon. Ribavirin suppressed viral load with some activity when given for SARS in 2003 at 400 mg TID. At that dose, 8% (of 75) or 0% (of 31) patients developed anemia (Peiris et al., 2003 [18]; So et al., 2003 [28]). The CRISIS trial will administer ribavirin at the labelled dose of 400 mg BID for 5 days. Given the recent evidence in a pre-clinical dengue virus model of disease that the misincorporation of ribavirin as a nucleoside analog into the replicating viral genome will be accentuated because the dose of ribavirin will be diluted into a smaller pool of host nucleotides, the labeled dose of 400 mg two times a day (BID) chosen should provide optimal safety with the potential for a benefit in combination with brequinar (Liu et al., 2020 [27]).

3.8.3 Risk/Benefit of Brequinar

As presented in the Brequinar IB [5], more than 800 cancer patients 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. Brequinar has also been utilized in studies 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. While no DHODHi has been tested to date in the clinic for infection with SARS-CoV-2 and no brequinar safety information is available in treatment of this disease, DHODHi therapy in the context of trials for patients with cancer has the expected side-effects of mucositis and bone marrow suppression. Chronic DHODHi therapy in patients with autoimmune disease has the expected (and desired) effects on T-cell suppression (activated T-cells have a particular dependence on pyrimidine synthesis). However, a single, relatively low dose of brequinar such as that proposed for administration in this study should be safe, well tolerated and manifest none of these potential side-effects.

The possible benefit in using brequinar to treat SARS-CoV-2 infection is the hypothesis that a single dose of brequinar will suppress host *de novo* pyrimidine synthesis for a period of up to 72 hours thus decreasing viral load. As discussed above, inhibition of DHODH is expected to reduce the ability of the virus to replicate and it is for this reason that study CCB-CRISIS-01 will administer brequinar to patients with COVID-19.

3.9 Risk/benefit of Ribavirin

Risks associated with ribavirin administration in 40% or greater of adult patients receiving ribavirin with interferon included fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability. Additional safety information is provided in the ribavirin generic SPC (Section 15.4).

The possible benefit in using ribavirin to treat SARS-CoV-2 infection is the hypothesis that the expected suppression of host nucleotide synthesis associated with ribavirin will prevent viral replication when used in conjunction with brequinar thereby reducing viral load.

3.10 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration of 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 drug administration. The majority of these adverse effects have been less than grade IV in severity and resolve following discontinuation of dosing.

Risks associated with ribavirin administration in hepatitis C patients who also received interferon-alpha are presented in the ribavirin generic SPC found in Section 15.4. The most commonly reported adverse reactions in adult subjects receiving PegIntron or INTRON A in combination with ribavirin were fatigue/asthenia, headache, rigors, fevers, nausea, myalgia, and anxiety/emotional lability/irritability.

3.11 Possible Interactions with Concomitant Medical Treatments

While not previously tested in patients with viral infections, brequinar has been administered to subjects taking a variety of concomitant medications that are typical in cancer patients. 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. Brequinar has also been used concomitantly with antibiotics, antifungals and other critical care medications.

There is no experience with brequinar for treatment of SARS-CoV-2 and other severe viral infections and no formal interaction studies have been conducted.

Experience with use of ribavirin and interferon in treatment of hepatitis C has concluded that ribavirin should not be given with nucleoside reverse transcriptase inhibitors such as didanosine or with azathioprine. There is limited experience with ribavirin for treatment of SARS-CoV-2 and other severe viral infections and no formal interaction studies have been conducted for use of ribavirin with concomitant medications that are typical in these patients. Ribavirin should be taken with food, when possible. See ribavirin generic package insert, Appendix D Section 15.4.

3.11.1 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).

Results of in vitro studies using both human and rat liver microsome preparations indicated little or no cytochrome P-450 enzyme-mediated metabolism of ribavirin, with minimal potential for P-450 enzyme-based interactions (ribavirin generic SPC Appendix D Section 15.4).

3.12 Steps to be Taken to Control or Mitigate Risks

All subjects will be treated in a hospital setting by highly experienced infectious disease specialists and other qualified staff familiar with the treatment of severe viral infections and their complications.

4 TRIAL OBJECTIVES

4.1 Primary Objective

- To determine the safety and tolerability of standard of care (SOC), SOC plus brequinar alone and SOC plus brequinar plus ribavirin in hospitalized COVID-19 subjects.

4.2 Secondary Objectives

The secondary objectives of this study are:

- To determine the changes in clinical status measures listed through Day 15:
  - Mortality (assessed through Day 29)
  - Hospitalization status
  - Duration of hospitalization
  - National Early Warning System 2 Score (NEWS2) Score

4.3 EXPLORATORY OBJECTIVES

- To determine the change in nasopharyngeal viral load (if collection kits available, otherwise oropharyngeal) through Day 15
- To determine the change in plasma viral load through Day 15
- To determine the change in inflammatory markers through Day 15

5 TRIAL DESIGN

This will be a phase 1a randomized, open label, multi-center study with approximately 72 subjects. All subjects will receive standard of care per institutional guidelines for treatment of patients with SARS-CoV-2 infection. In addition to standard of care, the brequinar alone group will receive 1 dose of brequinar 500 mg/m^2. In addition to standard of care, the brequinar plus ribavirin group will receive brequinar 500 mg/m^2 on Day 1 plus ribavirin 400 mg BID on Days 1 through 5. There are no restrictions on concomitant medications or treatments other than those contraindicated for use with ribavirin (see ribavirin generic SPC, Appendix D Section 15.4).

Subjects will have a Screening Visit followed as soon as possible with Study Day 1 (Day 1 may take place on the same day if entry criteria data are available). Study procedures are presented in detail in Section 8. Subjects will be followed through Day 15, with mortality assessed on Day 29.

Additional subjects may be enrolled following data review.

If discharge occurs prior to Day 5 for subjects in the brequinar plus ribavirin treatment group, the subject will be provided with sufficient ribavirin to take at home to complete the treatment course. In this case, the subject is to return to the clinic for Day 7 and Day 15 visits.

Missed assessments for discharged subjects (e.g. those collected on Day 6) will not be considered protocol deviations.

Study information such as vital signs is to be collected using the available EHR data when possible.

6 TRIAL ENDPOINTS

6.1 Primary Endpoint

- Safety/tolerability measured by rates of treatment-emergent adverse events (TEAEs), safety labs, and vital signs.

6.2 Secondary Endpoints

- Rates of/changes to the below clinical status measures through Day 15.
  - Mortality (also assessed through Day 29)
  - Hospitalization status
  - Duration of hospitalization in days
  - NEWS2 Criteria daily Days 1 – 7, and Day 15 for hospitalized subjects.

6.3 EXPLORATORY Endpoints

- Nasopharyngeal viral load (if available, otherwise oropharyngeal): Day 1 (pre-dose), Days 3, 5, 7, and 15
- Plasma viral load Days 1 through 7 and Day 15
- Inflammatory markers (to be specified in the Laboratory Manual, may include but are not limited to erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), D-dimer, serum ferritin, and fibrinogen, pro-calcitonin, IL-6, MCP-1, IL-5, KC/GRO(CXCL1), IL-2, IFN-ɣ, final list to be determined) on Day 1 pre-dose, D2, D5, D8, D11, D15

7 TRIAL POPULATION

7.1 Number of Subjects

Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 72 subjects have completed the study. Additional subjects may be enrolled following data review. Subjects will be randomized to either brequinar or brequinar plus ribavirin or standard of care in a 1:1:1 ratio (approximately 24 subjects on brequinar, 24 subjects on the brequinar plus ribavirin combination, and 24 assigned to standard of care).

7.2 Inclusion criteria

1. Willing and able to provide written informed consent for the trial (or designated care giver/healthcare power of attorney may consent if subject unable per institutional guidelines).
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 Food and Drug Administration (FDA)-cleared commercial or public health assay.
4. Life expectancy > 48h in the opinion of the investigator.
5. Hospitalized (in patient with expected duration ≥ 24 hours)
6. 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 treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study. participation, and for 90 days after completion of brequinar administration and for 6 months after completion of ribavirin administration.
7. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of brequinar and for 6 months after completion of ribavirin administration.

7.3 Exclusion Criteria

1. In intensive care unit (ICU) or equivalent level of care or expected to require ICU level of care within next 24 hours.
2. 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.

3. Active malignancy other than squamous cell carcinoma; anticancer treatment such as chemotherapy or radiation therapy within the past month.
4. Estimated creatinine clearance < 50 mL/min.
5. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test.
6. Treatment with ribavirin, mycophenolate, leflunomide or teriflunomide, didanosine, azathioprine, tacrolimus, sirolimus, or pre-existing prednisone at higher than 20 mg daily (ongoing or within 2 weeks of study entry).
7. Stevens-Johnson Syndrome or other hypersensitivity reactions to ribavirin or any component of the product.

7.4 Inclusion of Women and Minorities

Adult men and women of all races and ethnic groups are eligible for this trial.

8 STUDY TREATMENTS

8.1 Description of Study Medications

8.1.1 Brequinar

Brequinar will be supplied as 100 and 250 mg capsules. Dosing will be a single oral dose of 500 mg/m^2. The initial brequinar dose should be administered as soon as possible based on the availability of the investigational pharmacy.

8.1.2 Ribavirin

Ribavirin will be supplied as 200 mg capsules. Ribavirin should be taken with food, when possible. Dosing will be 400 mg BID for 5 days (Days 1 – 5) approximately 8 AM and 8 PM ± 4 hours.

8.2 Treatment Administration

This will be a phase 1a randomized, open label, multi-center study with approximately 72 subjects. All subjects will receive standard of care (SOC) per institutional guidelines for SARS-CoV-2 infection. Subjects will be randomly assigned in a 1:1:1 ratio to standard of care alone, standard of care plus brequinar, or standard of care plus brequinar plus ribavirin. The brequinar alone group will receive 1 dose of brequinar 500 mg/m^2 on Day 1. The brequinar plus ribavirin group will receive brequinar 500 mg/m^2 on Day 1 along with ribavirin 400 mg BID x 5 days (study days 1 – 5).

8.2.1 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE).

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 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 most instances, brequinar-related toxicities were clinically manageable and reversible upon discontinuation of brequinar treatment. In a study where brequinar was dosed twice-weekly to solid tumor subjects, no drug-related deaths occurred. Stomatitis/mucositis was observed in 13 of the 19 (68%) patients across all doses. Mild to moderate (Grades 1 and 2) stomatitis was observed in 10 patients with a more severe (Grade 3) stomatitis seen in 3 patients at doses over 600 mg/m^2.

One patient at 600 mg/m^2 had drug discontinuation due to drug-related stomatitis. Myelosuppression was the main dose-limiting toxicity (DLT) with thrombocytopenia (Grades 1-4), observed after 2 to 9 doses above 600 mg/m^2. Three patients in the ongoing AML study experienced severe (Grade 3 or 4) mucositis following administration of two or more doses of brequinar. Any of these events reported with brequinar use can be serious in nature and may result in death.

A single dose of brequinar at a low level relative to those administered in the cancer studies noted above is expected to be safe and well tolerated in the COVID-19 population.

For ribavirin, the primary toxicity is hemolytic anemia which has been reported in approximately 13% of subjects taking ribavirin and interferon alfa-2a on a chronic basis in combination with PegIntron A for hepatitis C. The most commonly reported adverse reactions in adult subjects receiving PegIntron or INTRON A in combination with ribavirin were fatigue/asthenia, headache, rigors, fevers, nausea, myalgia, and anxiety/emotional lability/irritability. See the ribavirin generic SPC for complete ribavirin safety information (ribavirin generic SPC, Section 15.4). It is expected that the proposed acute use of ribavirin using the 400 mg BID x 5-day regimen will 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 15 (or longer if needed to follow up study medication-related adverse events). Mortality is assessed at Day 29.

After treatment, participants will be monitored through Study Day 15. Participants may discontinue from the study by withdrawing consent at any time or for any reason as presented in Section 9.7.

If discharge occurs prior to Day 5 for subjects in the brequinar plus ribavirin treatment group, the subject will be provided with sufficient ribavirin to take at home to complete the treatment course. In this case, the subject is to return to the clinic for Day 7 and Day 15 visits.

The reason for study discontinuation will be recorded in the source document and the eCRF.

8.4 Concomitant Medication/Treatment

Record the name, start date, indication for use, 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. The use of other DHODH inhibitors and IMPDH inhibitors are not permitted during the study including ribavirin, mycophenolate, leflunomide or teriflunomide (see Section 8.6.6).

8.5 Treatment Compliance

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

8.6 Storage, Stability, Labeling and Packaging

8.6.1 Storage and Stability

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

8.6.2 Labeling and Packaging

Each brequinar bottle/dispensing container for subject use will be labeled with at least the following information:

For Clinical Trial Use Only
Study Number: CCB-CRISIS-01
Contents: 100 or 250 mg Brequinar capsules
For oral use only. Take with approximately 8 ounces water.
Subject Number: XX-XXXX
Treatment Duration: As directed
Clinical Batch Number: XXXXXXX
Expiration Date: TBD
Storage: Store at controlled room temperature
Study Sponsor: Clear Creek Bio, Inc., 585 Massachusetts Avenue, 4th Floor, Cambridge MA 02139
Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

Each ribavirin bottle/dispensing container for subject use will be labeled with at least the following information:

For Clinical Trial Use Only
Study Number: CCB-CRISIS-01
Contents: Ribavirin capsules (dosing per body weight)
For oral use only. Take with approximately 8 ounces water and with food (when possible)
Subject Number: XX-XXXX
Treatment Duration: As directed
Clinical Batch Number: XXXXXXX
Expiration Date: TBD
Storage: Store at controlled room temperature
Study Sponsor: Clear Creek Bio, Inc., 585 Massachusetts Avenue, 4th Floor, Cambridge MA 02139
Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

8.6.3 Blinding and Randomization

The trial will be conducted in an open-label manner with random assignment to standard of care, standard of care plus brequinar or standard of care plus the brequinar plus ribavirin combination. The brequinar and ribavirin capsules will be provided to each participating institution in bulk to be dispensed by the institution's pharmacist per the designated mg/m^2 dose (for brequinar) and ribavirin 400 mg BID x 5 days for each subject. Randomization assignments will be provided by the sponsor.

8.6.4 Unblinding/Expectedness

It is not necessary to break the blind for this open label study as the treatment will be known for each subject.

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

8.6.5 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, used and discarded. It must be clear from the records whether the subject received study medication or was assigned to standard of care. 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 detailing how to calculate the mg/m^2 dose together with examples of combinations of the 100 and 250 mg capsules to provide the most efficient use of the clinical supplies.

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.

8.6.6 Prohibited Medications

The use of didanosine and azathioprine are not permitted during the study. The use of other DHODH inhibitors and IMPDH inhibitors such as mycophenolate, leflunomide or teriflunomide are not permitted during the study.

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) 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.

Signed written informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to signing the informed consent but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. An original signed informed consent form will be subject to review by the Sponsor; a copy will be given to the subject and a copy will be filed with the subject's medical notes.

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.

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

Physical examinations, vital signs, laboratory assessments, SARS-CoV-2 testing, and other observations will be conducted by experienced personnel throughout the study based on the Schedule of Events.

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 (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium), lactate dehydrogenase (LDH). Plasma will be collected for inflammatory markers such as D-dimer, ferritin, CRP, and ESR. Inflammatory markers will be specified in the Laboratory Manual. Serum is to be collected for research purposes.

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

Nasopharyngeal (or oropharyngeal, if nasopharyngeal unavailable) swabs for viral load will be collected Days 1, 3, 5, 7, and 15. Plasma viral load samples will be collected on Days 1 to 7, and Day 15.

NEWS2 Criteria are available in Appendix C Section 15.3.

Hospitalization status is to be recorded as hospitalized not in ICU, hospitalized in ICU, or discharged.

9.5 Study Conduct

Screening Visit (Study Day -1)

These procedures must be completed within 24h prior to starting dosing. Obtain the subject's written informed consent (be sure to note time of consent), then collect baseline information.

- Demographics (date of birth, gender, race, ethnicity).
- Pertinent medical/surgical history and concomitant medications.
- History of current illness (date of first symptom, symptom(s) subject is experiencing (e.g. fever, sore throat, cough, fatigue, short of breath)
- Vital signs (heart rate, respiratory rate, blood pressure, body temperature, oxygen saturation)
- Physical examination (including height and weight).
- Pregnancy test for women of childbearing potential (WOCBP).
- NEWS2 Criteria
- Polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay for SARS-CoV-2 infection (may utilize test results from external laboratory to meet entry criteria provided such results are accurately documented and can be confirmed).

- Samples for nasopharyngeal viral load (if nasopharyngeal available, otherwise oropharyngeal) and plasma viral load.
- Serum sample for research purposes.
- Confirm subject meets all inclusion and no exclusion criteria.

Treatment

The treatment period is up to 5 days: standard of care alone (SOC); or SOC + brequinar 500 mg/m^2 on Day 1 only; or SOC + brequinar 500 mg/m^2 only on Day 1 plus ribavirin 400 mg given twice daily on Days 1 – 5 (a total of 10 doses). Data points such as Vital Signs are to be collected from the EHR when possible, a separate visit by study staff is not required. If subject is admitted and enrolled in the study after 12:00 PM, the first dose of brequinar is to be given as soon as possible depending on available of investigational pharmacy staff. If the subject is assigned to the brequinar + ribavirin treatment arm, give the brequinar ASAP and dose the ribavirin at 8 AM/8 PM ± 4 h, whichever is closer. If discharge occurs prior to Day 5 for subjects in the brequinar plus ribavirin treatment group, the subject will be provided with sufficient ribavirin to take at home to complete the treatment course. In this case, the subject is to return to the clinic for Day 7 and Day 15 visits. If the first ribavirin dose is PM, the subject will need to be dosed on Day 6 AM in order to complete the 10 ribavirin doses.

It is understood that some assessments may not be conducted if the subject is unable to return to the clinic after discharge due to restricted travel, e.g., if an assessment is missed on Day 6 due to hospital discharge; this will not be counted as a protocol deviation.

Days 1 - 7:

- Collect any adverse events or new concomitant medications since previous visit (may be omitted on Day 1 if Screening visit was conducted on same day as Study Day 1).
- Collect daily samples for hematology/chemistry including inflammatory markers (may be omitted if Screening visit conducted on same day as Study Day 1). Ensure that Day 1 samples are obtained prior to first dose of study drug, if applicable. Collect serum sample for research purposes.
- Collect Vital Signs including pO_2.
- Collect NEWS2 Criteria.
- Collect nasopharyngeal viral load samples (oropharyngeal may be substituted if nasopharyngeal not available) Days 1, 3, 5, 7.
- Collect plasma viral load samples and serum for research sample Days 1 – 7.
- Record hospitalization status (hospitalized, hospitalized in ICU, discharged).
- Dispense study medication (Day 1 only if in brequinar only group, brequinar + ribavirin Days 1 – 5 if assigned to this group and dispense ribavirin at 8 PM ± 4 hours on these days.

If first ribavirin dose is PM due to admission timing, subject will receive last ribavirin dose AM of Day 6.

Final Visit Day 15

- Collect information for any adverse events or new concomitant medications since Day 7.
- Collect samples for hematology/chemistry including inflammatory markers and serum sample for research purposes.
- Collect Vital signs including pO_2.
- Collect NEWS2 Criteria.
- Collect nasopharyngeal viral load sample (oropharyngeal may be substituted if not available).
- Collect plasma viral load samples.
- Collect hospital status (hospitalized, hospitalized in ICU, discharged).
- Determine survival status (also at Day 29).

9.5.1 Unscheduled Visits

Unscheduled visits and tests to assess AEs are permitted as needed providing the AE onset occurs within two (2) weeks after the study dose.

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. Provided that activities are carried out within the identified windows it will not be necessary to file a protocol deviation.

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 be withdrawn from the study 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 evaluations for subjects who withdraw from the study prior to completing the treatment period, unless consent is withdrawn.

If discharge occurs prior to Day 5 for subjects in the brequinar plus ribavirin treatment group, the subject will be provided with sufficient ribavirin to take at home to complete the treatment course. In this case, the subject is to return to the clinic for Day 7 and Day 15 visits.

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).

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 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.

AEs will be collected beginning from the time of informed consent through at least 14 days after the final dose of study medication. 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.

Any serious adverse events (SAEs) experienced after 30 days post the last dose of study drug should only be reported to the sponsor if the investigator suspects a causal relationship to the 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, or require therapy.

Death due to disease progression should not be reported as an SAE. Report death from disease progression on the End of Study and Death forms.

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 progression of the disease under study.

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 descriptions and grading scales found in the revised National Cancer Institute (NCI) Common Terminology *Criteria for Adverse Events (CTCAE) version 4.03* will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html)*.

10.1 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.

10.2 Classification of Severity

The descriptions and grading scales found in the revised NCI CTCAE version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria. The CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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.

10.3 Serious Adverse Event (SAE) Reporting

The regulatory definition of an SAE is any untoward medical occurrence or effect that at any dose:

- 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, or
- is a congenital anomaly / birth defect;
- all other events that are 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 the studied indication, 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;
- Note that 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 is not an SAE.

Death due to disease progression is considered to be an Expected event in patients with severe SARS-CoV-2 infection and does not require reporting on an expedited basis.

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 and fax telephone number 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 the Sponsor contact until the event has subsided or, in case of permanent impairment, it stabilizes, and the overall clinical outcome has been ascertained.

SAE REPORTING EMAIL: Safety-CCB-CRISIS-01@prosoftclinical.com

Medical Monitor:

Sharon Levy, MD	Telephone:	O: (484) 320-2062

Sponsor Representative:

Barbara Powers, MSN, Ph.D.	Telephone:	M: 484-686-0545
	Email:	bpowers@clearcreekbio.com

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

10.4 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 Medical Monitor 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 is to 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 the Medical Monitor/Sponsor. Follow-up information is to be subsequently communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs are to 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 knowledge by the Medical Monitor/Sponsor.

The Medical Monitor/Sponsor or designee must 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.

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

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as 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-up with 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.

10.6 Data Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be established to provide independent oversight to this trial. The primary responsibility of the DSMB 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 DSMB will be detailed in a separate DSMB charter. The DSMB 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 DSMB Chair will advise the Sponsor that the study be stopped, a treatment arm dropped, or that the study may continue per protocol.

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 analyses will be based on the ITT population, which is defined as all randomized subjects.

11.2 Safety Analyses

Safety and tolerability will be assessed in terms of AEs, SAEs, Vital Signs, 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 (TEAEs), defined as AEs occurring after randomization, will be tabulated by MedDRA preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results and vital sign measurements will be summarized using appropriate descriptive statistics.

11.3 Efficacy Analyses

Efficacy will be assessed in terms of mortality, hospitalization status and duration, NEWS2 score, viral load (plasma and nasopharyngeal), and inflammatory markers.

11.4 Sample Size Considerations

Formal sample size calculations are not applicable for this phase 1a, open label study. Up to 72 subjects are planned to be entered in this trial. Additional subjects may be enrolled following data review.

11.5 Randomization

A randomization scheme will be provided by the Sponsor to ensure subjects are randomly assigned to SOC, SOC + brequinar, or SOC + the brequinar plus ribavirin combination in a 1:1:1 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 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.

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 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.

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.

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15 APPENDICES

15.1 Appendix A: CCB-01 Schedule of Events

CCB-CRISIS-01 Schedule of Events **Procedures**	**Screen**	**D1**	**D2 - D7**	**Final Visit D15**	**F/U Phone Call 2 weeks/Survival**
Informed Consent	X				
AE/Concomitant Medications	X	X	X	X	X
Medical history / History of current illness	X				
Demographics	X				
Physical Exam incl. height and weight	X	X			
Vital Signs including BP, pulse, respirations, temperature, pO_2	X	X	X	X	
Pregnancy Test (urine or serum)	X				
Hematology/Chemistry/Inflammatory Markers/Serum for research purposes	X	X	X	X	
Plasma collection for viral load		X (pre-dose)	X	X	
Swab collection for nasopharyngeal (or if collection kit not available, oropharyngeal) viral load		X (pre-dose)	D3, D5, D7	X	
Clinical SARS-CoV-2 testing	X			X	
Hospital Status		X	X	X	
NEWS2 Criteria	X	X	X	X	
Dispense Study Medication		X	X (D2 – 5 if assigned to ribavirin combination)	X	
Survival Assessment Day 29					X

15.2 Appendix B: Investigator's Statement and Agreement

STUDY NUMBER: CCB-CRISIS-01

STUDY TITLE: The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of combined suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19).

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: _____

Site Address:

_____

_____

15.3 Appendix C: National Early Warning Score (NEWS2)

Use SpO_2 Scale 2 if target range is 88 – 92%, e.g., in hypercapnic respiratory failure.

National Early Warning System Score (NEWS) 2 Royal College of Physicians 2017 [20]

15.4 Appendix D: Ribavirin generic (ribavirin USP) capsules, for oral use Summary of Product Characteristics (SPC)

RIBAVIRIN - ribavirin capsule
Aurobindo Pharma Limited

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RIBAVIRIN CAPSULES safely and effectively. See full prescribing information for RIBAVIRIN CAPSULES.

RIBAVIRIN capsules, for oral use
Initial U.S. Approval: 1998

WARNING: EMBRYO-FETAL TOXICITY, HEMOLYTIC ANEMIA, and MONOTHERAPY NOT RECOMMENDED

See full prescribing information for complete boxed warning.

- **Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy. (4, 5.1, 8.1, 8.3, 13.1)**
- **The hemolytic anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. (2.5, 5.2, 6.1)**
- **Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C. (5.10)**

INDICATIONS AND USAGE

Ribavirin capsules are a nucleoside analogue indicated in combination with interferon alfa-2b (pegylated and nonpegylated) for the treatment of Chronic Hepatitis C (CHC) in patients 3 years of age or older with compensated liver disease. (1.1)

Patients with the following characteristics are less likely to benefit from re-treatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection.

DOSAGE AND ADMINISTRATION

Ribavirin capsules are administered according to body weight. (2.1, 2.2, 2.3)
Dose reduction or discontinuation is recommended in patients experiencing certain adverse reactions or renal dysfunction. (2.5, 2.6, 12.3)

DOSAGE FORMS AND STRENGTHS

- Ribavirin Capsules USP 200 mg (3)

CONTRAINDICATIONS

- Pregnancy and men whose female partners are pregnant (4, 5.1, 8.1, 8.3)
- Known hypersensitivity reactions such as Stevens-Johnson syndrome, toxic, epidermal necrolysis, and erythema multiforme to ribavirin or any component of the product (4)
- Autoimmune hepatitis (4)
- Hemoglobinopathies (4)
- Creatinine clearance less than 50 mL/min (4, 12.3)
- Coadministration with didanosine (4, 7.1)

WARNINGS AND PRECAUTIONS

- Embryo-Fetal Toxicity: May cause fetal harm. Patients should have a negative pregnancy test prior to therapy and use effective contraception and undergo periodic pregnancy tests. (5.1, 8.1, 8.3)

Patients exhibiting the following conditions should be closely monitored and may require dose reduction or discontinuation of therapy:

- Hemolytic anemia may occur with a significant initial drop in hemoglobin. (5.2)
- Pancreatitis. (5.3)
- Pulmonary infiltrates or pulmonary function impairment. (5.4)
- New or worsening ophthalmologic disorders. (5.5)
- Severe decreases in neutrophil and platelet counts, and hematologic, endocrine (e.g., TSH), and hepatic abnormalities.

(5.6)
- Dental/periodontal disorders reported with combination therapy. (5.7)
- Concomitant administration of azathioprine. (5.8)
- Weight loss and growth inhibition reported during combination therapy in pediatric patients. Long-term growth inhibition (height) reported in some patients. (5.9)
- Monotherapy with ribavirin is not permitted. (5.10)

ADVERSE REACTIONS

Hemolytic anemia occurred in more than 10% of adult patients receiving ribavirin/PegIntron or INTRON A combination therapy. (6.1)
Most common adverse reactions (40% or greater) in adult patients receiving ribavirin/PegIntron or INTRON A combination therapy are injection site reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability. (6.1) Most common adverse reactions (greater than 25%) in pediatric patients receiving ribavirin/PegIntron therapy are: pyrexia, headache, neutropenia, fatigue, anorexia, injection site erythema, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aurobindo Pharma USA, Inc. at 1-866-850-2876 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Nucleoside analogues: Closely monitor for toxicities. Discontinue nucleoside reverse transcriptase inhibitors or reduce dose or discontinue interferon, ribavirin or both with worsening toxicities. (7.2)

USE IN SPECIFIC POPULATIONS

- Pediatrics: Safety and efficacy in patients less than 3 years old have not been established. (8.4)
- Organ transplant recipients: Safety and efficacy not studied. (8.6)
- Co-infected patients: Safety and efficacy with HIV or HBV co-infection have not been established. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY, HEMOLYTIC ANEMIA, and MONOTHERAPY NOT RECOMMENDED

- **Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple-dose half-life of 12 days and may persist in non-plasma compartments for as long as 6 months. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy. Effective contraception must be utilized during treatment and during the 6-month post-treatment follow-up period *[see Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.1, 8.3), and Nonclinical Toxicology (13.1)]*.**
- **Hemolytic anemia has been reported with ribavirin therapy. The anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin *[see Dosage and Administration (2.5), Warnings and Precautions (5.2)*, and *Adverse Reactions (6.1)]*.**
- **Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication *[see Warnings and Precautions (5.10)]*.**

1 INDICATIONS AND USAGE

1.1 Chronic Hepatitis C (CHC)

Ribavirin capsules in combination with interferon alfa-2b (pegylated and nonpegylated) are indicated for the treatment of Chronic Hepatitis C (CHC) in patients 3 years of age and older with compensated liver disease *[see Warnings and Precautions (5.9, 5.10), and Use in Specific Populations (8.4)]*.

The following points should be considered when initiating ribavirin capsules combination therapy with PegIntron® or INTRON A®:

- Combination therapy with ribavirin capsules/PegIntron is preferred over ribavirin capsules/INTRON A as this combination provides substantially better response rates *[see Clinical Studies (14)]*.
- Patients with the following characteristics are less likely to benefit from re-treatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection *[see Clinical Studies (14)]*.
- No safety and efficacy data are available for treatment duration lasting longer than one year.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Do not open, crush or break ribavirin capsules. Ribavirin capsules should be taken with food *[see Clinical Pharmacology (12.3)]*.

2.2 Ribavirin capsules/PegIntron Combination Therapy

Adult Patients

The recommended dose of ribavirin capsules when used in combination with PegIntron is 800 mg to

1,400 mg based on patient body weight in two divided doses (see Table 1). Refer to PegIntron labeling for PegIntron dosing information.

Duration of Treatment – Interferon Alpha-naïve Patients

The treatment duration for patients with genotype 1 is 48 weeks. Discontinuation of therapy should be considered in patients who do not achieve at least a 2 $\log_{10}$ drop or loss of hepatitis C virus (HCV)-RNA at 12 weeks, or if HCV-RNA remains detectable after 24 weeks of therapy. Patients with genotype 2 and 3 should be treated for 24 weeks.

Duration of Treatment – Re-treatment with PegIntron/Ribavirin capsules of Prior Treatment Failures

The treatment duration for patients who previously failed therapy is 48 weeks, regardless of HCV genotype. Re-treated patients who fail to achieve undetectable HCV-RNA at Week 12 of therapy, or whose HCV-RNA remains detectable after 24 weeks of therapy, are highly unlikely to achieve SVR and discontinuation of therapy should be considered *[see Clinical Studies (14.1)]*.

Table 1: Recommended Adult Dosing for Ribavirin capsules in Combination with PegIntron

Body Weight (kg)	Ribavirin capsules Daily Dose	Ribavirin Number of Capsules
Less than 66	800 mg/day	2 x 200 mg capsules AM 2 x 200 mg capsules PM
66 to 80	1,000 mg/day	2 x 200 mg capsules AM 3 x 200 mg capsules PM
81 to 105	1,200 mg/day	3 x 200 mg capsules AM 3 x 200 mg capsules PM
Greater than 105	1,400 mg/day	3 x 200 mg capsules AM 4 x 200 mg capsules PM

Pediatric Patients

Dosing of ribavirin capsules in pediatric patients is determined by body weight. The recommended dose of ribavirin capsules when used in combination with PegIntron in pediatric patients ages 3 to 17 years is 15 mg/kg/day in two divided doses (see Table 2). Refer to PegIntron labeling for PegIntron dosing information. The treatment duration for patients with genotype 1 is 48 weeks. Patients with genotype 2 and 3 should be treated for 24 weeks.

Table 2: Recommended Pediatric Ribavirin capsules Dosing in Combination with PegIntron

Body Weight (kg)	Ribavirin capsules Daily Dose	Ribavirin Number of Capsules
Less than 47	15 mg/kg/day	Use Ribavirin Oral Solution*
47 to 59	800 mg/day	2 x 200 mg capsules AM 2 x 200 mg capsules PM
60 to 73	1,000 mg/day	2 x 200 mg capsules AM 3 x 200 mg capsules PM
Greater than 73	1,200 mg/day	3 x 200 mg capsules AM 3 x 200 mg capsules PM

* Ribavirin Oral Solution may be used in any patient regardless of body weight.

2.3 Ribavirin capsules/INTRON A Combination Therapy

Adults

Duration of Treatment – Interferon Alpha-naïve Patients

The recommended dose of ribavirin capsules when used in combination with INTRON A depends on the patient's body weight (see Table 3). Refer to Intron A labeling for interferon dosing information. The recommended duration of treatment for patients previously untreated with interferon is 24 to 48 weeks. The duration of treatment should be individualized to the patient depending on baseline disease characteristics, response to therapy, and tolerability of the regimen *[see Indications and Usage (1.1), Adverse Reactions (6.1), and Clinical Studies (14)]*. After 24 weeks of treatment, virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV-RNA below the limit of detection of the assay by 24 weeks. There are no safety and efficacy data for treatment duration lasting longer than 48 weeks in the previously untreated patient population.

Duration of Treatment – Re-treatment with INTRON A/Ribavirin capsules in Relapse Patients

In patients who relapse following nonpegylated interferon monotherapy, the recommended duration of treatment is 24 weeks.

Table 3: Recommended Ribavirin capsules Dosing in Combination with INTRON A

Body Weight	Ribavirin Capsules
At least 75 kg	2 x 200 mg capsules AM 3 x 200 mg capsules PM daily orally
Greater than 75 kg	3 x 200 mg capsules AM 3 x 200 mg capsules PM daily orally

Pediatrics The recommended dose of ribavirin capsules when used in combination with INTRON A is 15 mg/kg per day orally in two divided doses (see Table 2). Refer to Intron A labeling for interferon dosing information.

The recommended duration of treatment is 48 weeks for pediatric patients with genotype 1. After 24 weeks of treatment, virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV-RNA below the limit of detection of the assay by this time. The recommended duration of treatment for pediatric patients with genotype 2 and 3 is 24 weeks.

2.4 Testing Prior to Initiation of Ribavirin capsules

The following laboratory tests are recommended in all patients treated with ribavirin capsules prior to initiation of treatment and periodically thereafter.

- Standard hematologic tests - including hemoglobin (pretreatment, Week 2 and Week 4 of therapy, and as clinically appropriate *[see Warnings and Precautions (5.2, 5.6)]*, complete and differential white

blood cell counts, and platelet count.
- Blood chemistries - liver function tests and TSH.
- Pregnancy - in women of childbearing potential.
- ECG *[see Warnings and Precautions (5.2)]*.

2.5 Dose Modifications

If severe adverse reactions or laboratory abnormalities develop during ribavirin capsules combination therapy, modify or discontinue the dose until the adverse reaction abates or decreases in severity (see Table 4) *[see Warnings and Precautions (5)]*. If intolerance persists after dose adjustment, combination therapy should be discontinued. Refer to PegIntron labeling for additional information regarding dose reduction of PegIntron.

Dose reduction in pediatric patients is accomplished by modifying the recommended ribavirin capsules dose from the original starting dose of 15 mg/kg daily in a two-step process to 12 mg/kg/day, then to 8 mg/kg/day, if needed (see Table 4).

Ribavirin capsules are contraindicated in patients with creatinine clearance less than 50 mL/min *[see Contraindications (4)]*. Patients with impaired renal function and those over the age of 50 should be carefully monitored with respect to development of anemia *[see Warnings and Precautions (5.2), Use in Specific Populations (8.5), and Clinical Pharmacology (12.3)]*.

Ribavirin capsules should be administered with caution to patients with pre-existing cardiac disease. Assess cardiovascular status before initiation of treatment and during therapy. If there is any deterioration of cardiovascular status, discontinue combination therapy *[see Warnings and Precautions (5.2)]*.

In patients with a history of stable cardiovascular disease, a permanent dose reduction is required if the hemoglobin decreases by 2 g/dL or more during any 4-week period. If the hemoglobin level remains below 12 g/dL after 4 weeks on a reduced dose, discontinue combination therapy.

Modify or discontinue ribavirin capsules dosing in any patient whose hemoglobin level falls below 10 g/dL (see Table 4) *[see Warnings and Precautions (5.2)]*.

Table 4: Guidelines for Dose Modification and Discontinuation of Ribavirin capsules in combination with PegIntron or INTRON A Based on Laboratory Parameters in Adults and Pediatrics

Laboratory Parameters	Reduce Ribavirin capsules Daily Dose (see note 1) if:	Reduce PegIntron or INTRON A Dose (see note 2) if:	Discontinue Therapy if:
WBC	N/A	1.0 to <1.5 x 10^9/L	<1.0 x 10^9/L
Neutrophils	N/A	0.5 to <0.75 x 10^9/L	<0.5 x 10^9/L
Platelets	N/A	25 to < 50 x 10^9/L (adults)	<25 x 10^9/L (adults)
	N/A	50 to <70 x 10^9/L (pediatrics)	<50 x 10^9/L (pediatrics)
Creatinine	N/A	N/A	>2 mg/dL (pediatrics)
Hemoglobin in patients without history of cardiac disease	8.5 to <10 g/dL	N/A	<8.5 g/dL
	Reduce Ribavirin capsules Dose by 200 mg/day and		

	PegIntron or INTRON A Dose by Half if:	
Hemoglobin in patients with history of stable cardiac disease*†	≥2 g/dL decrease in hemoglobin during any four-week period during treatment	<8.5 g/dL or <12 g/dL after four weeks of dose reduction

Note 1: *Adult patients:* 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

Pediatric patients: 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

Note 2: *Adult patients treated with ribavirin capsules and PegIntron:* 1st dose reduction of PegIntron is to 1 mcg/kg/week. If needed, 2nd dose reduction of PegIntron is to 0.5 mcg/kg/week.

Pediatric patients treated with ribavirin capsules and PegIntron: 1st dose reduction of PegIntron is to 40 mcg/m^2/week, 2nd dose reduction of PegIntron is to 20 mcg/m^2/week.

For patients on ribavirin capsules/INTRON A combination therapy: reduce INTRON A dose by 50%.

* Pediatric patients who have pre-existing cardiac conditions and experience a hemoglobin decrease greater than or equal to 2 g/dL during any 4-week period during treatment should have weekly evaluations and hematology testing.

† These guidelines are for patients with stable cardiac disease. Patients with a history of significant or unstable cardiac disease should not be treated with PegIntron/ribavirin capsules combination therapy *[see Warnings and Precautions (5.2)]*.

Refer to labeling for INTRON A or PegIntron for additional information about how to reduce an INTRON A or PegIntron dose.

2.6 Discontinuation of Dosing

Adults In HCV genotype 1, interferon-alfa-naïve patients receiving PegIntron in combination with ribavirin, discontinue therapy if there is not at least a 2 $\log_{10}$ drop or loss of HCV-RNA at 12 weeks of therapy, or if HCV-RNA levels remain detectable after 24 weeks of therapy. Regardless of genotype, previously treated patients who have detectable HCV-RNA at Week 12 or 24 are highly unlikely to achieve SVR and discontinuation of therapy should be considered.

Pediatrics (3 to 17 years of age) In patients receiving PegIntron/ribavirin capsules combination (excluding HCV Genotype 2 and 3), discontinue therapy at 12 weeks if HCV-RNA has dropped less than 2 $\log_{10}$ compared to pretreatment level, or at 24 weeks if HCV-RNA is still detectable.

3 DOSAGE FORMS AND STRENGTHS

Ribavirin Capsules USP, 200 mg are white/white, size ‘1’ hard gelatin capsule filled with white to off-white granular powder and imprinted with ‘E’ on white cap and ‘81’ on white body with black ink.

4 CONTRAINDICATIONS

Ribavirin capsules combination therapy is contraindicated in:

- pregnancy. Ribavirin capsules may cause fetal harm when administered to a pregnant woman. Ribavirin capsules are contraindicated in women who are pregnant or planning to become pregnant. If a patient becomes pregnant while taking ribavirin capsules, the patient should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.1),* and *Use in Specific Populations*

(8.1, 8.3)].

- men whose female partners are pregnant *[see Use in Specific Populations (8.3)]*
- patients with known hypersensitivity reactions such as Stevens-Johnson syndrome, toxic, epidermal necrolysis, and erythema multiforme to ribavirin or any component of the product
- patients with autoimmune hepatitis
- patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)
- patients with creatinine clearance less than 50 mL/min *[see Clinical Pharmacology (12.3)]*
- when coadministered with didanosine because exposure to the active metabolite of didanosine (dideoxyadenosine 5'-triphosphate) is increased. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis, has been reported in patients receiving didanosine in combination with ribavirin *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Ribavirin capsules may cause birth defects, miscarriage or stillbirth. Ribavirin therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. Patients should use effective contraception and have periodic monitoring with pregnancy tests during treatment and during the 6-month period after treatment has been stopped. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin has demonstrated significant teratogenic and embryocidal effects in all animal species tested. These effects occurred at doses as low as one twentieth of the recommended human dose of ribavirin *[see Boxed Warning, Contraindications (4), and Use in Specific Populations (8.1, 8.3)]*.

5.2 Anemia

Hemolytic anemia was observed in approximately 10% of ribavirin/INTRON A-treated subjects in clinical trials. The anemia associated with ribavirin occurs within 1 to 2 weeks of initiation of therapy. Because the initial drop in hemoglobin may be significant, obtain hemoglobin or hematocrit levels before the start of treatment and at Week 2 and Week 4 of therapy, or more frequently if clinically indicated. Patients should then be followed as clinically appropriate *[see Dosage and Administration (2.5, 2.6)]*.

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued *[see Dosage and Administration (2.5, 2.6)]*. Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use ribavirin.

5.3 Pancreatitis

Suspend ribavirin and INTRON A or PegIntron combination therapy in patients with signs and symptoms of pancreatitis and discontinue in patients with confirmed pancreatitis.

5.4 Pulmonary Disorders

Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis, pulmonary hypertension, and pneumonia, have been reported during ribavirin with alpha interferon combination therapy; occasional cases of fatal pneumonia have occurred. In addition, sarcoidosis or the exacerbation of sarcoidosis has been reported. If there is evidence of pulmonary infiltrates or pulmonary function impairment, closely monitor the patient, and if appropriate, discontinue combination therapy.

5.5 Ophthalmologic Disorders

Ribavirin is used in combination therapy with INTRON A or PegIntron. Refer to labeling for PegIntron for additional information.

5.6 Laboratory Tests

PegIntron in combination with ribavirin may cause severe decreases in neutrophil and platelet counts, and hematologic, endocrine (e.g., TSH), and hepatic abnormalities.

Obtain hematology and blood chemistry testing in patients on PegIntron/ribavirin combination therapy before the start of treatment and then periodically thereafter. In the adult clinical trial, complete blood counts (including hemoglobin, neutrophil, and platelet counts) and chemistries (including AST, ALT, bilirubin, and uric acid) were measured during the treatment period at Weeks 2, 4, 8, 12, and then at 6-week intervals, or more frequently if abnormalities developed. In pediatric subjects, the same laboratory parameters were evaluated with additional assessment of hemoglobin at treatment Week 6. TSH levels were measured every 12 weeks during the treatment period. HCV-RNA should be measured periodically during treatment *[see Dosage and Administration (2)]*.

5.7 Dental and Periodontal Disorders

Dental and periodontal disorders have been reported in patients receiving ribavirin and interferon or peginterferon combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of ribavirin and pegylated or nonpegylated interferon alfa-2b. Advise patients to brush their teeth thoroughly twice daily and have regular dental examinations. If vomiting occurs, advise patients to rinse out their mouth thoroughly afterwards.

5.8 Concomitant Administration of Azathioprine

Pancytopenia (marked decreases in red blood cells, neutrophils, and platelets) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the concomitant administration of pegylated interferon/ribavirin and azathioprine. In this limited number of patients (n=8), myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of both HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone. Discontinue PegIntron, ribavirin, and azathioprine for pancytopenia, and do not reintroduce pegylated interferon/ribavirin with concomitant azathioprine *[see Drug Interactions (7.4)]*.

5.9 Impact on Growth in Pediatric Patients

Data on the effects of PegIntron and ribavirin on growth come from an open-label study in subjects 3 through 17 years of age, in which weight and height changes were compared to U.S. normative population data. In general, the weight and height gain of pediatric subjects treated with PegIntron and ribavirin lagged behind that predicted by normative population data for the entire length of treatment. Severely inhibited growth velocity (less than 3rd percentile) was observed in 70% of the subjects while on treatment. Following treatment, rebound growth and weight gain occurred in most subjects. Long-term follow-up data in pediatric subjects, however, indicates that PegIntron in combination therapy with ribavirin may induce a growth inhibition that results in reduced adult height in some patients *[see Adverse Reactions (6.1)]*.

Similarly, an impact on growth was seen in subjects after treatment with ribavirin and INTRON A combination therapy for one year. In a long-term follow-up trial of a limited number of these subjects, combination therapy resulted in reduced final adult height in some subjects *[see Adverse Reactions (6.1)]*.

5.10 Not Recommended for Monotherapy and Risks Associated with Combination Therapy

Based on results of clinical trials, ribavirin monotherapy is not effective for the treatment of chronic

hepatitis C virus infection; therefore, ribavirin capsules must not be used alone. The safety and efficacy of ribavirin capsules have only been established when used together with INTRON A or PegIntron (not other interferons) as combination therapy.

The safety and efficacy of ribavirin with INTRON A or PegIntron combination therapy for the treatment of HIV infection, adenovirus, RSV, parainfluenza, or influenza infections have not been established. Ribavirin capsules should not be used for these indications.

There are significant adverse reactions caused by ribavirin/INTRON A or PegIntron combination therapy, including severe depression and suicidal or homicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, pulmonary dysfunction, pancreatitis, and diabetes. Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up. Labeling for INTRON A and PegIntron should be reviewed in their entirety for additional safety information prior to initiation of combination treatment.

6 ADVERSE REACTIONS

The following serious adverse drug reactions are discussed in other sections of the labeling:

- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.1)]*
- Anemia *[see Warnings and Precautions (5.2)]*
- Pancreatitis *[see Warnings and Precautions (5.3)]*
- Pulmonary Disorders *[see Warnings and Precautions (5.4)]*
- Ophthalmic Disorders *[see Warnings and Precautions (5.5)]*
- Dental and Periodontal Disorders *[see Warnings and Precautions (5.7)]*
- Impact on Growth in Pediatric Patients *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trials with ribavirin in combination with PegIntron or INTRON A have been conducted in over 7,800 subjects from 3 to 76 years of age.

The primary toxicity of ribavirin is hemolytic anemia. Reductions in hemoglobin levels occurred within the first 1 to 2 weeks of oral therapy. Cardiac and pulmonary reactions associated with anemia occurred in approximately 10% of patients *[see Warnings and Precautions (5.2)]*.

Greater than 96% of all subjects in clinical trials experienced one or more adverse reactions. The most commonly reported adverse reactions in adult subjects receiving PegIntron or INTRON A in combination with ribavirin were injection site inflammation/reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability. The most common adverse reactions in pediatric subjects, ages 3 and older, receiving ribavirin in combination with PegIntron or INTRON A were pyrexia, headache, neutropenia, fatigue, anorexia, injection site erythema, and vomiting.

The Adverse Reactions section references the following clinical trials:

- Ribavirin/PegIntron Combination therapy trials:

- Clinical Study 1 – evaluated PegIntron monotherapy (not further described in this label; see labeling for PegIntron for information about this trial).
- Study 2 – evaluated ribavirin 800 mg/day flat dose in combination with 1.5 mcg/kg/week PegIntron or with INTRON A.
- Study 3 – evaluated PegIntron/weight-based ribavirin in combination with PegIntron/flat dose ribavirin regimen.
- Study 4 – compared two PegIntron (1.5 mcg/kg/week and 1 mcg/kg/week) doses in combination with ribavirin and a third treatment group receiving Pegasys® (180 mcg/week)/Copegus® (1000 to 1200 mg/day).
- Study 5 – evaluated PegIntron (1.5 mcg/kg/week) in combination with weight-based ribavirin in prior treatment failure subjects.

- PegIntron/Ribavirin Combination Therapy in Pediatric Patients
- Ribavirin/INTRON A Combination Therapy trials for adults and pediatrics

Serious adverse reactions have occurred in approximately 12% of subjects in clinical trials with PegIntron with or without ribavirin *[see Boxed Warning, Warnings and Precautions (5)]*. The most common serious events occurring in subjects treated with PegIntron and ribavirin were depression and suicidal ideation *[see Warnings and Precautions (5.10)]*, each occurring at a frequency of less than 1%. Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up *[see Warnings and Precautions (5.10)]*. The most common fatal reaction occurring in subjects treated with PegIntron and ribavirin was cardiac arrest, suicidal ideation, and suicide attempt *[see Warnings and Precautions (5.10)]*, all occurring in less than 1% of subjects.

Adverse Reaction - Ribavirin/PegIntron Combination Therapy

Adult Subjects

Adverse reactions that occurred in the clinical trial at greater than 5% incidence are provided by treatment group from the ribavirin/PegIntron Combination Therapy (Study 2) in Table 5.

Table 5: Adverse Reactions Occurring in Greater Than 5% of Adult Subjects

Adverse Reactions	***Percentage of Subjects Reporting Adverse Reactions****		**Adverse Reactions**	***Percentage of Subjects Reporting Adverse Reactions****	
	PegIntron 1.5 mcg/kg/Ribavirin (N=511)	**INTRON A/Ribavirin** (N=505)		**PegIntron 1.5 mcg/kg/Ribavirin** (N=511)	**INTRON A/Ribavirin** (N=505)
Application Site			**Musculoskeletal**		
Injection Site Inflammation	25	18	Myalgia	56	50
Injection Site Reaction	58	36	Arthralgia	34	28
Autonomic Nervous System			Musculoskeletal Pain	21	19
Dry Mouth	12	8	**Psychiatric**		
Increased Sweating	11	7	Insomnia	40	41
Flushing	4	3	Depression	31	34
			Anxiety/Emotional		

Body as a Whole			Anxiety/Emotional Lability/Irritability	47	47
Fatigue/Asthenia	66	63	Concentration Impaired	17	21
Headache	62	58	Agitation	8	5
Rigors	48	41	Nervousness	6	6
Fever	46	33	**Reproductive, Female**		
Weight Loss	29	20	Menstrual Disorder	7	6
Right Upper Quadrant Pain	12	6	**Resistance Mechanism**		
Chest Pain	8	7	Viral Infection	12	12
Malaise	4	6	Fungal Infection	6	1
Central/Peripheral Nervous System			**Respiratory System**		
Dizziness	21	17	Dyspnea	26	24
Endocrine			Coughing	23	16
Hypothyroidism	5	4	Pharyngitis	12	13
Gastrointestinal			Rhinitis	8	6
Nausea	43	33	Sinusitis	6	5
Anorexia	32	27	**Skin and Appendages**		
Diarrhea	22	17	Alopecia	36	32
Vomiting	14	12	Pruritus	29	28
Abdominal Pain	13	13	Rash	24	23
Dyspepsia	9	8	Skin Dry	24	23
Constipation	5	5	**Special Senses, Other**		
Hematologic Disorders			Taste Perversion	9	4
Neutropenia	26	14	**Vision Disorders**		
Anemia	12	17	Vision Blurred	5	6
Leukopenia	6	5	Conjunctivitis	4	5
Thrombocytopenia	5	2			
Liver and Biliary System					
Hepatomegaly	4	4			

* A subject may have reported more than one adverse reaction within a body system/organ class category.

Table 6 summarizes the treatment-related adverse reactions in Study 4 that occurred at a greater than or equal to 10% incidence.

Table 6: Treatment-Related Adverse Reactions (Greater Than or Equal to 10% Incidence) By Descending Frequency

	Study 4 *Percentage of Subjects Reporting Treatment-Related Adverse Reactions*		
Adverse Reactions	**PegIntron 1.5 mcg/kg with Ribavirin (N=1019)**	**PegIntron 1 mcg/kg with Ribavirin (N=1016)**	**Pegasys 180 mcg with Copegus (N=1035)**
Fatigue	67	68	64

Headache	50	47	41
Nausea	40	35	34
Chills	39	36	23
Insomnia	38	37	41
Anemia	35	30	34
Pyrexia	35	32	21
Injection Site Reactions	34	35	23
Anorexia	29	25	21
Rash	29	25	34
Myalgia	27	26	22
Neutropenia	26	19	31
Irritability	25	25	25
Depression	25	19	20
Alopecia	23	20	17
Dyspnea	21	20	22
Arthralgia	21	22	22
Pruritus	18	15	19
Influenza-like Illness	16	15	15
Dizziness	16	14	13
Diarrhea	15	16	14
Cough	15	16	17
Weight Decreased	13	10	10
Vomiting	12	10	9
Unspecified Pain	12	13	9
Dry Skin	11	11	12
Anxiety	11	11	10
Abdominal Pain	10	10	10
Leukopenia	9	7	10

The incidence of serious adverse reactions was comparable in all trials. In Study 2, the incidence of serious adverse reactions was 17% in the PegIntron/ribavirin groups compared to 14% in the INTRON A/ribavirin group. In Study 3, there was a similar incidence of serious adverse reactions reported for the weight-based ribavirin group (12%) and for the flat-dose ribavirin regimen.

In many but not all cases, adverse reactions resolved after dose reduction or discontinuation of therapy. Some subjects experienced ongoing or new serious adverse reactions during the 6-month follow-up period. In Study 2, many subjects continued to experience adverse reactions several months after discontinuation of therapy. By the end of the 6-month follow-up period, the incidence of ongoing adverse reactions by body class in the PegIntron 1.5/ribavirin group was 33% (psychiatric), 20% (musculoskeletal), and 10% (for endocrine and for GI). In approximately 10 to 15% of subjects, weight loss, fatigue, and headache had not resolved.

There have been 28 subject deaths that occurred during treatment or follow-up in Studies 2, 3, and 4. In Study 2, there was 1 suicide in a subject receiving PegIntron/ribavirin combination therapy; and 1 subject death in the INTRON A/ribavirin group (motor vehicle accident). In Study 3, there were 14 deaths, 2 of which were probable suicides and 1 was an unexplained death in a person with a relevant medical history of depression. In Study 4, there were 12 deaths, 6 of which occurred in subjects who received PegIntron/ribavirin combination therapy, 5 in the PegIntron 1.5 mcg/ribavirin arm (N=1019) and 1 in the PegIntron 1 mcg/ribavirin arm (N=1016), and 6 of which occurred in subjects receiving Pegasys/Copegus (N=1035); there were 3 suicides that occurred during the off treatment follow-up period in subjects who received PegIntron (1.5 mcg/kg)/ribavirin combination therapy.

In Studies 1 and 2, 10 to 14% of subjects receiving PegIntron, alone or in combination with ribavirin, discontinued therapy compared with 6% treated with INTRON A alone and 13% treated with INTRON A in combination with ribavirin. In Study 3, 15% of subjects receiving PegIntron in combination with weight-based ribavirin and 14% of subjects receiving PegIntron with flat-dose ribavirin discontinued therapy due to an adverse reaction. The most common reasons for discontinuation were related to known interferon effects of psychiatric, systemic (e.g., fatigue, headache), or gastrointestinal adverse reactions. In Study 4, 13% of subjects in the PegIntron 1.5 mcg/ribavirin arm, 10% in the PegIntron 1 mcg/ribavirin arm, and 13% in the Pegasys 180 mcg/Copegus arm discontinued due to adverse events.

In Study 2, dose reductions for ribavirin were similar across all three groups *[see Clinical Studies (14.1)]*, 33 to 35%. The most common reasons for dose modifications were neutropenia (18%), or anemia (9%) *(see Laboratory Values)*. Other common reasons included depression, fatigue, nausea, and thrombocytopenia. In Study 3, dose modifications due to adverse reactions occurred more frequently with weight-based ribavirin dosing compared to flat dosing (29% and 23%, respectively). In Study 4, 16% of subjects had a dose reduction of PegIntron to 1 mcg/kg in combination with ribavirin, with an additional 4% requiring the second dose reduction of PegIntron to 0.5 mcg/kg due to adverse events compared to 15% of subjects in the Pegasys/Copegus arm, who required a dose reduction to 135 mcg/week with Pegasys, with an additional 7% in the Pegasys/Copegus arm requiring a second dose reduction to 90 mcg/week with Pegasys.

In the PegIntron/ribavirin combination trials the most common adverse reactions were psychiatric, which occurred among 77% of subjects in Study 2 and 68% to 69% of subjects in Study 3. These psychiatric adverse reactions included most commonly depression, irritability, and insomnia, each reported by approximately 30% to 40% of subjects in all treatment groups. Suicidal behavior (ideation, attempts, and suicides) occurred in 2% of all subjects during treatment or during follow-up after treatment cessation *[see Warnings and Precautions (5)]*. In Study 4, psychiatric adverse reactions occurred in 58% of subjects in the PegIntron 1.5 mcg/ribavirin arm, 55% of subjects in the PegIntron 1 mcg/ribavirin arm, and 57% of subjects in the Pegasys 180 mcg/Copegus arm.

In Study 2, PegIntron/ribavirin combination therapy induced fatigue or headache in approximately two-thirds of subjects, with fever or rigors in approximately half of the subjects. The severity of some of these systemic symptoms (e.g., fever and headache) tended to decrease as treatment continued.

Subjects receiving ribavirin/PegIntron as re-treatment after failing a previous interferon combination regimen reported adverse reactions similar to those previously associated with this regimen during clinical trials of treatment-naïve subjects.

Pediatric Subjects

In general, the adverse reaction profile in the pediatric population was similar to that observed in adults. In the pediatric trial, the most prevalent adverse reactions were pyrexia (80%), headache (62%), neutropenia (33%), fatigue (30%), anorexia (29%), injection-site erythema (29%) and vomiting (27%). The majority of adverse reactions were mild or moderate in severity. Severe adverse reactions were reported in 7% (8/107) of all subjects and included injection site pain (1%), pain in extremity (1%), headache (1%), neutropenia (1%), and pyrexia (4%). Important adverse reactions that occurred in this subject population were nervousness (7%; 7/107), aggression (3%; 3/107), anger (2%; 2/107), and depression (1%; 1/107). Five subjects received levothyroxine treatment, three with clinical hypothyroidism and two with asymptomatic TSH elevations. Weight and height gain of pediatric subjects treated with PegIntron plus ribavirin lagged behind that predicted by normative population data for the entire length of treatment. Severely inhibited growth velocity (less than 3rd percentile) was

observed in 70% of the subjects while on treatment.

Dose modifications of PegIntron and/or ribavirin were required in 25% of subjects due to treatment-related adverse reactions, most commonly for anemia, neutropenia and weight loss. Two subjects (2%; 2/107) discontinued therapy as the result of an adverse reaction.

Adverse reactions that occurred with a greater than or equal to 10% incidence in the pediatric trial subjects are provided in Table 7.

Table 7: Percentage of Pediatric Subjects with Treatment-Related Adverse Reactions (in At Least 10% of All Subjects)

System Organ Class Preferred Term	**All Subjects** (N=107)
Blood and Lymphatic System Disorders	
Neutropenia	33%
Anemia	11%
Leukopenia	10%
Gastrointestinal Disorders	
Abdominal Pain	21%
Abdominal Pain Upper	12%
Vomiting	27%
Nausea	18%
General Disorders and Administration Site Conditions	
Pyrexia	80%
Fatigue	30%
Injection-site Erythema	29%
Chills	21%
Asthenia	15%
Irritability	14%
Investigations	
Weight Loss	19%
Metabolism and Nutrition Disorders	
Anorexia	29%
Decreased Appetite	22%
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	17%
Myalgia	17%
Nervous System Disorders	
Headache	62%
Dizziness	14%
Skin and Subcutaneous Tissue Disorders	
Alopecia	17%

Ninety-four of 107 subjects enrolled in a 5-year follow-up trial. The long-term effects on growth were less in subjects treated for 24 weeks than in those treated for 48 weeks. Twenty-four percent of subjects (11/46) treated for 24 weeks and 40% of subjects (19/48) treated for 48 weeks had a >15 percentile height-for-age decrease from pre-treatment baseline to the end of 5-year follow-up. Eleven percent of subjects (5/46) treated for 24 weeks and 13% of subjects (6/48) treated for 48 weeks had a >30 percentile height-for-age decrease from pre-treatment baseline to the end of the 5-year follow-up. While observed across all age groups, the highest risk for reduced height at the end of long-term follow-up appeared to be initiation of combination therapy during the years of expected peak growth

velocity *[see Warnings and Precautions (5.9)]*.

Laboratory Values

Adult and Pediatric Subjects

The adverse reaction profile in Study 3, which compared PegIntron/weight-based ribavirin combination to a PegIntron/flat dose ribavirin regimen, revealed an increased rate of anemia with weight-based dosing (29% vs. 19% for weight-based vs. flat dose regimens, respectively). However, the majority of cases of anemia were mild and responded to dose reductions.

Changes in selected laboratory values during treatment in combination with ribavirin treatment are described below. Decreases in hemoglobin, leukocytes, neutrophils, and platelets may require dose reduction or permanent discontinuation from therapy *[see Dosage and Administration (2.5)]*. Changes in selected laboratory values during therapy are described in Table 8. Most of the changes in laboratory values in the PegIntron/ribavirin trial with pediatrics were mild or moderate.

Table 8: Selected Laboratory Abnormalities During Treatment with Ribavirin and PegIntron or Ribavirin and INTRON A in Previously Untreated Subjects

Laboratory Parameters*	**Percentage of Subjects**		
	Adults (Study 2)		**Pediatrics**
	PegIntron/ Ribavirin (N=511)	**INTRON A/ Ribavirin** (N=505)	**PegIntron/Ribavirin** (N=107)*
Hemoglobin (g/dL)			
9.5 to <11.0	26	27	30
8.0 to <9.5	3	3	2
6.5 to 7.9	0.2	0.2	-
Leukocytes (x 10^9/L)			
2.0 to 2.9	46	41	39
1.5 to <2.0	24	8	3
1.0 to 1.4	5	1	-
Neutrophils (x 10^9/L)			
1.0 to 1.5	33	37	35
0.75 to <1.0	25	13	26
0.5 to <0.75	18	7	13
<0.5	4	2	3
Platelets (x 10^9/L)			
70 to 100	15	5	1
50 to <70	3	0.8	-
30 to 49	0.2	0.2	-
25 to <50	-	-	1
Total Bilirubin	**(mg/dL)**		**(µmole/L)**
1.5 to 3.0	10	13	-
1.26 to 2.59 x ULN†	-	-	7
3.1 to 6.0	0.6	0.2	-
2.6 to 5 x ULN†	-	-	-
6.1 to 12.0	0	0.2	-
ALT (U/L)			
2 x Baseline	0.6	0.2	1
2.1 to 5 x Baseline	3	1	5

5.1 to 10 x Baseline	0	0	3

* The table summarizes the worst category observed within the period per subject per laboratory test. Only subjects with at least one treatment value for a given laboratory test are included.
† ULN=Upper limit of normal.

Hemoglobin. In Study 2, hemoglobin levels decreased to less than 11 g/dL in about 30% of subjects. In Study 3, 47% of subjects receiving weight-based dosing of ribavirin and 33% on flat-dose ribavirin had decreases in hemoglobin levels to less than 11 g/dL. Reductions in hemoglobin to less than 9 g/dL occurred more frequently in subjects receiving weight-based dosing compared to flat dosing (4% and 2%, respectively). In Study 2, dose modification was required in 9% and 13% of subjects in the PegIntron/ribavirin and INTRON A/ribavirin groups. In Study 4, subjects receiving PegIntron (1.5 mcg/kg)/ribavirin had decreases in hemoglobin levels to between 8.5 to less than 10 g/dL (28%) and to less than 8.5 g/dL (3%), whereas in patients receiving Pegasys 180 mcg/Copegus these decreases occurred in 26% and 4% of subjects, respectively. On average, hemoglobin levels became stable by treatment Weeks 4 to 6. The typical pattern observed was a decrease in hemoglobin levels by treatment Week 4 followed by stabilization and a plateau, which was maintained to the end of treatment *[see Dosage and Administration (2.5)]*.

Neutrophils. In Study 2, decreases in neutrophil counts were observed in a majority of adult subjects treated with PegIntron/ribavirin (85%) and INTRON A/ribavirin (60%). Severe, potentially life-threatening neutropenia (less than 0.5 x 10^9/L) occurred in approximately 4% of subjects treated with PegIntron/ribavirin and 2% of subjects treated with INTRON A/ribavirin. Eighteen percent of subjects receiving PegIntron/ribavirin required modification of interferon dosage. Few subjects (less than 1%) required permanent discontinuation of treatment. Neutrophil counts generally returned to pre-treatment levels 4 weeks after cessation of therapy *[see Dosage and Administration (2.5)]*.

Platelets. In Study 2, platelet counts decreased to less than 100,000/mm^3 in approximately 20% of subjects treated with PegIntron alone or with ribavirin and in 6% of adult subjects treated with INTRON A/ribavirin. Severe decreases in platelet counts (less than 50,000/mm^3) occur in less than 4% of adult subjects. In Study 2, 1% or 3% of subjects required dose modification of INTRON A or PegIntron, respectively. Platelet counts generally returned to pretreatment levels 4 weeks after the cessation of therapy *[see Dosage and Administration (2.5)]*.

Thyroid Function. In Study 2, clinically apparent thyroid disorders occurred among subjects treated with either INTRON A or PegIntron (with or without ribavirin) at a similar incidence (5% for hypothyroidism and 3% for hyperthyroidism). Subjects developed new onset TSH abnormalities while on treatment and during the follow-up period. At the end of the follow-up period, 7% of subjects still had abnormal TSH values.

Bilirubin and Uric Acid. In Study 2, 10 to 14% of subjects developed hyperbilirubinemia and 33 to 38% developed hyperuricemia in association with hemolysis. Six subjects developed mild to moderate gout.

Adverse Reactions with Ribavirin/INTRON A Combination Therapy

Adult Subjects

In clinical trials, 19% and 6% of previously untreated and relapse subjects, respectively, discontinued therapy due to adverse reactions in the combination arms compared to 13% and 3% in the interferon-only arms. Selected treatment-related adverse reactions that occurred in the U.S. trials with incidence 5% or greater are provided by treatment group (see Table 9). In general, the selected treatment-related adverse reactions were reported with lower incidence in the international trials as compared to the U.S. trials, except for asthenia, influenza-like symptoms, nervousness, and pruritus.

Pediatric Subjects

In clinical trials of 118 pediatric subjects 3 to 16 years of age, 6% discontinued therapy due to adverse reactions. Dose modifications were required in 30% of subjects, most commonly for anemia and neutropenia. In general, the adverse-reaction profile in the pediatric population was similar to that observed in adults. Injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in pediatric subjects compared to adult subjects. Conversely, pediatric subjects experienced less fatigue, dyspepsia, arthralgia, insomnia, irritability, impaired concentration, dyspnea, and pruritus compared to adult subjects. Selected treatment-related adverse reactions that occurred with incidence 5% or greater among all pediatric subjects who received the recommended dose of ribavirin/INTRON A combination therapy are provided in Table 9.

Table 9: Selected Treatment-Related Adverse Reactions: Previously Untreated and Relapse Adult Subjects and Previously Untreated Pediatric Subjects

Subjects Reporting Adverse Reactions*	Percentage of Subjects						
	U.S. Previously Untreated Study				U.S. Relapse Study		Pediatric Subjects
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		48 weeks of treatment
	INTRON A/ Ribavirin (N=228)	INTRON A/ Placebo (N=231)	INTRON A/ Ribavirin (N=228)	INTRON A/ Placebo (N=225)	INTRON A/ Ribavirin (N=77)	INTRON A/ Placebo (N=76)	INTRON A/ Ribavirin (N=118)
Application Site Disorders							
Injection Site Inflammation	13	10	12	14	6	8	14
Injection Site Reaction	7	9	8	9	5	3	19
Body as a Whole - General Disorders							
Headache	63	63	66	67	66	68	69
Fatigue	68	62	70	72	60	53	58
Rigors	40	32	42	39	43	37	25
Fever	37	35	41	40	32	36	61
Influenza-like Symptoms	14	18	18	20	13	13	31
Asthenia	9	4	9	9	10	4	5
Chest Pain	5	4	9	8	6	7	5
Central & Peripheral Nervous System Disorders							
Dizziness	17	15	23	19	26	21	20
Gastrointestinal System Disorders							
Nausea	38	35	46	33	47	33	33
Anorexia	27	16	25	19	21	14	51
Dyspepsia	14	6	16	9	16	9	<1
Vomiting	11	10	9	13	12	8	42
Musculoskeletal System Disorders							
Myalgia	61	57	64	63	61	58	32
Arthralgia	30	27	33	36	29	29	15
Musculoskeletal	30	26	28	32	32	28	21

Pain	20	26	28	32	22	28	21
Psychiatric Disorders							
Insomnia	39	27	39	30	26	25	14
Irritability	23	19	32	27	25	20	10
Depression	32	25	36	37	23	14	13
Emotional Lability	7	6	11	8	12	8	16
Concentration Impaired	11	14	14	14	10	12	5
Nervousness	4	2	4	4	5	4	3
Respiratory System Disorders							
Dyspnea	19	9	18	10	17	12	5
Sinusitis	9	7	10	14	12	7	<1
Skin and Appendages Disorders							
Alopecia	28	27	32	28	27	26	23
Rash	20	9	28	8	21	5	17
Pruritus	21	9	19	8	13	4	12
Special Senses, Other Disorders							
Taste Perversion	7	4	8	4	6	5	<1

* Subjects reporting one or more adverse reactions. A subject may have reported more than one adverse reaction within a body system/organ class category.

During a 48-week course of therapy there was a decrease in the rate of linear growth (mean percentile assignment decrease of 7%) and a decrease in the rate of weight gain (mean percentile assignment decrease of 9%). A general reversal of these trends was noted during the 24-week post-treatment period. Long-term data in a limited number of patients, however, suggests that combination therapy may induce a growth inhibition that results in reduced final adult height in some patients *[see Warnings and Precautions (5.9)]*.

Laboratory Values

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below (see Table 10).

Hemoglobin. Hemoglobin decreases among subjects receiving ribavirin therapy began at Week 1, with stabilization by Week 4. In previously untreated subjects treated for 48 weeks, the mean maximum decrease from baseline was 3.1 g/dL in the U.S. trial and 2.9 g/dL in the international trial. In relapse subjects, the mean maximum decrease from baseline was 2.8 g/dL in the U.S. trial and 2.6 g/dL in the international trial. Hemoglobin values returned to pretreatment levels within 4 to 8 weeks of cessation of therapy in most subjects.

Bilirubin and Uric Acid. Increases in both bilirubin and uric acid, associated with hemolysis, were noted in clinical trials. Most changes were moderate and reversed within 4 weeks after treatment discontinuation. This observation occurred most frequently in subjects with a previous diagnosis of Gilbert's syndrome. This has not been associated with hepatic dysfunction or clinical morbidity.

Table 10: Selected Laboratory Abnormalities During Treatment with Ribavirin and INTRON A: Previously Untreated and Relapse Adult Subjects and Previously Untreated Pediatric Subjects

	Percentage of Subjects		
	U.S. Previously Untreated Study	U.S. Relapse Study	Pediatric

	U.S. Previously Untreated Study				U.S. Relapse Study		Subjects
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		48 weeks of treatment
	INTRON A/ Ribavirin (N=228)	INTRON A/ Placebo (N=231)	INTRON A/ Ribavirin (N=228)	INTRON A/ Placebo (N=225)	INTRON A/ Ribavirin (N=77)	INTRON A/ Placebo (N=76)	INTRON A/ Ribavirin (N=118)
Hemoglobin (g/dL)							
9.5 to 10.9	24	1	32	1	21	3	24
8.0 to 9.4	5	0	4	0	4	0	3
6.5 to 7.9	0	0	0	0.4	0	0	0
<6.5	0	0	0	0	0	0	0
Leukocytes (x 10^9/L)							
2.0 to 2.9	40	20	38	23	45	26	35
1.5 to 1.9	4	1	9	2	5	3	8
1.0 to 1.4	0.9	0	2	0	0	0	0
<1.0	0	0	0	0	0	0	0
Neutrophils (x 10^9/L)							
1.0 to 1.49	30	32	31	44	42	34	37
0.75 to 0.99	14	15	14	11	16	18	15
0.5 to 0.74	9	9	14	7	8	4	16
<0.5	11	8	11	5	5	8	3
Platelets (x 10^9/L)							
70 to 99	9	11	11	14	6	12	0.8
50 to 69	2	3	2	3	0	5	2
30 to 49	0	0.4	0	0.4	0	0	0
<30	0.9	0	1	0.9	0	0	0
Total Bilirubin (mg/dL)							
1.5 to 3.0	27	13	32	13	21	7	2
3.1 to 6.0	0.9	0.4	2	0	3	0	0
6.1 to 12.0	0	0	0.4	0	0	0	0
>12.0	0	0	0	0	0	0	0

6.2 Postmarketing Experiences

The following adverse reactions have been identified and reported during post approval use of ribavirin in combination with INTRON A or PegIntron. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System disorders
Pure red cell aplasia, aplastic anemia
Ear and Labyrinth disorders
Hearing disorder, vertigo
Respiratory, Thoracic and Mediastinal disorders
Pulmonary hypertension
Eye disorders
Serous retinal detachment
Endocrine disorders
Diabetes

7 DRUG INTERACTIONS

7.1 Didanosine

Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is coadministered with ribavirin, which could cause or worsen clinical toxicities; therefore, coadministration of ribavirin capsules and didanosine is contraindicated *[see Contraindications (4)]*. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials.

7.2 Nucleoside Analogues

Hepatic decompensation (some fatal) has occurred in cirrhotic HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alpha and ribavirin. Patients receiving interferon with ribavirin and nucleoside reverse transcriptase inhibitors (NRTIs) should be closely monitored for treatment-associated toxicities, especially hepatic decompensation and anemia. Discontinuation of NRTIs should be considered as medically appropriate *(see labeling for individual NRTI product)*. Dose reduction or discontinuation of interferon, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6).

Ribavirin may antagonize the cell culture antiviral activity of stavudine and zidovudine against HIV. Ribavirin has been shown in cell culture to inhibit phosphorylation of lamivudine, stavudine, and zidovudine, which could lead to decreased antiretroviral activity. However, in a study with another pegylated interferon in combination with ribavirin, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV virologic suppress) interaction was observed when ribavirin and lamivudine (n=18), stavudine (n=10), or zidovudine (n=6) were coadministered as part of a multidrug regimen in HIV/HCV co-infected subjects. Concomitant use of ribavirin with any of these drugs should be done with caution.

7.3 Drugs Metabolized by Cytochrome P-450

Results of *in vitro* studies using both human and rat liver microsome preparations indicated little or no cytochrome P-450 enzyme-mediated metabolism of ribavirin, with minimal potential for P-450 enzyme-based drug interactions.

No pharmacokinetic interactions were noted between INTRON A and ribavirin capsules in a multiple-dose pharmacokinetic study.

7.4 Azathioprine

The use of ribavirin for the treatment of chronic hepatitis C in patients receiving azathioprine has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity. Inosine monophosphate dehydrogenase (IMDH) is required for one of the metabolic pathways of azathioprine. Ribavirin is known to inhibit IMDH, thereby leading to accumulation of an azathioprine metabolite, 6-methylthioinosine monophosphate (6-MTITP), which is associated with myelotoxicity (neutropenia, thrombocytopenia, and anemia). Patients receiving azathioprine with ribavirin should have complete blood counts, including platelet counts, monitored weekly for the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage or other therapy changes are necessary *[see Warnings and Precautions (5.8)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Ribavirin is contraindicated for use in pregnant women and in men whose female partners are pregnant *[see Contraindications (4)]*. Based on animal data, ribavirin use in pregnancy may be associated with birth defects. Data from the Ribavirin Pregnancy Registry are insufficient to identify a drug-associated risk of birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*. Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. In animal studies, ribavirin exposure was shown to have teratogenic and/or embryocidal effects *(see Data)*.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Available data from the Ribavirin Pregnancy Registry on 88 live births from pregnancies in women directly exposed and 98 live births from pregnancies in women indirectly exposed (by a male partner) to ribavirin during pregnancy or during the 6 months prior to pregnancy show a higher rate of birth defects (9.09% and 6.12%, respectively) compared to a background birth defect rate of 2.72% in the Metropolitan Atlanta Congenital Defects Program (MACDP) birth defects surveillance system. No pattern of birth defects can be identified from these reports. The miscarriage rate was approximately 21%. The current sample size is insufficient for reaching definitive conclusions based on statistical analysis. Trends suggesting a common etiology or relationship with ribavirin exposure were not observed. Methodologic limitations of the Ribavirin Pregnancy Registry include the use of MACDP as the external comparator group. Limitations of using an external comparator include differences in methodology and populations, as well as confounding due to the underlying disease and comorbidities.

Animal Data

Embryotoxicity/teratogenicity studies with ribavirin were conducted in rats (oral doses of 0.3, 1 and 10 mg/kg on Gestation Days 6 to 15) and rabbits (oral dose of 0.1, 0.3 and 1 mg/kg on Gestation Days 6 to 18). Ribavirin demonstrated significant embryocidal and teratogenic effects at doses well below the recommended human dose in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

8.2 Lactation

Risk Summary

There are no data on the presence of ribavirin in human milk or the effects on the breastfed infant or milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ribavirin and any potential adverse effects on the breastfed infant from ribavirin or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Ribavirin may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Ribavirin therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of treatment. Patients should have periodic pregnancy tests during treatment and during the 6-month period after treatment has been stopped *[see Warnings and Precautions (5.1)]*.

Contraception

Females of reproductive potential should use effective contraception during treatment and for 6 months post-therapy based on a multiple-dose half-life ($t_{1/2}$) of ribavirin of 12 days (e.g., 15 half-lives for ribavirin clearance from the body).

Male patients and their female partners should use effective contraception during treatment with ribavirin and for the 6-month post-therapy period *[see Warnings and Precautions (5.1)]*.

Infertility

Based on animal data, ribavirin may impair male fertility. In animal studies, these effects were mostly reversible within a few months after drug cessation *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of ribavirin in combination with PegIntron has not been established in pediatric patients below the age of 3 years. For treatment with ribavirin/INTRON A, evidence of disease progression, such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load should be considered when deciding to treat a pediatric patient. The benefits of treatment should be weighed against the observed safety findings.

Long-term follow-up data in pediatric subjects indicates that ribavirin in combination with PegIntron or with INTRON A may induce a growth inhibition that results in reduced height in some patients *[see Warnings and Precautions (5.9) and Adverse Reactions (6.1)]*.

Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% vs. 1%) during treatment and off-therapy follow-up *[see Warnings and Precautions (5.10)]*. As in adult patients, pediatric patients experienced other psychiatric adverse reactions (e.g., depression, emotional lability, somnolence), anemia, and neutropenia *[see Warnings and Precautions (5.2)]*.

8.5 Geriatric Use

Clinical trials of ribavirin combination therapy did not include sufficient numbers of subjects aged 65 and over to determine if they respond differently from younger subjects.

Ribavirin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients often have decreased renal function, care should be taken in dose selection. Renal function should be monitored and dosage adjustments made accordingly. Ribavirin should not be used in patients with creatinine clearance less than 50 mL/min *[see Contraindications (4)]*.

In general, ribavirin capsules should be administered to elderly patients cautiously, starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic and cardiac function, and of concomitant disease or other drug therapy. In clinical trials, elderly subjects had a higher frequency of anemia (67%) than younger patients (28%) *[see Warnings and Precautions (5.2)]*.

8.6 Organ Transplant Recipients

The safety and efficacy of INTRON A and PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been established. In a small (n=16) single-center, uncontrolled case experience, renal failure in renal allograft recipients receiving interferon alpha and ribavirin combination therapy was more frequent than expected from the center's previous experience with renal allograft recipients not receiving combination therapy. The relationship of the renal failure to renal allograft rejection is not clear.

8.7 HIV or HBV Co-infection

The safety and efficacy of PegIntron/ribavirin and INTRON A/ribavirin for the treatment of patients with HCV co-infected with HIV or HBV have not been established.

10 OVERDOSAGE

There is limited experience with overdosage. Acute ingestion of up to 20 g of ribavirin capsules, INTRON A ingestion of up to 120 million units, and subcutaneous doses of INTRON A up to 10 times the recommended doses have been reported. Primary effects that have been observed are increased incidence and severity of the adverse reactions related to the therapeutic use of INTRON A and ribavirin. However, hepatic enzyme abnormalities, renal failure, hemorrhage, and myocardial infarction have been reported with administration of single subcutaneous doses of INTRON A that exceed dosing recommendations.

There is no specific antidote for INTRON A or ribavirin overdose, and hemodialysis and peritoneal dialysis are not effective for treatment of overdose of these agents.

11 DESCRIPTION

Ribavirin, is a synthetic nucleoside analogue (purine analogue). The chemical name of ribavirin is 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide and has the following structural formula (see Figure 1).

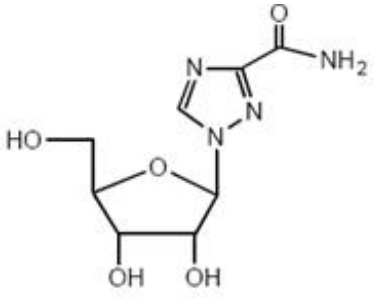

Figure 1: Structural Formula

Ribavirin USP is a white, crystalline powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. The molecular formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.21.

Ribavirin capsules USP consist of a white to off-white granular powder in a white, opaque, gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline cellulose,

lactose monohydrate, povidone-K 30, and magnesium stearate. The capsule shell consists of titanium dioxide, sodium lauryl sulfate, and gelatin. The capsule is printed with edible ink containing black iron oxide.

Meets USP dissolution test 2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ribavirin is an anti-HCV agent *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

Single- and multiple-dose pharmacokinetic properties in adults are summarized in Table 11. Ribavirin was rapidly and extensively absorbed following oral administration. However, due to first-pass metabolism, the absolute bioavailability averaged 64% (44%). There was a linear relationship between dose and AUC_{tf} (AUC from time zero to last measurable concentration) following single doses of 200 to 1200 mg ribavirin. The relationship between dose and C_{max} was curvilinear, tending to asymptote above single doses of 400 to 600 mg.

Upon multiple oral dosing, based on AUC_{12hr}, a 6-fold accumulation of ribavirin was observed in plasma. Following oral dosing with 600 mg twice daily, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 ng/mL (37%). Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which probably reflects slow elimination from nonplasma compartments.

Effect of Antacid on Absorption of Ribavirin: Coadministration of ribavirin capsules with an antacid containing magnesium, aluminum, and simethicone resulted in a 14% decrease in mean ribavirin AUC_{tf}. The clinical relevance of results from this single-dose study is unknown.

Table 11: Mean (% CV) Pharmacokinetic Parameters for Ribavirin When Administered Individually to Adults

Parameter	Ribavirin		
	Single-Dose 600 mg Oral Solution (N=14)	**Single-Dose 600 mg Capsules** (N=12)	**Multiple-Dose 600 mg Capsules twice daily** (N=12)
T_{max} (hr)	1.00 (34)	1.7 (46)*	3 (60)
C_{max} (ng/mL)	872 (42)	782 (37)	3680 (85)
AUC_{tf} (ng·hr/mL)	14,098 (38)	13,400 (48)	228,000 (25)
$T_{1/2}$ (hr)		43.6 (47)	298 (30)
Apparent Volume of Distribution (L)		2825 (9)†	
Apparent Clearance (L/hr)		38.2 (40)	
Absolute Bioavailability		64% (44)‡	

* N=11.
† Data obtained from a single-dose pharmacokinetic study using ^{14}C labeled ribavirin; N=5.
‡ N=6.

Tissue Distribution: Ribavirin transport into nonplasma compartments has been most extensively studied in red blood cells and has been identified to be primarily via an e_s-type equilibrative nucleoside transporter. This type of transporter is present on virtually all cell types and may account for the extensive volume of distribution. Ribavirin does not bind to plasma proteins.

Metabolism and Excretion: Ribavirin has two pathways of metabolism: (i) a reversible phosphorylation pathway in nucleated cells; and (ii) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally. After oral administration of 600 mg of ^{14}C-ribavirin, approximately 61% and 12% of the radioactivity was eliminated in the urine and feces, respectively, in 336 hours. Unchanged ribavirin accounted for 17% of the administered dose.

Special Populations:

Renal Dysfunction

The pharmacokinetics of ribavirin were assessed after administration of a single oral dose (400 mg) of ribavirin to non-HCV-infected subjects with varying degrees of renal dysfunction. The mean AUC_{tf} value was threefold greater in subjects with creatinine clearance values between 10 to 30 mL/min when compared to control subjects (creatinine clearance greater than 90 mL/min). In subjects with creatinine clearance values between 30 to 60 mL/min, AUC_{tf} was twofold greater when compared to control subjects. The increased AUC_{tf} appears to be due to reduction of renal and nonrenal clearance in these subjects. Phase 3 efficacy trials included subjects with creatinine clearance values greater than 50 mL/min. The multiple-dose pharmacokinetics of ribavirin cannot be accurately predicted in patients with renal dysfunction. Ribavirin is not effectively removed by hemodialysis. Patients with creatinine clearance less than 50 mL/min should not be treated with ribavirin *[see Contraindications (4)]*.

Hepatic Dysfunction

The effect of hepatic dysfunction was assessed after a single oral dose of ribavirin (600 mg). The mean AUC_{tf} values were not significantly different in subjects with mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B, or C) when compared to control subjects. However, the mean C_{max} values increased with severity of hepatic dysfunction and was twofold greater in subjects with severe hepatic dysfunction when compared to control subjects.

Elderly Patients

Pharmacokinetic evaluations in elderly subjects have not been performed.

Gender

There were no clinically significant pharmacokinetic differences noted in a single-dose trial of 18 male and 18 female subjects.

Pediatric Patients

Multiple-dose pharmacokinetic properties for ribavirin capsules and INTRON A in pediatric subjects with chronic hepatitis C between 5 and 16 years of age are summarized in Table 12. The pharmacokinetics of ribavirin and INTRON A (dose-normalized) are similar in adults and pediatric subjects.

Complete pharmacokinetic characteristics of ribavirin oral solution have not been determined in pediatric subjects. Ribavirin C_{min} values were similar following administration of ribavirin oral

solution or ribavirin capsules during 48 weeks of therapy in pediatric subjects (3 to 16 years of age).

Table 12: Mean (% CV) Multiple-dose Pharmacokinetic Parameters for INTRON A and Ribavirin Capsules When Administered to Pediatric Subjects with Chronic Hepatitis C

Parameter	Ribavirin 15 mg/kg/day as 2 divided doses (N=17)	INTRON A 3 MIU/m^2 three times weekly (N=54)
T_{max} (hr)	1.9 (83)	5.9 (36)
C_{max} (ng/mL)	3275 (25)	51 (48)
AUC*	29,774 (26)	622 (48)
Apparent Clearance L/hr/kg	0.27 (27)	ND†

* AUC_{12} (ng·hr/mL) for ribavirin; AUC_{0-24} (IU·hr/mL) for INTRON A.
† ND=not done.

Note: numbers in parenthesis indicate % coefficient of variation.

A clinical trial in pediatric subjects with chronic hepatitis C between 3 and 17 years of age was conducted in which pharmacokinetics for PegIntron and ribavirin (capsules and oral solution) were evaluated. In pediatric subjects receiving body surface area-adjusted dosing of PegIntron at 60 mcg/m^2/week, the log transformed ratio estimate of exposure during the dosing interval was predicted to be 58% [90% CI: 141%, 177%] higher than observed in adults receiving 1.5 mcg/kg/week. The pharmacokinetics of ribavirin (dose-normalized) in this trial were similar to those reported in a prior study of ribavirin in combination with INTRON A in pediatric subjects and in adults.

Effect of Food on Absorption of Ribavirin

Both AUC_{tf} and C_{max} increased by 70% when ribavirin capsules were administered with a high-fat meal (841 kcal, 53.8 g fat, 31.6 g protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic study *[see Dosage and Administration (2)]*.

12.4 Microbiology

Mechanism of Action

The mechanism by which ribavirin contributes to its antiviral efficacy in the clinic is not fully understood. Ribavirin has direct antiviral activity in cell culture against many RNA viruses. Ribavirin increases the mutation frequency in the genomes of several RNA viruses and ribavirin triphosphate inhibits HCV polymerase in a biochemical reaction.

Antiviral Activity in Cell Culture

The antiviral activity of ribavirin in the HCV replicon is not well understood and has not been defined because of the cellular toxicity of ribavirin. Direct antiviral activity has been observed in cell culture of other RNA viruses. The anti-HCV activity of interferon was demonstrated in cell culture using self-replicating HCV RNA (HCV replicon cells) or HCV infection.

Resistance

HCV genotypes show wide variability in their response to pegylated recombinant human interferon/ribavirin therapy. Genetic changes associated with the variable response have not been identified.

Cross-resistance

There is no reported cross-resistance between pegylated/non-pegylated interferons and ribavirin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Ribavirin did not cause an increase in any tumor type when administered for 6 months in the transgenic p53 deficient mouse model at doses up to 300 mg/kg (estimated human equivalent of 25 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 1.9 times the maximum recommended human daily dose). Ribavirin was noncarcinogenic when administered for 2 years to rats at doses up to 40 mg/kg (estimated human equivalent of 5.71 mg/kg based on body surface area adjustment for a 60 kg adult).

Mutagenesis

Ribavirin demonstrated increased incidences of mutation and cell transformation in multiple genotoxicity assays. Ribavirin was active in the Balb/3T3 *In Vitro* Cell Transformation Assay. Mutagenic activity was observed in the mouse lymphoma assay, and at doses of 20 to 200 mg/kg (estimated human equivalent of 1.67 to 16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1 to 1 times the maximum recommended human 24-hour dose of ribavirin) in a mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.

Impairment of Fertility

In studies in mice to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (estimated human equivalent of 1.25 to 12.5 mg/kg/day, based on body surface area adjustment for a 60-kg adult; 0.1 to 0.8 times the maximum human 24-hour dose of ribavirin) administered for 3 or 6 months, abnormalities in sperm occurred. Upon cessation of treatment, recovery from ribavirin-induced testicular toxicity was mostly apparent within 1 or 2 spermatogenesis cycles.

13.2 Animal Toxicology and Pharmacology

Long-term studies in the mouse and rat [18 to 24 months; doses of 20 to 75 and 10 to 40 mg/kg/day, respectively (estimated human equivalent doses of 1.67 to 6.25 and 1.43 to 5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult; approximately 0.1 to 0.4 times the maximum human 24-hour dose of ribavirin)] have demonstrated a relationship between chronic ribavirin exposure and increased incidences of vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in controls, but the incidence was increased in ribavirin-treated rats.

In a study in which rat pups were dosed postnatally with ribavirin at doses of 10, 25, and 50 mg/kg/day, drug-related deaths occurred at 50 mg/kg (at rat pup plasma concentrations below human plasma concentrations at the human therapeutic dose) between study Days 13 and 48. Rat pups dosed from postnatal Days 7 through 63 demonstrated a minor, dose-related decrease in overall growth at all doses, which was subsequently manifested as slight decreases in body weight, crown-rump length, and bone length. These effects showed evidence of reversibility, and no histopathological effects on bone were observed. No ribavirin effects were observed regarding neurobehavioral or reproductive development.

14 CLINICAL STUDIES

Clinical Study 1 evaluated PegIntron monotherapy. See PegIntron labeling for information about this trial.

14.1 Ribavirin/PegIntron Combination Therapy

Adult Subjects

Study 2

A randomized trial compared treatment with two PegIntron/ribavirin regimens [PegIntron 1.5 mcg/kg subcutaneously once weekly/ribavirin 800 mg orally daily (in divided doses); PegIntron 1.5 mcg/kg subcutaneously once weekly for 4 weeks then 0.5 mcg/kg subcutaneously once weekly for 44 weeks/ribavirin 1000 or 1200 mg orally daily (in divided doses)] with INTRON A [3 MIU subcutaneously three times weekly/ribavirin 1000 or 1200 mg orally daily (in divided doses)] in 1,530 adults with chronic hepatitis C. Interferon-naïve subjects were treated for 48 weeks and followed for 24 weeks post-treatment. Eligible subjects had compensated liver disease, detectable HCV-RNA, elevated ALT, and liver histopathology consistent with chronic hepatitis.

Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment (see Table 13). The response rate to the PegIntron 1.5 mcg/kg and ribavirin 800 mg dose was higher than the response rate to INTRON A/ribavirin (see Table 13). The response rate to PegIntron 1.5→0.5 mcg/kg/ribavirin was essentially the same as the response to INTRON A/ ribavirin (data not shown).

Table 13: Rates of Response to Combination Treatment – Study 2

	PegIntron 1.5 mcg/kg once weekly Ribavirin 800 mg once daily	**INTRON A 3 MIU three times weekly Ribavirin 1000/1200 mg once daily**
Overall response*,†	52% (264/511)	46% (231/505)
Genotype 1	41% (141/348)	33% (112/343)
Genotype 2 to 6	75% (123/163)	73% (119/162)

* Serum HCV-RNA was measured with a research-based quantitative polymerase chain reaction assay by a central laboratory.
† Difference in overall treatment response (PegIntron/ribavirin vs. INTRON A/ribavirin) is 6% with 95% confidence interval of (0.18, 11.63) adjusted for viral genotype and presence of cirrhosis at baseline. Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment.

Subjects with viral genotype 1, regardless of viral load, had a lower response rate to PegIntron (1.5 mcg/kg)/ribavirin (800 mg) compared to subjects with other viral genotypes. Subjects with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 30% (78/256) compared to a response rate of 29% (71/247) with INTRON A/ ribavirin combination therapy.

Subjects with lower body weight tended to have higher adverse-reaction rates *[see Adverse Reactions (6.1)]* and higher response rates than subjects with higher body weights. Differences in response rates between treatment arms did not substantially vary with body weight.

Treatment response rates with PegIntron/ribavirin combination therapy were 49% in men and 56% in women. Response rates were lower in African American and Hispanic subjects and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic

factors compared to Caucasians, the number of non-Caucasians studied (11% of the total) was insufficient to allow meaningful conclusions about differences in response rates after adjusting for prognostic factors in this trial.

Liver biopsies were obtained before and after treatment in 68% of subjects. Compared to baseline, approximately two-thirds of subjects in all treatment groups were observed to have a modest reduction in inflammation.

Study 3

In a large United States community-based trial, 4,913 subjects with chronic hepatitis C were randomized to receive PegIntron 1.5 mcg/kg subcutaneously once weekly in combination with a ribavirin dose of 800 to 1400 mg (weight-based dosing [WBD]) or 800 mg (flat) orally daily (in divided doses) for 24 or 48 weeks based on genotype. Response to treatment was defined as undetectable HCV-RNA (based on an assay with a lower limit of detection of 125 IU/mL) at 24 weeks post-treatment.

Treatment with PegIntron 1.5 mcg/kg and ribavirin 800 to 1400 mg resulted in a higher sustained virologic response compared to PegIntron in combination with a flat 800 mg daily dose of ribavirin. Subjects weighing greater than 105 kg obtained the greatest benefit with WBD, although a modest benefit was also observed in subjects weighing greater than 85 to 105 kg (see Table 14). The benefit of WBD in subjects weighing greater than 85 kg was observed with HCV genotypes 1 to 3. Insufficient data were available to reach conclusions regarding other genotypes. Use of WBD resulted in an increased incidence of anemia *[see Adverse Reactions (6.1)]*.

Table 14: SVR Rate by Treatment and Baseline Weight - Study 3

Treatment Group	Subject Baseline Weight			
	<65 kg (<143 lb)	**65 to 85 kg (143 to 188 lb)**	**>85 to 105 kg (>188 to 231 lb)**	**>105 kg (>231 lb)**
WBD*	50% (173/348)	45% (449/994)	42% (351/835)	47% (138/292)
Flat	51% (173/342)	44% (443/1011)	39% (318/819)	33% (91/272)

* *P*=0.01, primary efficacy comparison (based on data from subjects weighing 65 kg or higher at baseline and utilizing a logistic regression analysis that includes treatment [WBD or Flat], genotype and presence/absence of advanced fibrosis, in the model).

A total of 1,552 subjects weighing greater than 65 kg in Study 3 had genotype 2 or 3 and were randomized to 24 or 48 weeks of therapy. No additional benefit was observed with the longer treatment duration.

Study 4

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two PegIntron/ribavirin regimens [PegIntron 1.5 mcg/kg and 1 mcg/kg subcutaneously once weekly both in combination with ribavirin 800 to 1400 mg PO daily (in two divided doses)] and Pegasys 180 mcg subcutaneously once weekly in combination with Copegus 1000 to 1200 mg PO daily (in two divided doses) in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. In this trial, lack of early virologic response (undetectable HCV-RNA or greater than or equal to 2 $\log_{10}$ reduction from baseline) by treatment Week 12 was the criterion for discontinuation of treatment. SVR was defined as undetectable HCV-RNA (Roche COBAS TaqMan assay, a lower limit of quantitation of 27 IU/mL) at 24 weeks post-treatment (see Table 15).

Table 15: SVR Rate by Treatment – Study 4

% (number) of Subjects		
PegIntron 1.5 mcg/kg/Ribavirin	**PegIntron 1 mcg/kg/Ribavirin**	**Pegasys 180 mcg/Copegus**
40 (406/1019)	38 (386/1016)	41 (423/1035)

Overall SVR rates were similar among the three treatment groups. Regardless of treatment group, SVR rates were lower in subjects with poor prognostic factors. Subjects with poor prognostic factors randomized to PegIntron (1.5 mcg/kg)/ribavirin or Pegasys/Copegus, however, achieved higher SVR rates compared to similar subjects randomized to PegIntron 1 mcg/kg/ribavirin. For the PegIntron 1.5 mcg/kg and ribavirin dose, SVR rates for subjects with and without the following prognostic factors were as follows: cirrhosis (10% vs. 42%), normal ALT levels (32% vs. 42%), baseline viral load greater than 600,000 IU/mL (35% vs. 61%), 40 years of age and older (38% vs. 50%), and African American race (23% vs. 44%). In subjects with undetectable HCV-RNA at treatment Week 12 who received PegIntron (1.5 mcg/kg)/ribavirin, the SVR rate was 81% (328/407).

Study 5 - Ribavirin/PegIntron Combination Therapy in Prior Treatment Failures

In a noncomparative trial, 2,293 subjects with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were re-treated with PegIntron, 1.5 mcg/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Eligible subjects included prior nonresponders (subjects who were HCV-RNA positive at the end of a minimum 12 weeks of treatment) and prior relapsers (subjects who were HCV-RNA negative at the end of a minimum 12 weeks of treatment and subsequently relapsed after post-treatment follow-up). Subjects who were negative at Week 12 were treated for 48 weeks and followed for 24 weeks post-treatment. Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment (measured using a research-based test, limit of detection 125 IU/mL). The overall response rate was 22% (497/2293) (99% CI: 19.5, 23.9). Subjects with the following characteristics were less likely to benefit from re-treatment: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection.

The re-treatment sustained virologic response rates by baseline characteristics are summarized in Table 16.

Table 16: SVR Rates by Baseline Characteristics of Prior Treatment Failures - Study 5

HCV Genotype/Metavir Fibrosis Score	Overall SVR by Previous Response and Treatment			
	Nonresponder		Relapser	
	interferon alfa/ribavirin % (number of subjects)	peginterferon (2a and 2b combined)/ribavirin % (number of subjects)	interferon alfa/ribavirin % (number of subjects)	peginterferon (2a and 2b combined)/ribavirin % (number of subjects)
Overall	18 (158/903)	6 (30/476)	43 (130/300)	35 (113/344)
HCV 1	13 (98/761)	4 (19/431)	32 (67/208)	23 (56/243)
F2	18 (36/202)	6 (7/117)	42 (33/79)	32 (23/72)
F3	16 (38/233)	4 (4/112)	28 (16/58)	21 (14/67)
F4	7 (24/325)	4 (8/202)	26 (18/70)	18 (19/104)
HCV 2/3	49 (53/109)	36 (10/28)	67 (54/81)	57 (52/92)

F2	68 (23/34)	56 (5/9)	76 (19/25)	61 (11/18)
F3	39 (11/28)	38 (3/8)	67 (18/27)	62 (18/29)
F4	40 (19/47)	18 (2/11)	59 (17/29)	51 (23/45)
HCV 4	17 (5/29)	7 (1/15)	88 (7/8)	50 (4/8)

Achievement of an undetectable HCV-RNA at treatment Week 12 was a strong predictor of SVR. In this trial, 1,470 (64%) subjects did not achieve an undetectable HCV-RNA at treatment Week 12, and were offered enrollment into long-term treatment trials, due to an inadequate treatment response. Of the 823 (36%) subjects who were HCV-RNA undetectable at treatment Week 12, those infected with genotype 1 had an SVR of 48% (245/507), with a range of responses by fibrosis scores (F4-F2) of 39 to 55%. Subjects infected with genotype 2/3 who were HCV-RNA undetectable at treatment Week 12 had an overall SVR of 70% (196/281), with a range of responses by fibrosis scores (F4-F2) of 60 to 83%. For all genotypes, higher fibrosis scores were associated with a decreased likelihood of achieving SVR.

Pediatric Subjects

Previously untreated pediatric subjects 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were treated with ribavirin 15 mg/kg per day and PegIntron 60 mcg/m^2 once weekly for 24 or 48 weeks based on HCV genotype and baseline viral load. All subjects were to be followed for 24 weeks post-treatment. A total of 107 subjects received treatment, of which 52% were female, 89% were Caucasian, and 67% were infected with HCV Genotype 1. Subjects infected with Genotypes 1, 4 or Genotype 3 with HCV-RNA greater than or equal to 600,000 IU/mL received 48 weeks of therapy while those infected with Genotype 2 or Genotype 3 with HCV-RNA less than 600,000 IU/mL received 24 weeks of therapy. The trial results are summarized in Table 17.

Table 17: Sustained Virologic Response Rates by Genotype and Assigned Treatment Duration – Pediatric Trial

Genotype	All Subjects N=107	
	24 Weeks	48 Weeks
	Virologic Response N*,† (%)	Virologic Response N*,† (%)
All	26/27 (96.3)	44/80 (55.0)
1	-	38/72 (52.8)
2	14/15 (93.3)	-
3‡	12/12 (100)	2/3 (66.7)
4	-	4/5 (80.0)

* Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment.
† N=number of responders/number of subjects with given genotype and assigned treatment duration.
‡ Subjects with genotype 3 low viral load (less than 600,000 IU/mL) were to receive 24 weeks of treatment while those with genotype 3 and high viral load were to receive 48 weeks of treatment.

14.2 Ribavirin/INTRON A Combination Therapy

Adult Subjects

Previously Untreated Subjects

Adults with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) who were previously untreated with alpha interferon therapy were enrolled into two multicenter, double-blind trials (U.S. and international) and randomized to receive ribavirin capsules 1200 mg/day (1000 mg/day for subjects weighing less than or equal to 75 kg) and INTRON A 3 MIU three times weekly or INTRON A and placebo for 24 or 48 weeks followed by 24 weeks of off-therapy follow-up. The international trial did not contain a 24-week INTRON A and placebo treatment arm. The U.S. trial enrolled 912 subjects who, at baseline, were 67% male, 89% Caucasian with a mean Knodell HAI score (I+II+III) of 7.5, and 72% genotype 1. The international trial, conducted in Europe, Israel, Canada, and Australia, enrolled 799 subjects (65% male, 95% Caucasian, mean Knodell score 6.8, and 58% genotype 1).

Trial results are summarized in Table 18.

Table 18: Virologic and Histologic Responses: Previously Untreated Subjects*

	U.S. Trial				International Trial		
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	48 weeks of treatment	
	INTRON A/Ribavirin (N=228)	INTRON A/Placebo (N=231)	INTRON A/Ribavirin (N=228)	INTRON A/Placebo (N=225)	INTRON A/Ribavirin (N=265)	INTRON A/Ribavirin (N=268)	INTRON A/Placebo (N=266)
Virologic Response							
Responder†	65 (29)	13 (6)	85 (37)	27 (12)	86 (32)	113 (42)	46 (17)
Nonresponder	147 (64)	194 (84)	110 (48)	168 (75)	158 (60)	120 (45)	196 (74)
Missing Data	16 (7)	24 (10)	33 (14)	30 (13)	21 (8)	35 (13)	24 (9)
Histologic Response							
Improvement‡	102 (45)	77 (33)	96 (42)	65 (29)	103 (39)	102 (38)	69 (26)
No improvement	77 (34)	99 (43)	61 (27)	93 (41)	85 (32)	58 (22)	111 (41)
Missing Data	49 (21)	55 (24)	71 (31)	67 (30)	77 (29)	108 (40)	86 (32)

* Number (%) of subjects.
†Defined as HCV-RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.
‡Defined as post-treatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of greater than or equal to 2 points.

Of subjects who had not achieved HCV-RNA below the limit of detection of the research-based assay by Week 24 of ribavirin/INTRON A treatment, less than 5% responded to an additional 24 weeks of combination treatment.

Among subjects with HCV Genotype 1 treated with ribavirin/INTRON A therapy who achieved HCV-RNA below the detection limit of the research-based assay by 24 weeks, those randomized to 48 weeks of treatment had higher virologic responses compared to those in the 24-week treatment group. There was no observed increase in response rates for subjects with HCV non-genotype 1 randomized to ribavirin/INTRON A therapy for 48 weeks compared to 24 weeks.

Relapse Subjects

Subjects with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) who had relapsed following one or two courses of interferon therapy (defined as abnormal serum ALT levels) were enrolled into two multicenter, double-blind trials (U.S. and international) and randomized to receive ribavirin 1200 mg/day (1000 mg/day for subjects weighing ≤75 kg) and INTRON A 3 MIU three times weekly or INTRON A and placebo for 24 weeks followed by 24 weeks of off-therapy follow-up. The U.S. trial enrolled 153 subjects who, at baseline, were 67% male, 92% Caucasian with a mean Knodell HAI score (I+II+III) of 6.8, and 58% genotype 1. The international trial, conducted in Europe, Israel, Canada, and Australia, enrolled 192 subjects (64% male, 95% Caucasian, mean Knodell score 6.6, and 56% genotype 1). Trial results are summarized in Table 19.

Table 19: Virologic and Histologic Responses: Relapse Subjects*

	U.S. Trial		International Trial	
	INTRON A/ Ribavirin (N=77)	**INTRON A/ Placebo** (N=76)	**INTRON A/ Ribavirin** (N=96)	**INTRON A/ Placebo** (N=96)
Virologic Response				
Responder†	33 (43)	3 (4)	46 (48)	5 (5)
Nonresponder	36 (47)	66 (87)	45 (47)	91 (95)
Missing Data	8 (10)	7 (9)	5 (5)	0 (0)
Histologic Response				
Improvement‡	38 (49)	27 (36)	49 (51)	30 (31)
No improvement	23 (30)	37 (49)	29 (30)	44 (46)
Missing Data	16 (21)	12 (16)	18 (19)	22 (23)

* Number (%) of subjects.
† Defined as HCV-RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.
‡Defined as post-treatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of greater than or equal to 2 points.

Virologic and histologic responses were similar among male and female subjects in both the previously untreated and relapse trials.

Pediatric Subjects

Pediatric subjects 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were treated with ribavirin 15 mg/kg per day and INTRON A 3 MIU/m^2 three times weekly for 48 weeks followed by 24 weeks of off-therapy follow-up. A total of 118 subjects received treatment, of which 57% were male, 80% Caucasian, and 78% genotype 1. Subjects less than 5 years of age received ribavirin oral solution and those 5 years of age or older received either ribavirin oral solution or capsules.

Trial results are summarized in Table 20.

Table 20: Virologic Response: Previously Untreated Pediatric Subjects*

	INTRON A 3 MIU/m^2 three times weekly/Ribavirin 15 mg/kg/day

Overall Response† (N=118)	54 (46)
Genotype 1 (N=92)	33 (36)
Genotype non-1 (N=26)	21 (81)

* Number (%) of subjects.
† Defined as HCV-RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.

Subjects with viral genotype 1, regardless of viral load, had a lower response rate to INTRON A/ribavirin combination therapy compared to subjects with genotype non-1, 36% vs. 81%. Subjects with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 26% (13/50).

16 HOW SUPPLIED/STORAGE AND HANDLING

Ribavirin Capsules USP, 200 mg are white/white, size '1' hard gelatin capsule filled with white to off-white granular powder and imprinted with 'E' on white cap and '81' on white body with black ink.

Bottles of 42	NDC 65862-290-42
Bottles of 56	NDC 65862-290-56
Bottles of 70	NDC 65862-290-70
Bottles of 84	NDC 65862-290-84
Bottles of 180	NDC 65862-290-18
Bottles of 500	NDC 65862-290-05

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Anemia

The most common adverse experience occurring with ribavirin capsules is anemia, which may be severe *[see Warnings and Precautions (5.2) and Adverse Reactions (6)]*. Advise patients that laboratory evaluations are required prior to starting therapy and periodically thereafter *[see Dosage and Administration (2.4)]*. Advise patients to be well hydrated, especially during the initial stages of treatment.

Embryo-Fetal Toxicity

Inform females of reproductive potential and pregnant women that ribavirin capsules may cause birth defects, miscarriage, and stillbirth. Advise females of reproductive potential that they must have a pregnancy test prior to initiating treatment and periodically during therapy. Advise females of reproductive potential and male patients with female partners of reproductive potential to use effective contraception during treatment with ribavirin and for 6 months post therapy. Advise patients to notify the physician immediately in the event of a pregnancy *[see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.3)]*.

Missed Dose

Inform patients that in the event a dose is missed, the missed dose should be taken as soon as possible during the same day. Patients should not double the next dose. Advise patients to contact their healthcare provider if they have questions.

Dental and Periodontal Disorders

Advise patients to brush their teeth thoroughly twice daily and have regular dental examinations. If vomiting occurs, advise patients to rinse out their mouth thoroughly afterwards *[see Warnings and Precautions (5.7)]*.

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Dispense with Medication Guide available at: www.aurobindousa.com/product-medication-guides

MEDICATION GUIDE

Ribavirin Capsules USP
(rye'' ba vye' rin)

What is the most important information I should know about ribavirin capsules?

1. **Ribavirin capsules may cause birth defects, miscarriage or death of your unborn baby. Do not take ribavirin capsules if you or your sexual partner is pregnant or plan to become pregnant. Do not become pregnant during treatment or within 6 months after stopping treatment with ribavirin capsules.** You must use effective birth control during treatment with ribavirin capsules and for 6 months after stopping treatment.
- Females must have a pregnancy test before starting ribavirin capsules, during treatment with ribavirin capsules, and for 6 months after the last dose of ribavirin capsules.
- **If you or your female sexual partner becomes pregnant during treatment with ribavirin capsules or within 6 months after you stop taking ribavirin capsules, tell your healthcare provider right away.**

2. **Ribavirin capsules may cause a significant drop in your red blood cell count and cause anemia in some cases. Anemia has been associated with worsening of heart problems, and in rare cases can cause a heart attack and death.** Tell your healthcare provider if you have ever had any heart problems. Ribavirin capsules may not be right for you. **Get medical help right away if you experience chest pain.**

3. **Do not take ribavirin capsules alone to treat chronic hepatitis C infection.** Ribavirin capsules should be used in combination with **either interferon alfa-2b or peginterferon alfa-2b** to treat chronic hepatitis C infection.

What are ribavirin capsules?

Ribavirin capsules are a medicine used with either interferon alfa-2b or peginterferon alfa-2b to treat chronic (lasting a long time) hepatitis C infection in people 3 years and older with liver disease.

It is not known if ribavirin capsules use for longer than 1 year is safe and will work.

It is not known if ribavirin capsules use in children younger than 3 years old is safe and will work.

Who should not take ribavirin capsules?

See "What is the most important information I should know about ribavirin capsules?"

Do not take ribavirin capsules if you have:

- ever had serious allergic reactions to the ingredients in ribavirin capsules. See the end of this Medication Guide for a complete list of ingredients.
- certain types of hepatitis (autoimmune hepatitis).
- certain blood disorders (hemoglobinopathies).
- severe kidney disease.
- taken or currently take didanosine.

Talk to your healthcare provider before taking ribavirin capsules if you have any of these conditions.

What should I tell my healthcare provider before taking ribavirin capsules?

Before you take ribavirin capsules, tell your healthcare provider if you have or ever had:

- treatment for hepatitis C that did not work for you
- breathing problems. Ribavirin capsules may cause or worsen breathing problems you already have.
- vision problems. Ribavirin capsules may cause eye problems or worsen eye problems you already have. You should have an eye exam before you start treatment with ribavirin capsules.
- certain blood disorders such as anemia (low red blood cell count)
- high blood pressure, heart problems, or have had a heart attack. Your healthcare provider should check your blood and heart before you start treatment with ribavirin capsules.
- thyroid problems
- liver problems other than hepatitis C infection
- human immunodeficiency virus (HIV) or any immunity problems
- mental health problems, including depression and thoughts of hurting yourself or others
- kidney problems
- an organ transplant
- diabetes. Ribavirin capsules may make your diabetes worse or harder to treat.
- any other medical condition
- are breastfeeding. It is not known if ribavirin passes into your breast milk. You and your healthcare provider should decide if you will take ribavirin capsules or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription medicines, vitamins, and herbal supplements. Ribavirin capsules may affect the way other medicines work.

Especially tell your healthcare provider if you take didanosine or a medicine that contains azathioprine.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take ribavirin capsules?

- Take ribavirin capsules exactly as your healthcare provider tells you. Your healthcare provider will tell you how much ribavirin capsules to take and when to take them.
- Take ribavirin capsules with food.
- Take ribavirin capsules whole. Do not open, break, or crush ribavirin capsules before swallowing. If you cannot swallow ribavirin capsules whole, tell your healthcare provider.

- If you miss a dose of ribavirin capsules, take the missed dose as soon as possible during the same day. Do not double the next dose. If you have questions about what to do, call your healthcare provider.
- If you take too much ribavirin, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of ribavirin capsules?

Ribavirin capsules may cause serious side effects, including:

See "What is the most important information I should know about ribavirin capsules?"

- **Swelling and irritation of your pancreas (pancreatitis).** Symptoms may include: stomach pain, nausea, vomiting, or diarrhea.
- **Serious breathing problems.** Difficulty breathing may be a sign of a serious lung infection (pneumonia) that can lead to death.
- **Serious eye problems** that may lead to vision loss or blindness.
- **Dental problems.** Brush your teeth well 2 times each day. Get regular dental exams. If you vomit at any time during treatment with ribavirin capsules, rinse out your mouth well.
- **Severe blood disorders.** You may have an increased risk of developing severe blood disorders when ribavirin capsules is used in combination with pegylated alpha interferons and azathioprine. Your healthcare provider should do blood tests during your treatment with ribavirin capsules in combination with pegylated alpha interferon and azathioprine to check you for these problems.

- **Growth problems in children.** Weight loss and slowed growth are common in children during combination treatment with ribavirin capsules and peginterferon alfa-2b or interferon alfa-2b. Most children will go through a growth spurt and gain weight after treatment stops. Some children may not reach the height that they were expected to have before treatment. Talk to your healthcare provider if you are concerned about your child's growth during treatment with ribavirin capsules and peginterferon alfa-2b or with ribavirin capsules and interferon alfa-2b.
- **Severe depression.**
- **Thoughts of hurting yourself or others, and suicide attempts.** Adults and children who take ribavirin capsules, especially teenagers, are more likely to have suicidal thoughts or attempt to hurt themselves while taking ribavirin capsules. Call your healthcare provider right away or go to the nearest hospital emergency room if you have new or worse depression or thoughts about hurting yourself or others or dying.

The most common side effects of ribavirin capsules in adults include:

- flu-like symptoms - feeling tired or weak, headache, shaking chills along with high temperature (fever), nausea, and muscle aches
- mood changes, feeling irritable

The most common side effects of ribavirin capsules in children include:

- fever
- headache
- a decrease in blood cells that fight infection (neutropenia)
- tiredness
- decreased appetite
- vomiting

These are not all the possible side effects of ribavirin capsules. For more information ask your healthcare provider or pharmacist.

Call your healthcare provider if you have any side effect that bothers you or that does not go away, and for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ribavirin capsules?

- Store **ribavirin capsules** between 15° to 30°C (59° to 86°F).

Keep ribavirin capsules and all medicines out of the reach of children.

General information about the safe and effective use of ribavirin capsules.

It is not known if treatment with ribavirin capsules will cure hepatitis C virus infections or prevent cirrhosis, liver failure, or liver cancer that can be caused by hepatitis C virus infections. It is not known if taking ribavirin capsules will prevent you from infecting another person with the hepatitis C virus.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ribavirin capsules for a condition for which it was not prescribed. Do not give ribavirin capsules to other people, even if they have the same symptoms that you have. They may harm them.

You can ask your pharmacist or healthcare provider for information about ribavirin capsules that is written for health professionals.

What are the ingredients in ribavirin capsules?

Active ingredient: ribavirin

Inactive ingredients: microcrystalline cellulose, lactose monohydrate, povidone-K 30, and magnesium stearate. The capsule shell consists of titanium dioxide, sodium lauryl sulfate, and gelatin. The capsule is printed with edible ink containing black iron oxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

For more information, call Aurobindo Pharma USA, Inc. at 1-866-850-2876.

Dispense with Medication Guide available at: www.aurobindousa.com/product-medication-guides

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Manufactured by:
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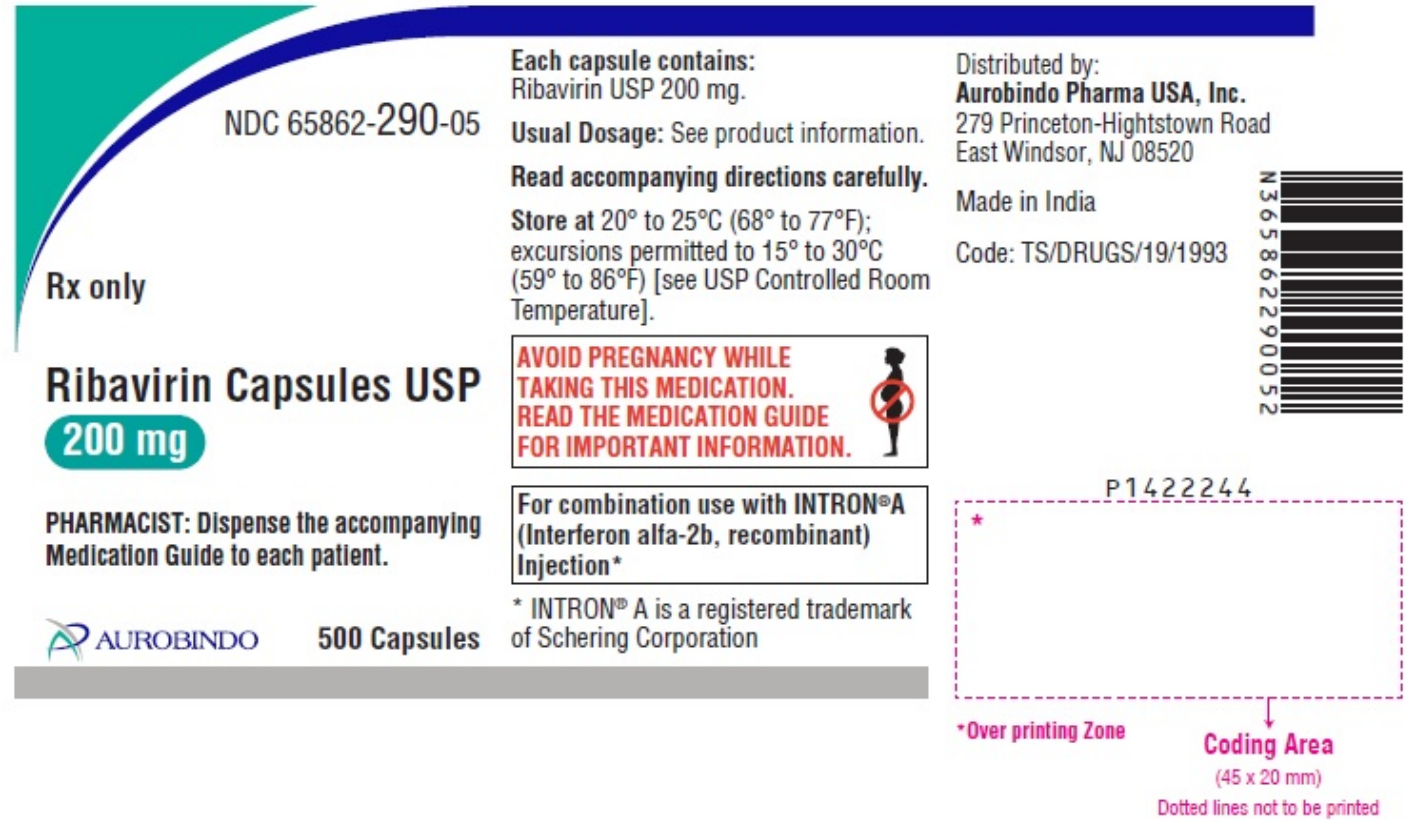
Hyderabad-500 038, India

Revised: 02/2020

PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 200 mg (500 Capsules Bottle)

NDC 65862-290-05

Rx only
Ribavirin Capsules USP
200 mg
PHARMACIST: Dispense the accompanying
Medication Guide to each patient.
AUROBINDO 500 Capsules



RIBAVIRIN

ribavirin capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:65862-290
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
RIBAVIRIN (UNII: 49717AWG6K) (RIBAVIRIN - UNII:49717AWG6K)	RIBAVIRIN	200 mg

Inactive Ingredients	
Ingredient Name	**Strength**
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
POVIDONE K30 (UNII: U725QWY32X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	E;81
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:65862-290-42	42 in 1 BOTTLE; Type 0: Not a Combination Product	09/17/2009	
2	NDC:65862-290-56	56 in 1 BOTTLE; Type 0: Not a Combination Product	09/17/2009	
3	NDC:65862-290-70	70 in 1 BOTTLE; Type 0: Not a Combination Product	09/17/2009	
4	NDC:65862-290-84	84 in 1 BOTTLE; Type 0: Not a Combination Product	09/17/2009	
5	NDC:65862-290-18	180 in 1 BOTTLE; Type 0: Not a Combination Product	09/17/2009	
6	NDC:65862-290-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	09/17/2009	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA079117	09/17/2009	

Labeler - Aurobindo Pharma Limited (650082092)

Establishment

Name	Address	ID/FEI	Business Operations
Aurobindo Pharma Limited		918917642	ANALYSIS(65862-290) , MANUFACTURE(65862-290)

Revised: 2/2020 Aurobindo Pharma Limited

PROTOCOL NUMBER: CCB-CRISIS-01
PROTOCOL VERSION DATE: 10APR2020

CCB-01 Approvals and Revision History

Protocol agreed by:

Clinical Development Barbara L Powers PRINT NAME: Barbara L. Powers, MSN, Ph.D.	Date: 10 April 2020

Research & Development David P. Hesson PRINT NAME: David P. Hesson, Ph.D.	Date: 10 April 2020

Chemistry and Manufacturing/Quality David P. Hesson PRINT NAME: David P. Hesson, Ph.D.	Date: 10 April 2020

Sponsor Representative Vikram Sheel Kumar PRINT NAME: Vikram Sheel Kumar, MD	Date: 31MAR2020

Revision History/Amendments:

Version Number	Date
1.0	31 March 2020
N/A	10 April 2020

STUDY PROTOCOL

The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of combined suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)

Study No: CCB-CRISIS-01

Version Date: 10 April 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

TABLE OF CONTENTS

LIST OF FIGURES

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
BID	Bis in die (two times a day)
BRQ	Brequinar
BUN	Blood urea nitrogen
C6min	Concentration at 6 minutes
CHO/HGPRT	Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase
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
EHR	Electronic health record
ESR	Erythrocyte Sedimentation Rate
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
IMPDH	Inosine-5’-monophosphate
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
SARS	Severe Acute Respiratory Syndrome
SOC	Standard of Care
SPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
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-01 SYNOPSIS	
IND	149291
Title	The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of combined suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)
Protocol	CCB-CRISIS-01
Investigational Product and Dosage	Brequinar is available as 100 and 250 mg oral capsules. One 500 mg/m^2 dose is to be administered on Study Day 1. Ribavirin is available as 200 mg capsules. A dose of 400 mg is to be administered BID x 5 days (Study Days 1 – 5). Subjects will be randomized in a 1:1:1 ratio to either standard of care (SOC) alone, SOC + brequinar, or SOC + brequinar + ribavirin. Treatment assignment will be randomized, open label.
Primary Objective	● To determine the safety and tolerability of SOC, SOC plus brequinar, and SOC plus brequinar plus ribavirin in hospitalized COVID-19 subjects.
Secondary Objectives	● To determine the rates of/changes in clinical status measures listed through Day 15: – Hospitalization status – Duration of hospitalization – NEWS2 Score ● Mortality through Day 29
Exploratory Objectives	• To determine the change in nasopharyngeal viral load through Day 15 ● To determine the change in inflammatory markers through Day 15
Design	This will be a phase 1a randomized, open label, multi-center study with approximately 72 subjects. All subjects will receive SOC per institutional guidelines for treatment of patients with COVID-19 infection. In addition to SOC, the brequinar alone group will receive 1 dose of brequinar 500 mg/m^2. In addition to SOC, the brequinar plus ribavirin group will receive brequinar 500 mg/m^2 on Day 1 plus ribavirin 400 mg BID on Days 1 through 5. Additional subjects may be enrolled following data review. Subjects will have a Screening Visit followed as soon as possible with Study Day 1 (Day 1 may take place on the same day if entry criteria data are available). Study

	procedures are presented in detail in the procedures section, see below. Subjects will be followed through Day 15. Mortality will be assessed at Day 29. If discharge occurs prior to Day 5 for subjects in the brequinar plus ribavirin treatment group, the subject will be provided with sufficient ribavirin to take at home to complete the treatment course. In this case, subsequent study visits are to be conducted by telephone or other digital media as per institutional guidelines. Study information such as hematology and chemistry and NEWS2 criteria is to be collected using the available EHR data.
Sample Size:	Approximately 72 subjects will be randomized to either brequinar or brequinar plus ribavirin or standard of care in a 1:1:1 ratio (approximately 24 subjects on brequinar, 24 subjects on the brequinar plus ribavirin combination, and 24 assigned to standard of care). Additional subjects may be enrolled following data review.
Number of Sites:	1 - 8
Study Period:	An enrollment period of 3 months is expected.
Inclusion Criteria:	1. Willing and able to provide written informed consent for the trial (or designated care giver/healthcare power of attorney may consent if subject unable per institutional guidelines). 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-cleared commercial or public health assay. 4. Life expectancy > 48h in the opinion of the investigator. 5. Hospitalized (in patient with expected duration ≥ 24 hours) 6. The effects of brequinar on the developing human fetus are unknown and ribavirin is contraindicated in women who are pregnant as well as in the male partners of women who are pregnant. 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 treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study. participation, and for 90 days after completion of brequinar administration and for 6 months after completion of ribavirin administration. 7. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of brequinar and for 6 months after completion of ribavirin administration.

	8. ≤ 10 days since first COVID-19 symptom as determined by treating clinician.
Exclusion Criteria:	1. In intensive care unit (ICU) or equivalent level of care or expected to require ICU level of care within next 24 hours. 2. 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 3. Active malignancy other than squamous cell carcinoma; anticancer treatment such as chemotherapy or radiation therapy within the past month. 4. Estimated creatinine clearance < 50 mL/min. 5. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test. 6. Treatment with ribavirin, mycophenolate, leflunomide or teriflunomide, didanosine, azathioprine, tacrolimus, sirolimus, or pre-existing prednisone at higher than 20 mg daily (ongoing or within 2 weeks of study entry). 7. Stevens-Johnson Syndrome or other hypersensitivity reactions to ribavirin or any component of the product.
Treatment	All subjects will receive standard of care (SOC) per institutional guidelines. Subjects will be randomly assigned to SOC alone or SOC plus brequinar alone (1 dose of brequinar 500 mg/m^2) or SOC plus brequinar plus ribavirin (brequinar 500 mg/m^2 on Day 1 plus ribavirin 400 mg BID on Days 1 through 5).
Procedures	**Screening Visit (Study Day -1)** These procedures must be completed within 24h prior to starting dosing. Obtain the subject's written informed consent (be sure to note time of consent), then collect baseline information. Collect information from EHR. Do not perform study-specific procedures for data available from EHR. • Demographics (height, weight, date of birth, gender, race, ethnicity). • Recent (within one year unless ongoing) and relevant medical/surgical history and concomitant medications. • Date of first symptom. • Record any abnormal physical examination findings. • Pregnancy test for women of childbearing potential (WOCBP). • Hematology/chemistry from EHR. • NEWS2 Criteria from EHR. • Polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay for SARS-CoV-2 infection (may utilize test results from

	external laboratory to meet entry criteria provided such results are accurately documented and can be confirmed). • Confirm subject meets all inclusion and no exclusion criteria. **Treatment** The treatment period is up to 5 days: standard of care alone (SOC); or SOC + brequinar 500 mg/m^2 on Day 1 only; or SOC + brequinar 500 mg/m^2 only on Day 1 plus ribavirin 400 mg given twice daily on Days 1 – 5 (a total of 10 doses). Data points such as NEWS2 Criteria and safety labs are to be collected from the EHR when possible, a separate visit by study staff is not required. Give the first dose of brequinar as soon as possible. If assigned to the brequinar + ribavirin group, administer the brequinar as soon as possible and give the first ribavirin dose at the next occurring 8 AM or PM ± 4 h dosing time. If a subject's first ribavirin dose occurs in the PM, the subject will receive the final ribavirin dose on Day 6 in the AM to complete all 10 ribavirin doses. **Days 1 – 7 (8 AM ± 8 hours):** • Collect any adverse events or new concomitant medications since previous visit (may be omitted on Day 1 if Screening visit is conducted on same day as Study Day 1). • Collect NEWS2 Criteria from EHR Days 1 (pre-dose), 3, 5, 7. • Collect SOC hematology/chemistry results from EHR on Day 1 and Day 7 (may be omitted if Screening visit conducted on same day as Study Day 1). Ensure that Day 1 samples are obtained prior to first dose of study drug, if applicable. • Collect samples for inflammatory markers Days 1 (pre-dose), 3, 5, 7; process locally or send to central lab as appropriate. • Collect nasopharyngeal viral load samples Days 1 (pre-dose), 3, 5, 7. • Record hospitalization status (hospitalized, hospitalized in ICU, discharged). • Dispense study medication (Day 1 only if in brequinar only group, brequinar + ribavirin Days 1 – 5 (or 6) if assigned to this group and dispense ribavirin at 8 PM ± 4 hours on these days. • Drug accountability Day 7. **Final Visit Day 15** (8 AM ± 24 hours) • Collect information for any adverse events or new concomitant medications since Day 7 from EHR. • Collect results for SOC hematology/chemistry. • Collect sample for inflammatory markers; process locally or send to central lab as appropriate.

	• Collect NEWS2 Criteria from EHR. • Collect nasopharyngeal viral load sample. • Collect hospital status (hospitalized, hospitalized in ICU, discharged) from EHR. **Day 29 (8 AM ± 72 hours)** • Determine survival status from EHR if available or by telephone/digital media per institutional guidelines to subject. Note: If discharge occurs prior to Day 5 for subjects in the brequinar plus ribavirin treatment group, the subject will be provided with sufficient ribavirin to take at home to complete the treatment course. In this case, the Day 7 (including drug accountability) and Day 15 visits are to be conducted via telephone or other digital media as permitted by the institution.
Safety/ Tolerability	**Safety/Tolerability** Adverse events will be collected beginning from the time of informed consent through at least 14 days after the final dose of study medication.
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, safety laboratory data, and NEWS2 Criteria. Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of treatment-emergent adverse events (TEAEs), defined as AEs 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, NEWS2 Criteria, and other clinical measures will be summarized using appropriate descriptive statistics.

STUDY PERSONNEL

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3 INTRODUCTION

3.1 Background

3.2 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]).

3.2.1 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 [22]).

3.3 Host Nucleotide Synthesis

Host *de novo* nucleotide synthesis is divided into two arms: purine synthesis (A, G) and pyrimidine synthesis (U, T, C). Host *de novo* pyrimidine synthesis generates uridine monophosphate (UMP) as the building block for all pyrimidine ribonucleotides and deoxyribonucleotides (Figure 3-1). Host *de novo* purine synthesis has more redundancy with parallel paths of adenosine and guanosine synthesis.

These pathways of pyrimidine and purine synthesis are non-overlapping and differ in two salient aspects: [1] the pool of intracellular purines (A, G) tends to be larger than the pool of pyrimidines (U, T, C) and [2] there exists no salvage pathway for the synthesis of UMP, the fundamental building block of pyrimidines. For these reasons, inhibition of enzymatic steps upstream of UMP (Figure 3-1) leads to a more rapid and more profound depletion of intracellular pyrimidines than inhibition of enzymatic steps upstream of GMP (Figure 3-2).

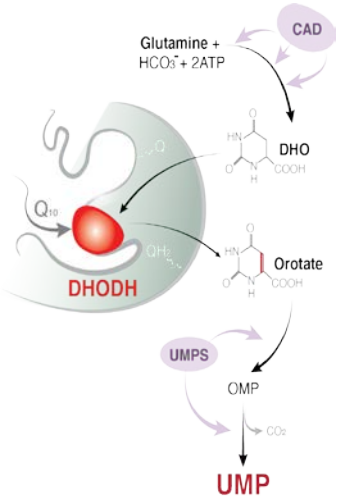

Figure 3-1. DHODH is a mitochondrial enzyme that catalyzes the 4th step of pyrimidine synthesis; it is completely essential for the generation of UMP.

3.4 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.

3.5 Inosine monophosphate dehydrogenase (IMPDH)

Inosine monophosphate dehydrogenase (IMPDH) catalyzes the conversion of IMP to XMP en route to the *de novo* synthesis of GMP (Figure 3-2). Inhibition of IMPDH results in a depletion of intracellular guanosine monophosphate.

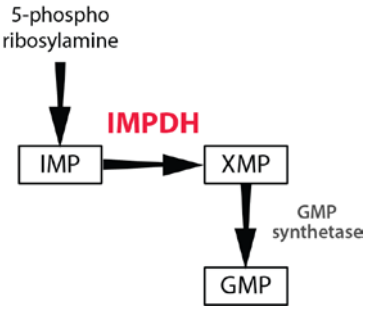

Figure 3-2. IMPDH catalyzes the conversion of IMP to XMP in the synthesis of guanosine monophosphate.

3.6 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.

The antiviral activity of brequinar has been demonstrated in studies of rotavirus replication in human intestinal Caco2 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 [13]**).** 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]).

3.7 Ribavirin

Ribavirin is an FDA-approved anti-viral agent and is marketed in combination with interferon alfa-2b for the treatment of chronic hepatitis C (ribavirin generic SPC, Appendix E, Section 15.5).

Ribavirin is a purine nucleoside analog with multiple mechanisms of action. It is known to inhibit the host enzyme inosine-5'-monophosphate dehydrogenase (IMPDH), the enzyme that catalyzes the conversion of inosine 5'-phosphate (IMP) to xanthosine 5'-phosphate (XMP), the first committed and rate-limiting step in the *de novo* synthesis of guanine nucleotides. In addition, ribavirin binds to and inhibits the SARS-CoV-2 viral enzyme – the RNA dependent RNA polymerase (RdRp) (Elfiky et al., 2020 [26]). And finally, another important mechanism of action that may contribute to ribavirin's antiviral effect is the ability to act as a ribonucleotide analog which can be incorporated into the viral RNA genome and lead to detrimental mutations in a process termed hypermutagenesis (Ortega-Prieto et al., 2013 [24]).

In pre-clinical studies, ribavirin has a demonstrated broad spectrum *in vitro* anti-viral activity and acts as an immunomodulator in a mouse hepatitis coronavirus model (Ning et al, 1998 [21]).

Ribavirin and mycophenolate mofetil (a more potent IMPDH inhibitor) were proposed for the treatment of MERS CoV infection with hints of clinical activity in small case studies (Ghamdi et al., 2016 [11]; Chong et al., 2015 [12]). Ribavirin as a single agent showed hints of activity in the previous SARS outbreak (Poutanen et al., 2003 [25]). Ribavirin and other IMPDH inhibitors are currently being proposed as possible treatments for the current COVID-19 pandemic (Gordon et al., 2020 [26]). Ribavirin as a single-agent may not be highly-effective based on the clinical progression of patients with SARS who were treated only with ribavirin (Peiris et al., 2003 [18]). There is currently an active combination trial of lopinavir/ritonavir, ribavirin and IFN-beta in Hong Kong for COVID-19 (NCT04276688).

3.8 Rationale for the Planned Trial

The CRISIS trial studies standard of care (SOC), SOC with DHODH inhibition, and SOC with DHODH inhibition and IMPDH inhibition. SOC is evolving rapidly for COVID-19 and at institutions includes approved FDA drugs such as lopinavir/ritonavir that have shown activity in coronaviruses. These may be combined into this trial.

In particular this trial combines brequinar – an inhibitor of host pyrimidine synthesis (DHODH) – with the anti-viral ribavirin, a nucleoside analog that acts as an inhibitor of host IMPDH and an inhibitor of the viral RNA dependent RNA polymerase (RdRp). In addition, the misincorporation of ribavirin as a nucleoside analog into the replicating viral genome will be accentuated because the dose of ribavirin will be diluted into a smaller pool of host nucleotides, thereby increasing its effective intracellular concentration (Liu et al., 2020 [27]).

The temporary depletion of the host pyrimidine and purine pools in combination with the ribavirin effect on viral RdRp is hypothesized to lead to a significant reduction in virus replication at a critical point in the COVID-19 disease, restoring the balance in favor of the host immune system for ultimate clearance of SARS-CoV-2. This combination has been recently been shown to be effective in a pre-clinical model of disease where the authors demonstrated that inhibitors of DHODH could potentiate the activity of inhibitors of RdRp in the treatment of dengue virus, another single-stranded RNA virus (Liu et al., 2020 [27]).

DHODH is already considered a potential therapeutic target in antiviral, oncology and autoimmune indications. Multiple doses of high-potency DHODH inhibitors are under investigation in the treatment of patients with hematologic malignancies. In addition to an anticancer effect when delivered in multiple high-doses, DHODHi may also prove effective in inhibiting viral replication

by starving the host cell - and thus the replicating virus - of nucleotides, thereby acutely reducing the viral load in diseases such as COVID-19.

Emerging data from SARS-CoV-2 infections show peaks of viral load 5 to 6 days after the onset of symptoms; the viremia then resolves within 10-14 days. This may be distinct from previous coronavirus infections where viral loads peaked approximately 10 days after the start of symptoms (Peiris et al., 2003 [18]). The timed and transient inhibition of DHODH and depletion of host pyrimidine nucleotides during the early period of the disease is expected to suppress viral replication during its peak and decrease viral load, leading to a rapid resolution of clinical symptoms.

Due to the relatively short course of active viral replication in COVID-19, a single dose of brequinar administered at the right time may provide clinical benefit in patients requiring hospitalization due to the coronavirus infection. See Figure 3-3 for changes in viral load versus day of symptom onset in two patients with SARS-CoV-2 (Pan et al., 2020 [19]).

Clear Creek hypothesizes that the timed inhibition of DHODHi or DHODHi + IMPDHi and depletion of host pyrimidine and purine nucleotides during the period of increased viral load will suppress viral replication leading to a more rapid resolution of clinical symptoms.

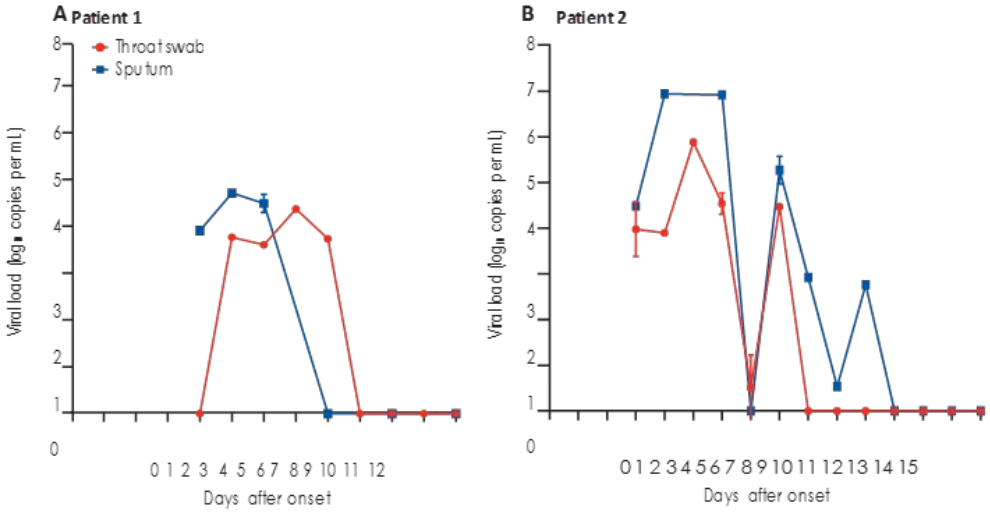

Figure 3-3. Changes in viral load versus day of symptom onset – COVID-19

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.

It is also hypothesized that the suppression of host nucleotide synthesis and therefore viral replication would be most effective early in the course of disease while there is still ongoing viral replication.

3.8.1 Brequinar Dose Selection

Safety data from previous oncology clinical studies of brequinar with maximum tolerated doses as high as 2250 mg/m^2 repeated every 3 weeks and from the active brequinar study in acute myeloid leukemia (AML) patients suggest that a single dose of 500 mg/m^2 p.o. will be safe and well tolerated. Brequinar has *in vitro* antiviral EC50s that range from 0.04-1.0 µM that equal 0.016-0.40 µg/mL of brequinar. If the effective concentration to inhibit 90% of virus replication (EC90) is assumed to be one log great, then a plasma concentration of 0.1-4 µg/mL would be needed. A single oral dose of 500 mg/m^2 maintains a plasma level of at least 4 µg/mL for 48-72 hours (see Brequinar IB [5]).

3.8.2 Ribavirin Dose Selection

Ribavirin is marketed in combination with interferon-alpha for treatment of chronic hepatitis caused by the RNA virus hepatitis C. The proposed dose for the COVID-19 study is based on the ribavirin generic Summary of Product Characteristics (SPC) found in Section 15.5. In chronic hepatitis C patients, ribavirin at 400 mg BID has shown 13% anemia when combined with interferon. Ribavirin suppressed viral load with some activity when given for SARS in 2003 at 400 mg TID. At that dose, 8% (of 75) or 0% (of 31) patients developed anemia (Peiris et al., 2003 [18]; So et al., 2003 [28]). The CRISIS trial will administer ribavirin at the labelled dose of 400 mg BID for 5 days. Given the recent evidence in a pre-clinical dengue virus model of disease that the misincorporation of ribavirin as a nucleoside analog into the replicating viral genome will be accentuated because the dose of ribavirin will be diluted into a smaller pool of host nucleotides, the labeled dose of 400 mg two times a day (BID) chosen should provide optimal safety with the potential for a benefit in combination with brequinar (Liu et al., 2020 [27]).

3.8.3 Risk/Benefit of Brequinar

As presented in the Brequinar IB [5], more than 800 cancer patients 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. Brequinar has also been utilized in studies 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. While no DHODHi has been tested to date in the clinic for infection with SARS-CoV-2 and no brequinar safety information is available in treatment of this disease, DHODHi therapy in the context of trials for patients with cancer has the expected side-effects of mucositis and bone marrow suppression. Chronic DHODHi therapy in patients with autoimmune disease has the expected (and desired) effects on T-cell suppression (activated T-cells have a particular dependence on pyrimidine synthesis). However, a single, relatively low dose of brequinar such as that proposed for administration in this study should be safe, well tolerated and manifest none of these potential side-effects.

The possible benefit in using brequinar to treat SARS-CoV-2 infection is the hypothesis that a single dose of brequinar will suppress host *de novo* pyrimidine synthesis for a period of up to 72 hours thus decreasing viral load. As discussed above, inhibition of DHODH is expected to reduce the ability of the virus to replicate and it is for this reason that study CCB-CRISIS-01 will administer brequinar to patients with COVID-19.

3.9 Risk/benefit of Ribavirin

Risks associated with ribavirin administration in 40% or greater of adult patients receiving ribavirin with interferon included fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability. Additional safety information is provided in the ribavirin generic SPC (Section 15.5).

The possible benefit in using ribavirin to treat SARS-CoV-2 infection is the hypothesis that the expected suppression of host nucleotide synthesis associated with ribavirin will prevent viral replication when used in conjunction with brequinar thereby reducing viral load.

3.10 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration of 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 drug administration. The majority of these adverse effects have been less than grade IV in severity and resolve following discontinuation of dosing.

Risks associated with ribavirin administration in hepatitis C patients who also received interferon-alpha are presented in the ribavirin generic SPC found in Section 15.5. The most commonly reported adverse reactions in adult subjects receiving PegIntron or INTRON A in combination with ribavirin were fatigue/asthenia, headache, rigors, fevers, nausea, myalgia, and anxiety/emotional lability/irritability.

3.11 Possible Interactions with Concomitant Medical Treatments

While not previously tested in patients with viral infections, brequinar has been administered to subjects taking a variety of concomitant medications that are typical in cancer patients. 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. Brequinar has also been used concomitantly with antibiotics, antifungals and other critical care medications.

There is no experience with brequinar for treatment of SARS-CoV-2 and other severe viral infections and no formal interaction studies have been conducted.

Experience with use of ribavirin and interferon in treatment of hepatitis C has concluded that ribavirin should not be given with nucleoside reverse transcriptase inhibitors such as didanosine or with azathioprine. There is limited experience with ribavirin for treatment of SARS-CoV-2 and other severe viral infections and no formal interaction studies have been conducted for use of

ribavirin with concomitant medications that are typical in these patients. Ribavirin should be taken with food, when possible. See ribavirin generic package insert, Appendix E Section 15.5.

3.11.1 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).

Results of in vitro studies using both human and rat liver microsome preparations indicated little or no cytochrome P-450 enzyme-mediated metabolism of ribavirin, with minimal potential for P-450 enzyme-based interactions (ribavirin generic SPC Appendix E Section 15.5).

3.12 Steps to be Taken to Control or Mitigate Risks

All subjects will be treated in a hospital setting by highly experienced infectious disease specialists and other qualified staff familiar with the treatment of severe viral infections and their complications.

4 TRIAL OBJECTIVES

4.1 Primary Objective

- To determine the safety and tolerability of standard of care (SOC), SOC plus brequinar alone and SOC plus brequinar plus ribavirin in hospitalized COVID-19 subjects.

4.2 Secondary Objectives

The secondary objectives of this study are:

- To determine the changes in clinical status measures listed through Day 15:
  - Hospitalization status
  - Duration of hospitalization
  - National Early Warning System 2 Score (NEWS2) Score
- To determine survival status through Day 29

4.3 EXPLORATORY OBJECTIVES

- To determine the change in nasopharyngeal viral load through Day 15
- To determine the change in inflammatory markers through Day 15

5 TRIAL DESIGN

This will be a phase 1a randomized, open label, multi-center study with approximately 72 subjects. All subjects will receive standard of care per institutional guidelines for treatment of patients with SARS-CoV-2 infection. In addition to standard of care, the brequinar alone group will receive 1 dose of brequinar 500 mg/m^2. In addition to standard of care, the brequinar plus ribavirin group will receive brequinar 500 mg/m^2 on Day 1 plus ribavirin 400 mg BID on Days 1 through 5.

The Massachusetts General Hospital (MGH) COVID-19 Treatment Guidance is provided in Appendix D Section 15.5. This guidance provides an example of standard of care instructions for treatment of COVID-19. It is not required that this guidance be used.

Subjects will have a Screening Visit followed as soon as possible with Study Day 1 (Day 1 may take place on the same day if entry criteria data are available). Study procedures are presented in detail in Section 8. Subjects will be followed through Day 15, with mortality assessed via a phone call/other digital media acceptable to institution on Day 29.

Additional subjects may be enrolled following data review.

If discharge occurs prior to Day 5 for subjects in the brequinar plus ribavirin treatment group, the subject will be provided with sufficient ribavirin to take at home to complete the treatment course. In this case, the Day 7 (including drug accountability) and Day 15 visits are to be conducted by telephone.

It is understood that some assessments may not be conducted if the subject is unable to return to the clinic after discharge due to restricted travel. If an assessment is missed due to after hospital discharge, e.g., samples or blood draws, this will not be counted as a protocol deviation. Any of the study visits may be conducted via telephone if the subject has been discharged from the hospital and is not permitted to or is unable to return to the hospital/clinic for these visits.

Information is to be collected using the electronic health record (EHR) whenever possible. It is not required to perform study-specific laboratory assessments, NEWS 2 criteria, etc.

6 TRIAL ENDPOINTS

6.1 Primary Endpoint

- Safety/tolerability measured by rates of treatment-emergent adverse events (TEAEs) and hematology/chemistry safety labs.

6.2 Secondary Endpoints

- Rates of/changes to the below clinical status measures through Day 15.
  - Hospitalization status
  - Duration of hospitalization in days
  - NEWS2 Criteria Days 1, 3, 5, 7, and Day 15 for hospitalized subjects.
- Mortality through Day 29

6.3 EXPLORATORY Endpoints

- Nasopharyngeal viral load: Day 1 (pre-dose), Days 3, 5, 7, and 15

- Inflammatory markers (to be specified in the Laboratory Manual, may include but are not limited to erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), D-dimer, serum ferritin, and fibrinogen (if submitted to central lab), procalcitonin, IL-6, MCP-1, IL-5, KC/GRO(CXCL1), IL-2, IFN-ɣ, final list to be determined) on Day 1 pre-dose, D3, D5, D7, D15 or at frequency per institutional standard of care. The markers are to be tested locally when possible; requested tests as listed in the Laboratory Manual that are not analyzed locally are to be shipped to the central laboratory.

7 TRIAL POPULATION

7.1 Number of Subjects

Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 72 subjects have completed the study. Additional subjects may be enrolled following data review. Subjects will be randomized to either brequinar or brequinar plus ribavirin or standard of care in a 1:1:1 ratio (approximately 24 subjects on brequinar, 24 subjects on the brequinar plus ribavirin combination, and 24 assigned to standard of care).

7.2 Inclusion criteria

1. Willing and able to provide written informed consent for the trial (or designated care giver/healthcare power of attorney may consent if subject unable per institutional guidelines).
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 Food and Drug Administration (FDA)-cleared commercial or public health assay.
4. Life expectancy > 48h in the opinion of the investigator.
5. Hospitalized (in patient with expected duration ≥ 24 hours)
6. 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 treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study. participation, and for 90 days after completion of brequinar administration and for 6 months after completion of ribavirin administration.
7. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of brequinar and for 6 months after completion of ribavirin administration.
8. ≤ 10 days since first COVID-19 symptom as determined by treating clinician.

7.3 Exclusion Criteria

1. In intensive care unit (ICU) or equivalent level of care or expected to require ICU level of care within next 24 hours.
2. 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.
3. Active malignancy other than squamous cell carcinoma; anticancer treatment such as chemotherapy or radiation therapy within the past month.
4. Estimated creatinine clearance < 50 mL/min.

5. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test.
6. Treatment with ribavirin, mycophenolate, leflunomide or teriflunomide, didanosine, azathioprine, tacrolimus, sirolimus, or pre-existing prednisone at higher than 20 mg daily (ongoing or within 2 weeks of study entry).
7. Stevens-Johnson Syndrome or other hypersensitivity reactions to ribavirin or any component of the product.

7.4 Inclusion of Women and Minorities

Adult men and women of all races and ethnic groups are eligible for this trial.

8 STUDY TREATMENTS

8.1 Description of Study Medications

8.1.1 Brequinar

Brequinar will be supplied as 100 and 250 mg capsules. Dosing will be a single oral dose of 500 mg/m^2. The initial brequinar dose should be administered as soon as possible based on the availability of the investigational pharmacy.

8.1.2 Ribavirin

Ribavirin will be supplied as 200 mg capsules. Ribavirin should be taken with food, when possible. Dosing will be 400 mg BID for 5 days (Days 1 – 5) approximately 8 AM and 8 PM ± 4 hours.

8.2 Treatment Administration

This will be a phase 1a randomized, open label, multi-center study with approximately 72 subjects. All subjects will receive standard of care (SOC) per institutional guidelines for SARS-CoV-2 infection. Subjects will be randomly assigned in a 1:1:1 ratio to standard of care alone, standard of care plus brequinar, or standard of care plus brequinar plus ribavirin. The brequinar alone group will receive 1 dose of brequinar 500 mg/m^2 on Day 1. The brequinar plus ribavirin group will receive brequinar 500 mg/m^2 on Day 1 along with ribavirin 400 mg BID x 5 days (study days 1 – 5).

8.2.1 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE).

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 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 most instances, brequinar-related toxicities were clinically manageable and reversible upon discontinuation of brequinar treatment. In a study where brequinar was dosed twice-weekly to solid tumor subjects, no drug-related deaths occurred. Stomatitis/mucositis was observed in 13 of the 19 (68%) patients across all doses. Mild to moderate (Grades 1 and 2) stomatitis was observed in 10 patients with a more severe (Grade 3) stomatitis seen in 3 patients at doses over 600 mg/m^2. One patient at 600 mg/m^2 had drug discontinuation due to drug-related stomatitis. Myelosuppression was the main dose-limiting toxicity (DLT) with thrombocytopenia (Grades 1-4), observed after 2 to 9 doses above 600 mg/m^2. Three patients in the ongoing AML study experienced severe (Grade 3 or 4) mucositis following administration of two or more doses of

brequinar. Any of these events reported with brequinar use can be serious in nature and may result in death.

A single dose of brequinar at a low level relative to those administered in the cancer studies noted above is expected to be safe and well tolerated in the COVID-19 population.

For ribavirin, the primary toxicity is hemolytic anemia which has been reported in approximately 13% of subjects taking ribavirin and interferon alfa-2a on a chronic basis in combination with PegIntron A for hepatitis C. The most commonly reported adverse reactions in adult subjects receiving PegIntron or INTRON A in combination with ribavirin were fatigue/asthenia, headache, rigors, fevers, nausea, myalgia, and anxiety/emotional lability/irritability. See the ribavirin generic SPC for complete ribavirin safety information (ribavirin generic SPC, Section 15.5). It is expected that the proposed acute use of ribavirin using the 400 mg BID x 5-day regimen will 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 15 (or longer if needed to follow up study medication-related adverse events). Mortality is assessed at Day 29.

After treatment, participants will be monitored through Study Day 15. Participants may discontinue from the study by withdrawing consent at any time or for any reason as presented in Section 9.7.

If discharge occurs prior to Day 5 for subjects in the brequinar plus ribavirin treatment group, the subject will be provided with sufficient ribavirin to take at home to complete the treatment course. In this case, conduct any subsequent visits (such as the Day 7 (including drug accountability) and Day 15 visits) over the phone or other digital media as permitted by the institution.

The reason for study discontinuation will be recorded in the source document and the eCRF.

8.4 Concomitant Medication/Treatment

Record the name, start date, indication for use, 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. The use of other DHODH inhibitors and IMPDH inhibitors are not permitted during the study including ribavirin, mycophenolate, leflunomide or teriflunomide (see Section 8.6.6).

8.5 Treatment Compliance

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

8.6 Storage, Stability, Labeling and Packaging

8.6.1 Storage and Stability

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

8.6.2 Labeling and Packaging

Each brequinar bottle/dispensing container for subject use will be labeled with at least the following information:

For Clinical Trial Use Only
Study Number: CCB-CRISIS-01
Contents: 100 or 250 mg Brequinar capsules
For oral use only. Take with approximately 8 ounces water.
Subject Number: XX-XXXX
Treatment Duration: As directed
Clinical Batch Number: XXXXXXX
Expiration Date: TBD
Storage: Store at controlled room temperature
Study Sponsor: Clear Creek Bio, Inc., 585 Massachusetts Avenue, 4th Floor, Cambridge MA 02139
Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

Each ribavirin bottle/dispensing container for subject use will be labeled with at least the following information:

For Clinical Trial Use Only
Study Number: CCB-CRISIS-01
Contents: Ribavirin capsules (dosing per body weight)
For oral use only. Take with approximately 8 ounces water and with food (when possible)
Subject Number: XX-XXXX
Treatment Duration: As directed
Clinical Batch Number: XXXXXXX
Expiration Date: TBD
Storage: Store at controlled room temperature
Study Sponsor: Clear Creek Bio, Inc., 585 Massachusetts Avenue, 4th Floor, Cambridge MA 02139
Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

8.6.3 Blinding and Randomization

The trial will be conducted in an open-label manner with random assignment to standard of care, standard of care plus brequinar or standard of care plus the brequinar plus ribavirin combination. The brequinar and ribavirin capsules will be provided to each participating institution in bulk to be dispensed by the institution's pharmacist per the designated mg/m^2 dose (for brequinar) and ribavirin 400 mg BID x 5 days for each subject. Randomization assignments will be provided by the sponsor.

8.6.4 Unblinding/Expectedness

It is not necessary to break the blind for this open label study as the treatment will be known for each subject.

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

8.6.5 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, used and discarded. It must be clear from the records whether the subject received study medication or was assigned to standard of care. 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 detailing how to calculate the mg/m^2 dose together with examples of combinations of the 100 and 250 mg capsules to provide the most efficient use of the clinical supplies.

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.

If the subject is discharged prior to completing ribavirin dosing, the subject is to be given sufficient supplies to complete the 10-dose course. Drug accountability should be checked at the Day 7 visit in this case.

8.6.6 Prohibited Medications

The use of didanosine and azathioprine are not permitted during the study. The use of other DHODH inhibitors and IMPDH inhibitors such as mycophenolate, leflunomide or teriflunomide are not permitted during the study.

8.6.7 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 telephone or other digital media. Study information is to be collected from the EHR as much as possible such as NEWS2 Criteria, height, weight, hematology/chemistry.

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) 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.

Signed written informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to signing the informed consent but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. An original signed informed consent form will be subject to review by the Sponsor; a copy will be given to the subject and a copy will be filed with the subject's medical notes.

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.

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

NEWS2 Criteria, laboratory assessments, SARS-CoV-2 testing, and other observations will be conducted by experienced personnel throughout the study based on the Schedule of Events. The majority of study information is to be collected from the EHR.

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 (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium), lactate dehydrogenase (LDH).

Inflammatory markers including D-dimer, ferritin, CRP, ESR, troponin, and procalcitonin. Additional inflammatory markers will be specified in the Laboratory Manual.

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

Nasopharyngeal swabs for viral load will be collected Days 1, 3, 5, 7, and 15.

NEWS2 Criteria are available in Appendix C Section 15.3.

Hospitalization status is to be recorded as hospitalized not in ICU, hospitalized in ICU, or discharged.

9.5 Study Conduct

Screening Visit (Study Day -1)

These procedures must be completed within 24h prior to starting dosing. Obtain the subject's written informed consent (be sure to note time of consent), then collect baseline information from the EHR.

- Demographics (date of birth, gender, race, ethnicity, height and weight).
- Recent (within one year unless ongoing) and relevant medical/surgical history and concomitant medications.
- Date of first symptom.
- Record any abnormal physical examination findings as recorded in EHR.
- Hematology/chemistry from EHR.
- Pregnancy test for women of childbearing potential (WOCBP).
- NEWS2 Criteria.
- Polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay for SARS-CoV-2 infection (may utilize test results from external laboratory to meet entry criteria provided such results are accurately documented and can be confirmed).
- Samples for nasopharyngeal viral load.
- Confirm subject meets all inclusion and no exclusion criteria.

Treatment

The treatment period is up to 5 days: standard of care alone (SOC); or SOC + brequinar 500 mg/m^2 on Day 1 only; or SOC + brequinar 500 mg/m^2 only on Day 1 plus ribavirin 400 mg given twice daily on Days 1 – 5 (a total of 10 doses). Data points such as NEWS2 Criteria are to be collected from the EHR when possible, a separate visit by study staff is not required. The first dose of

brequinar is to be given as soon as possible depending on availability of investigational pharmacy staff. If the subject is assigned to the brequinar + ribavirin treatment arm, give the brequinar as soon as possible and dose the ribavirin at 8 AM/8 PM ± 4 h, whichever is closer. If discharge occurs prior to Day 5 for subjects in the brequinar plus ribavirin treatment group, the subject will be provided with sufficient ribavirin to take at home to complete the treatment course. In this case, any subsequent visits are to be conducted by telephone/digital media, e.g. for the Day 7 and Day 15 visits. If the first ribavirin dose is afternoon/evening, the subject will need to be dosed on Day 6 in the morning in order to complete the 10 ribavirin doses.

It is understood that some assessments may not be conducted if the subject is unable to return to the clinic after discharge due to restricted travel; this will not be counted as a protocol deviation. The Day 7 and 15 visits are to be conducted via telephone if the subject has been discharged from the hospital and is not permitted to or is unable to return to the hospital/clinic for these visits. Collect information from the EHR. It is not necessary to make study-specific assessments.

Days 1 - 7 (8 AM ± 8 hours)

- Collect any adverse events or new concomitant medications since previous visit (may be omitted on Day 1 if Screening visit was conducted on same day as Study Day 1).
- Collect hematology/chemistry results from the EHR on Day 1 (pre-dose) and Day 7 (may be omitted for Day 1 if Screening visit conducted on same day as Study Day 1). Ensure that Day 1 samples are obtained prior to first dose of study drug, if applicable.
- Collect inflammatory markers Days 1, 3, 5, and 7 from EHR for those analyzed locally. Collect, process and ship samples for additional central laboratory analysis as needed per Laboratory Manual.
- Collect NEWS2 Criteria from the EHR Days 1, 3, 5, 7.
- Collect nasopharyngeal viral load samples Days 1, 3, 5, 7.
- Record hospitalization status (hospitalized, hospitalized in ICU, discharged).
- Dispense study medication (Day 1 only if in brequinar only group, brequinar + ribavirin Days 1 – 5 if assigned to this group and dispense ribavirin at 8 PM ± 4 hours on these days. If first ribavirin dose is PM due to admission timing, subject will receive last ribavirin dose AM of Day 6.
- Drug accountability Day 7.

Final Visit Day 15 (8 AM ± 24 hours)

- Collect information for any adverse events or new concomitant medications since Day 7 from EHR.
- Collect results for SOC hematology/chemistry from the EHR.
- Collect inflammatory markers from EHR for those analyzed locally. Obtain and ship those to be analyzed at the central laboratory.
- Collect NEWS2 Criteria from the EHR.
- Collect nasopharyngeal viral load sample.

- Collect hospital status (hospitalized, hospitalized in ICU, discharged).

Day 29 (8 AM ± 72 hours)

- Phone call/digital media as acceptable to the institution to the subject to check survival status.

9.5.1 Unscheduled Visits

Unscheduled visits and tests to assess AEs are permitted as needed providing the AE onset occurs within two (2) weeks after the final study dose.

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. Provided that activities are carried out within the identified windows it will not be necessary to file a protocol deviation. It is understood that some scheduled study assessments may not be able to be conducted if the subject is unable to return to the clinic after discharge due to COVID-19 restricted travel; it is also understood that crowded hospital conditions/lack of personnel may make it impossible to carry out all requested study procedures; this will not be counted as a protocol deviation. The Day 7 and 15 visits are to be conducted via telephone if the subject has been discharged from the hospital.

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 be withdrawn from the study 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 evaluations for subjects who withdraw from the study prior to completing the treatment period, unless consent is withdrawn.

If discharge occurs prior to Day 5 for subjects in the brequinar plus ribavirin treatment group, the subject will be provided with sufficient ribavirin to take at home to complete the treatment course. In this case, the subject is to return to the clinic for Day 7 and Day 15 visits.

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).

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 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.

AEs will be collected beginning from the time of informed consent through at least 14 days after the final dose of study medication. 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.

Any serious adverse events (SAEs) experienced after 30 days post the last dose of study drug should only be reported to the sponsor if the investigator suspects a causal relationship to the 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, or require therapy.

Death due to disease progression should not be reported as an SAE. Report death from disease progression on the End of Study and Death forms.

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 progression of the disease under study.

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 descriptions and grading scales found in the revised National Cancer Institute (NCI) Common Terminology *Criteria for Adverse Events (CTCAE) version 4.03* will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html)*.

10.1 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.

10.2 Classification of Severity

The descriptions and grading scales found in the revised NCI CTCAE version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria. The CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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.

10.3 Serious Adverse Event (SAE) Reporting

The regulatory definition of an SAE is any untoward medical occurrence or effect that at any dose:

- 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, or
- is a congenital anomaly / birth defect;
- all other events that are 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 the studied indication, 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;
- Note that 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 is not an SAE.

Death due to disease progression is considered to be an Expected event in patients with severe SARS-CoV-2 infection and does not require reporting on an expedited basis.

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 and fax telephone number 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 the Sponsor contact until the event has subsided or, in case of permanent impairment, it stabilizes, and the overall clinical outcome has been ascertained.

SAE REPORTING EMAIL: Safety-CCB-CRISIS-01@prosoftclinical.com

Medical Monitor:

Sharon Levy, MD	Telephone:	O: (484) 320-2062

Sponsor Representative:

Barbara Powers, MSN, Ph.D.	Telephone:	M: 484-686-0545
	Email:	bpowers@clearcreekbio.com

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

10.4 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 Medical Monitor 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 is to 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 the Medical Monitor/Sponsor. Follow-up information is to be subsequently communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs are to 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 knowledge by the Medical Monitor/Sponsor.

The Medical Monitor/Sponsor or designee must 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.

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

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as 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-up with 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.

10.6 Data Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be established to provide independent oversight to this trial. The primary responsibility of the DSMB 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 DSMB will be detailed in a separate DSMB charter. The DSMB 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 DSMB Chair will advise the Sponsor that the study be stopped, a treatment arm dropped, or that the study may continue per protocol.

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 analyses will be based on the ITT population, which is defined as all randomized subjects.

11.2 Safety Analyses

Safety and tolerability will be assessed in terms of AEs, SAEs, NEWS2 Criteria, 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 (TEAEs), defined as AEs occurring after randomization, will be tabulated by MedDRA preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results and NEWS2 Criteria will be summarized using appropriate descriptive statistics.

11.3 Efficacy Analyses

Efficacy will be assessed in terms of mortality, hospitalization status and duration, NEWS2 score, viral load (plasma and nasopharyngeal), and inflammatory markers.

11.4 Sample Size Considerations

Formal sample size calculations are not applicable for this phase 1a, open label study. Up to 72 subjects are planned to be entered in this trial. Additional subjects may be enrolled following data review.

11.5 Randomization

A randomization scheme will be provided by the Sponsor to ensure subjects are randomly assigned to SOC, SOC + brequinar, or SOC + the brequinar plus ribavirin combination in a 1:1:1 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.

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) 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.

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15 APPENDICES

15.1 Appendix A: CCB-01 Schedule of Events

CCB-CRISIS-01 Schedule of Events **Procedures**	**Screen**	**D1**	**D2 - D7**	**Final Visit D15**	**F/U Phone Call 2 weeks/ Survival**
Informed Consent	X				
AE/Concomitant Medications	X	X	X	X	
Medical history / History of current illness	X				
Demographics, collect Height and weight	X				
Check for Physical Exam abnormalities	X	X			
Pregnancy Test (urine or serum)	X				
Hematology/Chemistry	X	X (pre-dose)	D7	X	
Inflammatory Markers*		X (pre-dose)	D3, D5, D7	X	
Swab collection for nasopharyngeal viral load		X (pre-dose)	D3, D5, D7	X	
Clinical SARS-CoV-2 testing RT-PCR	X				
Hospital Status		X	X D7	X	
NEWS2 Criteria	X	X	D3, D5, D7	X	
Dispense Study Medication		X	X (D2 – 5 if assigned to ribavirin combination)	X	
Drug Accountability			X D7		
Survival Assessment Day 29					X

Collect information from available electronic health record (EHR) whenever possible; a special visit by research staff is not to be performed. Hematology, Results for Chemistry and available inflammatory markers analyzed locally are to be obtained from the EHR; do not draw another set of labs. Missed samples due to hospital staff too busy or for technical reasons unable to obtain samples will not be counted as protocol deviations.

Note that any visits other than Screening/Day 1 may be conducted via telephone or digital media. Missed samples/assessments when phone visits occur will not be counted as protocol deviations.

*Inflammatory markers including D-dimer, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), D-dimer, serum ferritin, and procalcitonin, IL-6 are to be collected from the EHR when available; otherwise process and ship samples to the central laboratory per the Laboratory Manual.

15.2 Appendix B: Investigator's Statement and Agreement

STUDY NUMBER: CCB-CRISIS-01

STUDY TITLE: The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of combined suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19).

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:** _____

Site Address:

_____

_____

15.3 Appendix C: National Early Warning Score (NEWS2)

Chart 1: The NEWS scoring system

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Use SpO_2 Scale 2 if target range is 88 – 92%, e.g., in hypercapnic respiratory failure.

National Early Warning System Score (NEWS) 2 Royal College of Physicians 2017 [20]

15.4 Appendix D: Massachusetts General Hospital COVID-19 Treatment Guidance.

Recommended daily labs:

- CBC with diff
- CMP
- CPK (creatine kinase)

Recommended repeated labs q 2-3 days:

- 1. D-dimer
- 2. Ferritin/CRP/ESR
- 3. LDH
- 4. Troponin
- 5. Baseline ECG

Viral Serologies:

- 1. HBV serologies (sAb, cAb, sAg)
- 2. HCV antibody
- 3. HIV ½ Ab/Ag

If Clinically Indicated:

- 1. Blood cultures
- 2. For acute kidney injury- urinalysis and spot urine protein creatinine
- 3. Procalcitonin
- 4. IL-6

Radiology:

- Chest X-ray at admission

15.5 Appendix E: Ribavirin generic (ribavirin USP) capsules, for oral use Summary of Product Characteristics (SPC)

RIBAVIRIN - ribavirin capsule
Aurobindo Pharma Limited

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use RIBAVIRIN CAPSULES safely and effectively. See full prescribing information for RIBAVIRIN CAPSULES.

RIBAVIRIN capsules, for oral use
Initial U.S. Approval: 1998

WARNING: EMBRYO-FETAL TOXICITY, HEMOLYTIC ANEMIA, and MONOTHERAPY NOT RECOMMENDED

See full prescribing information for complete boxed warning.

- **Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy. (4, 5.1, 8.1, 8.3, 13.1)**
- **The hemolytic anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. (2.5, 5.2, 6.1)**
- **Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C. (5.10)**

INDICATIONS AND USAGE

Ribavirin capsules are a nucleoside analogue indicated in combination with interferon alfa-2b (pegylated and nonpegylated) for the treatment of Chronic Hepatitis C (CHC) in patients 3 years of age or older with compensated liver disease. (1.1)

Patients with the following characteristics are less likely to benefit from re-treatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection.

DOSAGE AND ADMINISTRATION

Ribavirin capsules are administered according to body weight. (2.1, 2.2, 2.3)
Dose reduction or discontinuation is recommended in patients experiencing certain adverse reactions or renal dysfunction. (2.5, 2.6, 12.3)

DOSAGE FORMS AND STRENGTHS

- Ribavirin Capsules USP 200 mg (3)

CONTRAINDICATIONS

- Pregnancy and men whose female partners are pregnant (4, 5.1, 8.1, 8.3)
- Known hypersensitivity reactions such as Stevens-Johnson syndrome, toxic, epidermal necrolysis, and erythema multiforme to ribavirin or any component of the product (4)
- Autoimmune hepatitis (4)
- Hemoglobinopathies (4)
- Creatinine clearance less than 50 mL/min (4, 12.3)
- Coadministration with didanosine (4, 7.1)

WARNINGS AND PRECAUTIONS

- Embryo-Fetal Toxicity: May cause fetal harm. Patients should have a negative pregnancy test prior to therapy and use effective contraception and undergo periodic pregnancy tests. (5.1, 8.1, 8.3)

Patients exhibiting the following conditions should be closely monitored and may require dose reduction or discontinuation of therapy:

- Hemolytic anemia may occur with a significant initial drop in hemoglobin. (5.2)
- Pancreatitis. (5.3)
- Pulmonary infiltrates or pulmonary function impairment. (5.4)
- New or worsening ophthalmologic disorders. (5.5)
- Severe decreases in neutrophil and platelet counts, and hematologic, endocrine (e.g., TSH), and hepatic abnormalities.

(5.6)
- Dental/periodontal disorders reported with combination therapy. (5.7)
- Concomitant administration of azathioprine. (5.8)
- Weight loss and growth inhibition reported during combination therapy in pediatric patients. Long-term growth inhibition (height) reported in some patients. (5.9)
- Monotherapy with ribavirin is not permitted. (5.10)

ADVERSE REACTIONS

Hemolytic anemia occurred in more than 10% of adult patients receiving ribavirin/PegIntron or INTRON A combination therapy. (6.1)
Most common adverse reactions (40% or greater) in adult patients receiving ribavirin/PegIntron or INTRON A combination therapy are injection site reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability. (6.1) Most common adverse reactions (greater than 25%) in pediatric patients receiving ribavirin/PegIntron therapy are: pyrexia, headache, neutropenia, fatigue, anorexia, injection site erythema, and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Aurobindo Pharma USA, Inc. at 1-866-850-2876 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Nucleoside analogues: Closely monitor for toxicities. Discontinue nucleoside reverse transcriptase inhibitors or reduce dose or discontinue interferon, ribavirin or both with worsening toxicities. (7.2)

USE IN SPECIFIC POPULATIONS

- Pediatrics: Safety and efficacy in patients less than 3 years old have not been established. (8.4)
- Organ transplant recipients: Safety and efficacy not studied. (8.6)
- Co-infected patients: Safety and efficacy with HIV or HBV co-infection have not been established. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 2/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY, HEMOLYTIC ANEMIA, and MONOTHERAPY NOT RECOMMENDED

- **Significant teratogenic and embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple-dose half-life of 12 days and may persist in non-plasma compartments for as long as 6 months. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are taking ribavirin therapy. Effective contraception must be utilized during treatment and during the 6-month post-treatment follow-up period *[see Contraindications (4), Warnings and Precautions (5.1), Use in Specific Populations (8.1, 8.3), and Nonclinical Toxicology (13.1)].***
- **Hemolytic anemia has been reported with ribavirin therapy. The anemia associated with ribavirin therapy may result in worsening of cardiac disease that has led to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin *[see Dosage and Administration (2.5), Warnings and Precautions (5.2),* and *Adverse Reactions (6.1)].***
- **Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication *[see Warnings and Precautions (5.10)].***

1 INDICATIONS AND USAGE

1.1 Chronic Hepatitis C (CHC)

Ribavirin capsules in combination with interferon alfa-2b (pegylated and nonpegylated) are indicated for the treatment of Chronic Hepatitis C (CHC) in patients 3 years of age and older with compensated liver disease *[see Warnings and Precautions (5.9, 5.10), and Use in Specific Populations (8.4)]*.

The following points should be considered when initiating ribavirin capsules combination therapy with PegIntron® or INTRON A®:

- Combination therapy with ribavirin capsules/PegIntron is preferred over ribavirin capsules/INTRON A as this combination provides substantially better response rates *[see Clinical Studies (14)].*
- Patients with the following characteristics are less likely to benefit from re-treatment after failing a course of therapy: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection *[see Clinical Studies (14)]*.
- No safety and efficacy data are available for treatment duration lasting longer than one year.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

Do not open, crush or break ribavirin capsules. Ribavirin capsules should be taken with food *[see Clinical Pharmacology (12.3)*].

2.2 Ribavirin capsules/PegIntron Combination Therapy

Adult Patients

The recommended dose of ribavirin capsules when used in combination with PegIntron is 800 mg to

1,400 mg based on patient body weight in two divided doses (see Table 1). Refer to PegIntron labeling for PegIntron dosing information.

Duration of Treatment – Interferon Alpha-naïve Patients

The treatment duration for patients with genotype 1 is 48 weeks. Discontinuation of therapy should be considered in patients who do not achieve at least a 2 $\log_{10}$ drop or loss of hepatitis C virus (HCV)-RNA at 12 weeks, or if HCV-RNA remains detectable after 24 weeks of therapy. Patients with genotype 2 and 3 should be treated for 24 weeks.

Duration of Treatment – Re-treatment with PegIntron/Ribavirin capsules of Prior Treatment Failures

The treatment duration for patients who previously failed therapy is 48 weeks, regardless of HCV genotype. Re-treated patients who fail to achieve undetectable HCV-RNA at Week 12 of therapy, or whose HCV-RNA remains detectable after 24 weeks of therapy, are highly unlikely to achieve SVR and discontinuation of therapy should be considered *[see Clinical Studies (14.1)]*.

Table 1: Recommended Adult Dosing for Ribavirin capsules in Combination with PegIntron

Body Weight (kg)	Ribavirin capsules Daily Dose	Ribavirin Number of Capsules
Less than 66	800 mg/day	2 x 200 mg capsules AM 2 x 200 mg capsules PM
66 to 80	1,000 mg/day	2 x 200 mg capsules AM 3 x 200 mg capsules PM
81 to 105	1,200 mg/day	3 x 200 mg capsules AM 3 x 200 mg capsules PM
Greater than 105	1,400 mg/day	3 x 200 mg capsules AM 4 x 200 mg capsules PM

Pediatric Patients

Dosing of ribavirin capsules in pediatric patients is determined by body weight. The recommended dose of ribavirin capsules when used in combination with PegIntron in pediatric patients ages 3 to 17 years is 15 mg/kg/day in two divided doses (see Table 2). Refer to PegIntron labeling for PegIntron dosing information. The treatment duration for patients with genotype 1 is 48 weeks. Patients with genotype 2 and 3 should be treated for 24 weeks.

Table 2: Recommended Pediatric Ribavirin capsules Dosing in Combination with PegIntron

Body Weight (kg)	Ribavirin capsules Daily Dose	Ribavirin Number of Capsules
Less than 47	15 mg/kg/day	Use Ribavirin Oral Solution*
47 to 59	800 mg/day	2 x 200 mg capsules AM 2 x 200 mg capsules PM
60 to 73	1,000 mg/day	2 x 200 mg capsules AM 3 x 200 mg capsules PM
Greater than 73	1,200 mg/day	3 x 200 mg capsules AM 3 x 200 mg capsules PM

* Ribavirin Oral Solution may be used in any patient regardless of body weight.

2.3 Ribavirin capsules/INTRON A Combination Therapy

Adults

Duration of Treatment – Interferon Alpha-naïve Patients

The recommended dose of ribavirin capsules when used in combination with INTRON A depends on the patient's body weight (see Table 3). Refer to Intron A labeling for interferon dosing information. The recommended duration of treatment for patients previously untreated with interferon is 24 to 48 weeks. The duration of treatment should be individualized to the patient depending on baseline disease characteristics, response to therapy, and tolerability of the regimen *[see Indications and Usage (1.1), Adverse Reactions (6.1), and Clinical Studies (14)]*. After 24 weeks of treatment, virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV-RNA below the limit of detection of the assay by 24 weeks. There are no safety and efficacy data for treatment duration lasting longer than 48 weeks in the previously untreated patient population.

Duration of Treatment – Re-treatment with INTRON A/Ribavirin capsules in Relapse Patients

In patients who relapse following nonpegylated interferon monotherapy, the recommended duration of treatment is 24 weeks.

Table 3: Recommended Ribavirin capsules Dosing in Combination with INTRON A

Body Weight	Ribavirin Capsules
At least 75 kg	2 x 200 mg capsules AM 3 x 200 mg capsules PM daily orally
Greater than 75 kg	3 x 200 mg capsules AM 3 x 200 mg capsules PM daily orally

Pediatrics The recommended dose of ribavirin capsules when used in combination with INTRON A is 15 mg/kg per day orally in two divided doses (see Table 2). Refer to Intron A labeling for interferon dosing information.

The recommended duration of treatment is 48 weeks for pediatric patients with genotype 1. After 24 weeks of treatment, virologic response should be assessed. Treatment discontinuation should be considered in any patient who has not achieved an HCV-RNA below the limit of detection of the assay by this time. The recommended duration of treatment for pediatric patients with genotype 2 and 3 is 24 weeks.

2.4 Testing Prior to Initiation of Ribavirin capsules

The following laboratory tests are recommended in all patients treated with ribavirin capsules prior to initiation of treatment and periodically thereafter.

- Standard hematologic tests - including hemoglobin (pretreatment, Week 2 and Week 4 of therapy, and as clinically appropriate *[see Warnings and Precautions (5.2, 5.6)]*, complete and differential white

blood cell counts, and platelet count.
- Blood chemistries - liver function tests and TSH.
- Pregnancy - in women of childbearing potential.
- ECG *[see Warnings and Precautions (5.2)]*.

2.5 Dose Modifications

If severe adverse reactions or laboratory abnormalities develop during ribavirin capsules combination therapy, modify or discontinue the dose until the adverse reaction abates or decreases in severity (see Table 4) *[see Warnings and Precautions (5)]*. If intolerance persists after dose adjustment, combination therapy should be discontinued. Refer to PegIntron labeling for additional information regarding dose reduction of PegIntron.

Dose reduction in pediatric patients is accomplished by modifying the recommended ribavirin capsules dose from the original starting dose of 15 mg/kg daily in a two-step process to 12 mg/kg/day, then to 8 mg/kg/day, if needed (see Table 4).

Ribavirin capsules are contraindicated in patients with creatinine clearance less than 50 mL/min *[see Contraindications (4)]*. Patients with impaired renal function and those over the age of 50 should be carefully monitored with respect to development of anemia *[see Warnings and Precautions (5.2), Use in Specific Populations (8.5), and Clinical Pharmacology (12.3)*].

Ribavirin capsules should be administered with caution to patients with pre-existing cardiac disease. Assess cardiovascular status before initiation of treatment and during therapy. If there is any deterioration of cardiovascular status, discontinue combination therapy *[see Warnings and Precautions (5.2)]*.

In patients with a history of stable cardiovascular disease, a permanent dose reduction is required if the hemoglobin decreases by 2 g/dL or more during any 4-week period. If the hemoglobin level remains below 12 g/dL after 4 weeks on a reduced dose, discontinue combination therapy.

Modify or discontinue ribavirin capsules dosing in any patient whose hemoglobin level falls below 10 g/dL (see Table 4) *[see Warnings and Precautions (5.2)]*.

Table 4: Guidelines for Dose Modification and Discontinuation of Ribavirin capsules in combination with PegIntron or INTRON A Based on Laboratory Parameters in Adults and Pediatrics

Laboratory Parameters	Reduce Ribavirin capsules Daily Dose (see note 1) if:	Reduce PegIntron or INTRON A Dose (see note 2) if:	Discontinue Therapy if:
WBC	N/A	1.0 to <1.5 x 10^9/L	<1.0 x 10^9/L
Neutrophils	N/A	0.5 to <0.75 x 10^9/L	<0.5 x 10^9/L
Platelets	N/A	25 to < 50 x 10^9/L (adults)	<25 x 10^9/L (adults)
	N/A	50 to <70 x 10^9/L (pediatrics)	<50 x 10^9/L (pediatrics)
Creatinine	N/A	N/A	>2 mg/dL (pediatrics)
Hemoglobin in patients without history of cardiac disease	8.5 to <10 g/dL	N/A	<8.5 g/dL
	Reduce Ribavirin capsules Dose by 200 mg/day and		

	PegIntron or INTRON A Dose by Half if:	
Hemoglobin in patients with history of stable cardiac disease*†	≥2 g/dL decrease in hemoglobin during any four-week period during treatment	<8.5 g/dL or <12 g/dL after four weeks of dose reduction

Note 1: *Adult patients:* 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.

Pediatric patients: 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

Note 2: *Adult patients treated with ribavirin capsules and PegIntron:* 1st dose reduction of PegIntron is to 1 mcg/kg/week. If needed, 2nd dose reduction of PegIntron is to 0.5 mcg/kg/week.

Pediatric patients treated with ribavirin capsules and PegIntron: 1st dose reduction of PegIntron is to 40 mcg/m^2/week, 2nd dose reduction of PegIntron is to 20 mcg/m^2/week.

For patients on ribavirin capsules/INTRON A combination therapy: reduce INTRON A dose by 50%.

* Pediatric patients who have pre-existing cardiac conditions and experience a hemoglobin decrease greater than or equal to 2 g/dL during any 4-week period during treatment should have weekly evaluations and hematology testing.

† These guidelines are for patients with stable cardiac disease. Patients with a history of significant or unstable cardiac disease should not be treated with PegIntron/ribavirin capsules combination therapy *[see Warnings and Precautions (5.2)]*.

Refer to labeling for INTRON A or PegIntron for additional information about how to reduce an INTRON A or PegIntron dose.

2.6 Discontinuation of Dosing

Adults In HCV genotype 1, interferon-alfa-naïve patients receiving PegIntron in combination with ribavirin, discontinue therapy if there is not at least a 2 $\log_{10}$ drop or loss of HCV-RNA at 12 weeks of therapy, or if HCV-RNA levels remain detectable after 24 weeks of therapy. Regardless of genotype, previously treated patients who have detectable HCV-RNA at Week 12 or 24 are highly unlikely to achieve SVR and discontinuation of therapy should be considered.

Pediatrics (3 to 17 years of age) In patients receiving PegIntron/ribavirin capsules combination (excluding HCV Genotype 2 and 3), discontinue therapy at 12 weeks if HCV-RNA has dropped less than 2 $\log_{10}$ compared to pretreatment level, or at 24 weeks if HCV-RNA is still detectable.

3 DOSAGE FORMS AND STRENGTHS

Ribavirin Capsules USP, 200 mg are white/white, size ‘1’ hard gelatin capsule filled with white to off-white granular powder and imprinted with ‘E’ on white cap and ‘81’ on white body with black ink.

4 CONTRAINDICATIONS

Ribavirin capsules combination therapy is contraindicated in:

- pregnancy. Ribavirin capsules may cause fetal harm when administered to a pregnant woman. Ribavirin capsules are contraindicated in women who are pregnant or planning to become pregnant. If a patient becomes pregnant while taking ribavirin capsules, the patient should be apprised of the potential hazard to the fetus *[see Warnings and Precautions (5.1),* and *Use in Specific Populations*

(8.1, 8.3)].

- men whose female partners are pregnant *[see Use in Specific Populations (8.3)]*
- patients with known hypersensitivity reactions such as Stevens-Johnson syndrome, toxic, epidermal necrolysis, and erythema multiforme to ribavirin or any component of the product
- patients with autoimmune hepatitis
- patients with hemoglobinopathies (e.g., thalassemia major, sickle-cell anemia)
- patients with creatinine clearance less than 50 mL/min *[see Clinical Pharmacology (12.3)]*
- when coadministered with didanosine because exposure to the active metabolite of didanosine (dideoxyadenosine 5'-triphosphate) is increased. Fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis, has been reported in patients receiving didanosine in combination with ribavirin *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

Ribavirin capsules may cause birth defects, miscarriage or stillbirth. Ribavirin therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of therapy. Patients should use effective contraception and have periodic monitoring with pregnancy tests during treatment and during the 6-month period after treatment has been stopped. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin has demonstrated significant teratogenic and embryocidal effects in all animal species tested. These effects occurred at doses as low as one twentieth of the recommended human dose of ribavirin *[see Boxed Warning, Contraindications (4), and Use in Specific Populations (8.1, 8.3)]*.

5.2 Anemia

Hemolytic anemia was observed in approximately 10% of ribavirin/INTRON A-treated subjects in clinical trials. The anemia associated with ribavirin occurs within 1 to 2 weeks of initiation of therapy. Because the initial drop in hemoglobin may be significant, obtain hemoglobin or hematocrit levels before the start of treatment and at Week 2 and Week 4 of therapy, or more frequently if clinically indicated. Patients should then be followed as clinically appropriate *[see Dosage and Administration (2.5, 2.6)]*.

Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by ribavirin. Patients should be assessed for underlying cardiac disease before initiation of ribavirin therapy. Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued *[see Dosage and Administration (2.5, 2.6)]*. Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use ribavirin.

5.3 Pancreatitis

Suspend ribavirin and INTRON A or PegIntron combination therapy in patients with signs and symptoms of pancreatitis and discontinue in patients with confirmed pancreatitis.

5.4 Pulmonary Disorders

Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneumonitis, pulmonary hypertension, and pneumonia, have been reported during ribavirin with alpha interferon combination therapy; occasional cases of fatal pneumonia have occurred. In addition, sarcoidosis or the exacerbation of sarcoidosis has been reported. If there is evidence of pulmonary infiltrates or pulmonary function impairment, closely monitor the patient, and if appropriate, discontinue combination therapy.

5.5 Ophthalmologic Disorders

Ribavirin is used in combination therapy with INTRON A or PegIntron. Refer to labeling for PegIntron for additional information.

5.6 Laboratory Tests

PegIntron in combination with ribavirin may cause severe decreases in neutrophil and platelet counts, and hematologic, endocrine (e.g., TSH), and hepatic abnormalities.

Obtain hematology and blood chemistry testing in patients on PegIntron/ribavirin combination therapy before the start of treatment and then periodically thereafter. In the adult clinical trial, complete blood counts (including hemoglobin, neutrophil, and platelet counts) and chemistries (including AST, ALT, bilirubin, and uric acid) were measured during the treatment period at Weeks 2, 4, 8, 12, and then at 6-week intervals, or more frequently if abnormalities developed. In pediatric subjects, the same laboratory parameters were evaluated with additional assessment of hemoglobin at treatment Week 6. TSH levels were measured every 12 weeks during the treatment period. HCV-RNA should be measured periodically during treatment *[see Dosage and Administration (2)]*.

5.7 Dental and Periodontal Disorders

Dental and periodontal disorders have been reported in patients receiving ribavirin and interferon or peginterferon combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of ribavirin and pegylated or nonpegylated interferon alfa-2b. Advise patients to brush their teeth thoroughly twice daily and have regular dental examinations. If vomiting occurs, advise patients to rinse out their mouth thoroughly afterwards.

5.8 Concomitant Administration of Azathioprine

Pancytopenia (marked decreases in red blood cells, neutrophils, and platelets) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the concomitant administration of pegylated interferon/ribavirin and azathioprine. In this limited number of patients (n=8), myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of both HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone. Discontinue PegIntron, ribavirin, and azathioprine for pancytopenia, and do not reintroduce pegylated interferon/ribavirin with concomitant azathioprine *[see Drug Interactions (7.4)]*.

5.9 Impact on Growth in Pediatric Patients

Data on the effects of PegIntron and ribavirin on growth come from an open-label study in subjects 3 through 17 years of age, in which weight and height changes were compared to U.S. normative population data. In general, the weight and height gain of pediatric subjects treated with PegIntron and ribavirin lagged behind that predicted by normative population data for the entire length of treatment. Severely inhibited growth velocity (less than 3rd percentile) was observed in 70% of the subjects while on treatment. Following treatment, rebound growth and weight gain occurred in most subjects. Long-term follow-up data in pediatric subjects, however, indicates that PegIntron in combination therapy with ribavirin may induce a growth inhibition that results in reduced adult height in some patients *[see Adverse Reactions (6.1)]*.

Similarly, an impact on growth was seen in subjects after treatment with ribavirin and INTRON A combination therapy for one year. In a long-term follow-up trial of a limited number of these subjects, combination therapy resulted in reduced final adult height in some subjects *[see Adverse Reactions (6.1)]*.

5.10 Not Recommended for Monotherapy and Risks Associated with Combination Therapy

Based on results of clinical trials, ribavirin monotherapy is not effective for the treatment of chronic

hepatitis C virus infection; therefore, ribavirin capsules must not be used alone. The safety and efficacy of ribavirin capsules have only been established when used together with INTRON A or PegIntron (not other interferons) as combination therapy.

The safety and efficacy of ribavirin with INTRON A or PegIntron combination therapy for the treatment of HIV infection, adenovirus, RSV, parainfluenza, or influenza infections have not been established. Ribavirin capsules should not be used for these indications.

There are significant adverse reactions caused by ribavirin/INTRON A or PegIntron combination therapy, including severe depression and suicidal or homicidal ideation, hemolytic anemia, suppression of bone marrow function, autoimmune and infectious disorders, pulmonary dysfunction, pancreatitis, and diabetes. Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up. Labeling for INTRON A and PegIntron should be reviewed in their entirety for additional safety information prior to initiation of combination treatment.

6 ADVERSE REACTIONS

The following serious adverse drug reactions are discussed in other sections of the labeling:

- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.1)]*
- Anemia *[see Warnings and Precautions (5.2)]*
- Pancreatitis *[see Warnings and Precautions (5.3)]*
- Pulmonary Disorders *[see Warnings and Precautions (5.4)]*
- Ophthalmic Disorders *[see Warnings and Precautions (5.5)]*
- Dental and Periodontal Disorders *[see Warnings and Precautions (5.7)]*
- Impact on Growth in Pediatric Patients *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trials with ribavirin in combination with PegIntron or INTRON A have been conducted in over 7,800 subjects from 3 to 76 years of age.

The primary toxicity of ribavirin is hemolytic anemia. Reductions in hemoglobin levels occurred within the first 1 to 2 weeks of oral therapy. Cardiac and pulmonary reactions associated with anemia occurred in approximately 10% of patients *[see Warnings and Precautions (5.2)]*.

Greater than 96% of all subjects in clinical trials experienced one or more adverse reactions. The most commonly reported adverse reactions in adult subjects receiving PegIntron or INTRON A in combination with ribavirin were injection site inflammation/reaction, fatigue/asthenia, headache, rigors, fevers, nausea, myalgia and anxiety/emotional lability/irritability. The most common adverse reactions in pediatric subjects, ages 3 and older, receiving ribavirin in combination with PegIntron or INTRON A were pyrexia, headache, neutropenia, fatigue, anorexia, injection site erythema, and vomiting.

The Adverse Reactions section references the following clinical trials:

- Ribavirin/PegIntron Combination therapy trials:

- Clinical Study 1 – evaluated PegIntron monotherapy (not further described in this label; see labeling for PegIntron for information about this trial).
- Study 2 – evaluated ribavirin 800 mg/day flat dose in combination with 1.5 mcg/kg/week PegIntron or with INTRON A.
- Study 3 – evaluated PegIntron/weight-based ribavirin in combination with PegIntron/flat dose ribavirin regimen.
- Study 4 – compared two PegIntron (1.5 mcg/kg/week and 1 mcg/kg/week) doses in combination with ribavirin and a third treatment group receiving Pegasys® (180 mcg/week)/Copegus® (1000 to 1200 mg/day).
- Study 5 – evaluated PegIntron (1.5 mcg/kg/week) in combination with weight-based ribavirin in prior treatment failure subjects.

- PegIntron/Ribavirin Combination Therapy in Pediatric Patients
- Ribavirin/INTRON A Combination Therapy trials for adults and pediatrics

Serious adverse reactions have occurred in approximately 12% of subjects in clinical trials with PegIntron with or without ribavirin *[see Boxed Warning, Warnings and Precautions (5)]*. The most common serious events occurring in subjects treated with PegIntron and ribavirin were depression and suicidal ideation *[see Warnings and Precautions (5.10)]*, each occurring at a frequency of less than 1%. Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% versus 1%) during treatment and off-therapy follow-up *[see Warnings and Precautions (5.10)]*. The most common fatal reaction occurring in subjects treated with PegIntron and ribavirin was cardiac arrest, suicidal ideation, and suicide attempt *[see Warnings and Precautions (5.10)]*, all occurring in less than 1% of subjects.

Adverse Reaction - Ribavirin/PegIntron Combination Therapy

Adult Subjects

Adverse reactions that occurred in the clinical trial at greater than 5% incidence are provided by treatment group from the ribavirin/PegIntron Combination Therapy (Study 2) in Table 5.

Table 5: Adverse Reactions Occurring in Greater Than 5% of Adult Subjects

Adverse Reactions	***Percentage of Subjects Reporting Adverse Reactions****		**Adverse Reactions**	***Percentage of Subjects Reporting Adverse Reactions****	
	PegIntron 1.5 mcg/kg/Ribavirin (N=511)	**INTRON A/Ribavirin** (N=505)		**PegIntron 1.5 mcg/kg/Ribavirin** (N=511)	**INTRON A/Ribavirin** (N=505)
Application Site			**Musculoskeletal**		
Injection Site Inflammation	25	18	Myalgia	56	50
Injection Site Reaction	58	36	Arthralgia	34	28
Autonomic Nervous System			Musculoskeletal Pain	21	19
Dry Mouth	12	8	**Psychiatric**		
Increased Sweating	11	7	Insomnia	40	41
Flushing	4	3	Depression	31	34
			Anxiety/Emotional		

Body as a Whole			Anxiety/Emotional Lability/Irritability	47	47
Fatigue/Asthenia	66	63	Concentration Impaired	17	21
Headache	62	58	Agitation	8	5
Rigors	48	41	Nervousness	6	6
Fever	46	33	**Reproductive, Female**		
Weight Loss	29	20	Menstrual Disorder	7	6
Right Upper Quadrant Pain	12	6	**Resistance Mechanism**		
Chest Pain	8	7	Viral Infection	12	12
Malaise	4	6	Fungal Infection	6	1
Central/Peripheral Nervous System			**Respiratory System**		
Dizziness	21	17	Dyspnea	26	24
Endocrine			Coughing	23	16
Hypothyroidism	5	4	Pharyngitis	12	13
Gastrointestinal			Rhinitis	8	6
Nausea	43	33	Sinusitis	6	5
Anorexia	32	27	**Skin and Appendages**		
Diarrhea	22	17	Alopecia	36	32
Vomiting	14	12	Pruritus	29	28
Abdominal Pain	13	13	Rash	24	23
Dyspepsia	9	8	Skin Dry	24	23
Constipation	5	5	**Special Senses, Other**		
Hematologic Disorders			Taste Perversion	9	4
Neutropenia	26	14	**Vision Disorders**		
Anemia	12	17	Vision Blurred	5	6
Leukopenia	6	5	Conjunctivitis	4	5
Thrombocytopenia	5	2			
Liver and Biliary System					
Hepatomegaly	4	4			

* A subject may have reported more than one adverse reaction within a body system/organ class category.

Table 6 summarizes the treatment-related adverse reactions in Study 4 that occurred at a greater than or equal to 10% incidence.

Table 6: Treatment-Related Adverse Reactions (Greater Than or Equal to 10% Incidence) By Descending Frequency

	Study 4 *Percentage of Subjects Reporting Treatment-Related Adverse Reactions*		
Adverse Reactions	**PegIntron 1.5 mcg/kg with Ribavirin (N=1019)**	**PegIntron 1 mcg/kg with Ribavirin (N=1016)**	**Pegasys 180 mcg with Copegus (N=1035)**
Fatigue	67	68	64

Headache	50	47	41
Nausea	40	35	34
Chills	39	36	23
Insomnia	38	37	41
Anemia	35	30	34
Pyrexia	35	32	21
Injection Site Reactions	34	35	23
Anorexia	29	25	21
Rash	29	25	34
Myalgia	27	26	22
Neutropenia	26	19	31
Irritability	25	25	25
Depression	25	19	20
Alopecia	23	20	17
Dyspnea	21	20	22
Arthralgia	21	22	22
Pruritus	18	15	19
Influenza-like Illness	16	15	15
Dizziness	16	14	13
Diarrhea	15	16	14
Cough	15	16	17
Weight Decreased	13	10	10
Vomiting	12	10	9
Unspecified Pain	12	13	9
Dry Skin	11	11	12
Anxiety	11	11	10
Abdominal Pain	10	10	10
Leukopenia	9	7	10

The incidence of serious adverse reactions was comparable in all trials. In Study 2, the incidence of serious adverse reactions was 17% in the PegIntron/ribavirin groups compared to 14% in the INTRON A/ribavirin group. In Study 3, there was a similar incidence of serious adverse reactions reported for the weight-based ribavirin group (12%) and for the flat-dose ribavirin regimen.

In many but not all cases, adverse reactions resolved after dose reduction or discontinuation of therapy. Some subjects experienced ongoing or new serious adverse reactions during the 6-month follow-up period. In Study 2, many subjects continued to experience adverse reactions several months after discontinuation of therapy. By the end of the 6-month follow-up period, the incidence of ongoing adverse reactions by body class in the PegIntron 1.5/ribavirin group was 33% (psychiatric), 20% (musculoskeletal), and 10% (for endocrine and for GI). In approximately 10 to 15% of subjects, weight loss, fatigue, and headache had not resolved.

There have been 28 subject deaths that occurred during treatment or follow-up in Studies 2, 3, and 4. In Study 2, there was 1 suicide in a subject receiving PegIntron/ribavirin combination therapy; and 1 subject death in the INTRON A/ribavirin group (motor vehicle accident). In Study 3, there were 14 deaths, 2 of which were probable suicides and 1 was an unexplained death in a person with a relevant medical history of depression. In Study 4, there were 12 deaths, 6 of which occurred in subjects who received PegIntron/ribavirin combination therapy, 5 in the PegIntron 1.5 mcg/ribavirin arm (N=1019) and 1 in the PegIntron 1 mcg/ribavirin arm (N=1016), and 6 of which occurred in subjects receiving Pegasys/Copegus (N=1035); there were 3 suicides that occurred during the off treatment follow-up period in subjects who received PegIntron (1.5 mcg/kg)/ribavirin combination therapy.

In Studies 1 and 2, 10 to 14% of subjects receiving PegIntron, alone or in combination with ribavirin, discontinued therapy compared with 6% treated with INTRON A alone and 13% treated with INTRON A in combination with ribavirin. In Study 3, 15% of subjects receiving PegIntron in combination with weight-based ribavirin and 14% of subjects receiving PegIntron with flat-dose ribavirin discontinued therapy due to an adverse reaction. The most common reasons for discontinuation were related to known interferon effects of psychiatric, systemic (e.g., fatigue, headache), or gastrointestinal adverse reactions. In Study 4, 13% of subjects in the PegIntron 1.5 mcg/ribavirin arm, 10% in the PegIntron 1 mcg/ribavirin arm, and 13% in the Pegasys 180 mcg/Copegus arm discontinued due to adverse events.

In Study 2, dose reductions for ribavirin were similar across all three groups *[see Clinical Studies (14.1)]*, 33 to 35%. The most common reasons for dose modifications were neutropenia (18%), or anemia (9%) *(see Laboratory Values)*. Other common reasons included depression, fatigue, nausea, and thrombocytopenia. In Study 3, dose modifications due to adverse reactions occurred more frequently with weight-based ribavirin dosing compared to flat dosing (29% and 23%, respectively). In Study 4, 16% of subjects had a dose reduction of PegIntron to 1 mcg/kg in combination with ribavirin, with an additional 4% requiring the second dose reduction of PegIntron to 0.5 mcg/kg due to adverse events compared to 15% of subjects in the Pegasys/Copegus arm, who required a dose reduction to 135 mcg/week with Pegasys, with an additional 7% in the Pegasys/Copegus arm requiring a second dose reduction to 90 mcg/week with Pegasys.

In the PegIntron/ribavirin combination trials the most common adverse reactions were psychiatric, which occurred among 77% of subjects in Study 2 and 68% to 69% of subjects in Study 3. These psychiatric adverse reactions included most commonly depression, irritability, and insomnia, each reported by approximately 30% to 40% of subjects in all treatment groups. Suicidal behavior (ideation, attempts, and suicides) occurred in 2% of all subjects during treatment or during follow-up after treatment cessation *[see Warnings and Precautions (5)]*. In Study 4, psychiatric adverse reactions occurred in 58% of subjects in the PegIntron 1.5 mcg/ribavirin arm, 55% of subjects in the PegIntron 1 mcg/ribavirin arm, and 57% of subjects in the Pegasys 180 mcg/Copegus arm.

In Study 2, PegIntron/ribavirin combination therapy induced fatigue or headache in approximately two-thirds of subjects, with fever or rigors in approximately half of the subjects. The severity of some of these systemic symptoms (e.g., fever and headache) tended to decrease as treatment continued.

Subjects receiving ribavirin/PegIntron as re-treatment after failing a previous interferon combination regimen reported adverse reactions similar to those previously associated with this regimen during clinical trials of treatment-naïve subjects.

Pediatric Subjects

In general, the adverse reaction profile in the pediatric population was similar to that observed in adults. In the pediatric trial, the most prevalent adverse reactions were pyrexia (80%), headache (62%), neutropenia (33%), fatigue (30%), anorexia (29%), injection-site erythema (29%) and vomiting (27%). The majority of adverse reactions were mild or moderate in severity. Severe adverse reactions were reported in 7% (8/107) of all subjects and included injection site pain (1%), pain in extremity (1%), headache (1%), neutropenia (1%), and pyrexia (4%). Important adverse reactions that occurred in this subject population were nervousness (7%; 7/107), aggression (3%; 3/107), anger (2%; 2/107), and depression (1%; 1/107). Five subjects received levothyroxine treatment, three with clinical hypothyroidism and two with asymptomatic TSH elevations. Weight and height gain of pediatric subjects treated with PegIntron plus ribavirin lagged behind that predicted by normative population data for the entire length of treatment. Severely inhibited growth velocity (less than 3rd percentile) was

observed in 70% of the subjects while on treatment.

Dose modifications of PegIntron and/or ribavirin were required in 25% of subjects due to treatment-related adverse reactions, most commonly for anemia, neutropenia and weight loss. Two subjects (2%; 2/107) discontinued therapy as the result of an adverse reaction.

Adverse reactions that occurred with a greater than or equal to 10% incidence in the pediatric trial subjects are provided in Table 7.

Table 7: Percentage of Pediatric Subjects with Treatment-Related Adverse Reactions (in At Least 10% of All Subjects)

System Organ Class Preferred Term	**All Subjects** (N=107)
Blood and Lymphatic System Disorders	
Neutropenia	33%
Anemia	11%
Leukopenia	10%
Gastrointestinal Disorders	
Abdominal Pain	21%
Abdominal Pain Upper	12%
Vomiting	27%
Nausea	18%
General Disorders and Administration Site Conditions	
Pyrexia	80%
Fatigue	30%
Injection-site Erythema	29%
Chills	21%
Asthenia	15%
Irritability	14%
Investigations	
Weight Loss	19%
Metabolism and Nutrition Disorders	
Anorexia	29%
Decreased Appetite	22%
Musculoskeletal and Connective Tissue Disorders	
Arthralgia	17%
Myalgia	17%
Nervous System Disorders	
Headache	62%
Dizziness	14%
Skin and Subcutaneous Tissue Disorders	
Alopecia	17%

Ninety-four of 107 subjects enrolled in a 5-year follow-up trial. The long-term effects on growth were less in subjects treated for 24 weeks than in those treated for 48 weeks. Twenty-four percent of subjects (11/46) treated for 24 weeks and 40% of subjects (19/48) treated for 48 weeks had a >15 percentile height-for-age decrease from pre-treatment baseline to the end of 5-year follow-up. Eleven percent of subjects (5/46) treated for 24 weeks and 13% of subjects (6/48) treated for 48 weeks had a >30 percentile height-for-age decrease from pre-treatment baseline to the end of the 5-year follow-up. While observed across all age groups, the highest risk for reduced height at the end of long-term follow-up appeared to be initiation of combination therapy during the years of expected peak growth

velocity *[see Warnings and Precautions (5.9)]*.

Laboratory Values

Adult and Pediatric Subjects

The adverse reaction profile in Study 3, which compared PegIntron/weight-based ribavirin combination to a PegIntron/flat dose ribavirin regimen, revealed an increased rate of anemia with weight-based dosing (29% vs. 19% for weight-based vs. flat dose regimens, respectively). However, the majority of cases of anemia were mild and responded to dose reductions.

Changes in selected laboratory values during treatment in combination with ribavirin treatment are described below. Decreases in hemoglobin, leukocytes, neutrophils, and platelets may require dose reduction or permanent discontinuation from therapy *[see Dosage and Administration (2.5)]*. Changes in selected laboratory values during therapy are described in Table 8. Most of the changes in laboratory values in the PegIntron/ribavirin trial with pediatrics were mild or moderate.

Table 8: Selected Laboratory Abnormalities During Treatment with Ribavirin and PegIntron or Ribavirin and INTRON A in Previously Untreated Subjects

Laboratory Parameters*	**Percentage of Subjects**		
	Adults (Study 2)		**Pediatrics**
	PegIntron/ Ribavirin (N=511)	**INTRON A/ Ribavirin** (N=505)	**PegIntron/Ribavirin** (N=107)*
Hemoglobin (g/dL)			
9.5 to <11.0	26	27	30
8.0 to <9.5	3	3	2
6.5 to 7.9	0.2	0.2	-
Leukocytes (x 10^9/L)			
2.0 to 2.9	46	41	39
1.5 to <2.0	24	8	3
1.0 to 1.4	5	1	-
Neutrophils (x 10^9/L)			
1.0 to 1.5	33	37	35
0.75 to <1.0	25	13	26
0.5 to <0.75	18	7	13
<0.5	4	2	3
Platelets (x 10^9/L)			
70 to 100	15	5	1
50 to <70	3	0.8	-
30 to 49	0.2	0.2	-
25 to <50	-	-	1
Total Bilirubin	**(mg/dL)**		**(µmole/L)**
1.5 to 3.0	10	13	-
1.26 to 2.59 x ULN†	-	-	7
3.1 to 6.0	0.6	0.2	-
2.6 to 5 x ULN†	-	-	-
6.1 to 12.0	0	0.2	-
ALT (U/L)			
2 x Baseline	0.6	0.2	1
2.1 to 5 x Baseline	3	1	5

5.1 to 10 x Baseline	0	0	3

* The table summarizes the worst category observed within the period per subject per laboratory test. Only subjects with at least one treatment value for a given laboratory test are included.
† ULN=Upper limit of normal.

Hemoglobin. In Study 2, hemoglobin levels decreased to less than 11 g/dL in about 30% of subjects. In Study 3, 47% of subjects receiving weight-based dosing of ribavirin and 33% on flat-dose ribavirin had decreases in hemoglobin levels to less than 11 g/dL. Reductions in hemoglobin to less than 9 g/dL occurred more frequently in subjects receiving weight-based dosing compared to flat dosing (4% and 2%, respectively). In Study 2, dose modification was required in 9% and 13% of subjects in the PegIntron/ribavirin and INTRON A/ribavirin groups. In Study 4, subjects receiving PegIntron (1.5 mcg/kg)/ribavirin had decreases in hemoglobin levels to between 8.5 to less than 10 g/dL (28%) and to less than 8.5 g/dL (3%), whereas in patients receiving Pegasys 180 mcg/Copegus these decreases occurred in 26% and 4% of subjects, respectively. On average, hemoglobin levels became stable by treatment Weeks 4 to 6. The typical pattern observed was a decrease in hemoglobin levels by treatment Week 4 followed by stabilization and a plateau, which was maintained to the end of treatment *[see Dosage and Administration (2.5)]*.

Neutrophils. In Study 2, decreases in neutrophil counts were observed in a majority of adult subjects treated with PegIntron/ribavirin (85%) and INTRON A/ribavirin (60%). Severe, potentially life-threatening neutropenia (less than 0.5 x 10^9/L) occurred in approximately 4% of subjects treated with PegIntron/ribavirin and 2% of subjects treated with INTRON A/ribavirin. Eighteen percent of subjects receiving PegIntron/ribavirin required modification of interferon dosage. Few subjects (less than 1%) required permanent discontinuation of treatment. Neutrophil counts generally returned to pre-treatment levels 4 weeks after cessation of therapy *[see Dosage and Administration (2.5)]*.

Platelets. In Study 2, platelet counts decreased to less than 100,000/mm^3 in approximately 20% of subjects treated with PegIntron alone or with ribavirin and in 6% of adult subjects treated with INTRON A/ribavirin. Severe decreases in platelet counts (less than 50,000/mm^3) occur in less than 4% of adult subjects. In Study 2, 1% or 3% of subjects required dose modification of INTRON A or PegIntron, respectively. Platelet counts generally returned to pretreatment levels 4 weeks after the cessation of therapy *[see Dosage and Administration (2.5)]*.

Thyroid Function. In Study 2, clinically apparent thyroid disorders occurred among subjects treated with either INTRON A or PegIntron (with or without ribavirin) at a similar incidence (5% for hypothyroidism and 3% for hyperthyroidism). Subjects developed new onset TSH abnormalities while on treatment and during the follow-up period. At the end of the follow-up period, 7% of subjects still had abnormal TSH values.

Bilirubin and Uric Acid. In Study 2, 10 to 14% of subjects developed hyperbilirubinemia and 33 to 38% developed hyperuricemia in association with hemolysis. Six subjects developed mild to moderate gout.

Adverse Reactions with Ribavirin/INTRON A Combination Therapy

Adult Subjects

In clinical trials, 19% and 6% of previously untreated and relapse subjects, respectively, discontinued therapy due to adverse reactions in the combination arms compared to 13% and 3% in the interferon-only arms. Selected treatment-related adverse reactions that occurred in the U.S. trials with incidence 5% or greater are provided by treatment group (see Table 9). In general, the selected treatment-related adverse reactions were reported with lower incidence in the international trials as compared to the U.S. trials, except for asthenia, influenza-like symptoms, nervousness, and pruritus.

Pediatric Subjects

In clinical trials of 118 pediatric subjects 3 to 16 years of age, 6% discontinued therapy due to adverse reactions. Dose modifications were required in 30% of subjects, most commonly for anemia and neutropenia. In general, the adverse-reaction profile in the pediatric population was similar to that observed in adults. Injection site disorders, fever, anorexia, vomiting, and emotional lability occurred more frequently in pediatric subjects compared to adult subjects. Conversely, pediatric subjects experienced less fatigue, dyspepsia, arthralgia, insomnia, irritability, impaired concentration, dyspnea, and pruritus compared to adult subjects. Selected treatment-related adverse reactions that occurred with incidence 5% or greater among all pediatric subjects who received the recommended dose of ribavirin/INTRON A combination therapy are provided in Table 9.

Table 9: Selected Treatment-Related Adverse Reactions: Previously Untreated and Relapse Adult Subjects and Previously Untreated Pediatric Subjects

Subjects Reporting Adverse Reactions*	Percentage of Subjects						
	U.S. Previously Untreated Study				U.S. Relapse Study		Pediatric Subjects
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		48 weeks of treatment
	INTRON A/ Ribavirin (N=228)	INTRON A/ Placebo (N=231)	INTRON A/ Ribavirin (N=228)	INTRON A/ Placebo (N=225)	INTRON A/ Ribavirin (N=77)	INTRON A/ Placebo (N=76)	INTRON A/ Ribavirin (N=118)
Application Site Disorders							
Injection Site Inflammation	13	10	12	14	6	8	14
Injection Site Reaction	7	9	8	9	5	3	19
Body as a Whole - General Disorders							
Headache	63	63	66	67	66	68	69
Fatigue	68	62	70	72	60	53	58
Rigors	40	32	42	39	43	37	25
Fever	37	35	41	40	32	36	61
Influenza-like Symptoms	14	18	18	20	13	13	31
Asthenia	9	4	9	9	10	4	5
Chest Pain	5	4	9	8	6	7	5
Central & Peripheral Nervous System Disorders							
Dizziness	17	15	23	19	26	21	20
Gastrointestinal System Disorders							
Nausea	38	35	46	33	47	33	33
Anorexia	27	16	25	19	21	14	51
Dyspepsia	14	6	16	9	16	9	<1
Vomiting	11	10	9	13	12	8	42
Musculoskeletal System Disorders							
Myalgia	61	57	64	63	61	58	32
Arthralgia	30	27	33	36	29	29	15
Musculoskeletal	30	26	28	32	32	28	21

Pain	20	26	28	32	22	28	21
Psychiatric Disorders							
Insomnia	39	27	39	30	26	25	14
Irritability	23	19	32	27	25	20	10
Depression	32	25	36	37	23	14	13
Emotional Lability	7	6	11	8	12	8	16
Concentration Impaired	11	14	14	14	10	12	5
Nervousness	4	2	4	4	5	4	3
Respiratory System Disorders							
Dyspnea	19	9	18	10	17	12	5
Sinusitis	9	7	10	14	12	7	<1
Skin and Appendages Disorders							
Alopecia	28	27	32	28	27	26	23
Rash	20	9	28	8	21	5	17
Pruritus	21	9	19	8	13	4	12
Special Senses, Other Disorders							
Taste Perversion	7	4	8	4	6	5	<1

* Subjects reporting one or more adverse reactions. A subject may have reported more than one adverse reaction within a body system/organ class category.

During a 48-week course of therapy there was a decrease in the rate of linear growth (mean percentile assignment decrease of 7%) and a decrease in the rate of weight gain (mean percentile assignment decrease of 9%). A general reversal of these trends was noted during the 24-week post-treatment period. Long-term data in a limited number of patients, however, suggests that combination therapy may induce a growth inhibition that results in reduced final adult height in some patients *[see Warnings and Precautions (5.9)]*.

Laboratory Values

Changes in selected hematologic values (hemoglobin, white blood cells, neutrophils, and platelets) during therapy are described below (see Table 10).

Hemoglobin. Hemoglobin decreases among subjects receiving ribavirin therapy began at Week 1, with stabilization by Week 4. In previously untreated subjects treated for 48 weeks, the mean maximum decrease from baseline was 3.1 g/dL in the U.S. trial and 2.9 g/dL in the international trial. In relapse subjects, the mean maximum decrease from baseline was 2.8 g/dL in the U.S. trial and 2.6 g/dL in the international trial. Hemoglobin values returned to pretreatment levels within 4 to 8 weeks of cessation of therapy in most subjects.

Bilirubin and Uric Acid. Increases in both bilirubin and uric acid, associated with hemolysis, were noted in clinical trials. Most changes were moderate and reversed within 4 weeks after treatment discontinuation. This observation occurred most frequently in subjects with a previous diagnosis of Gilbert's syndrome. This has not been associated with hepatic dysfunction or clinical morbidity.

Table 10: Selected Laboratory Abnormalities During Treatment with Ribavirin and INTRON A: Previously Untreated and Relapse Adult Subjects and Previously Untreated Pediatric Subjects

	Percentage of Subjects		
	U.S. Previously Untreated Study	U.S. Relapse Study	Pediatric

	U.S. Previously Untreated Study				U.S. Relapse Study		Subjects
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment		48 weeks of treatment
	INTRON A/ Ribavirin (N=228)	INTRON A/ Placebo (N=231)	INTRON A/ Ribavirin (N=228)	INTRON A/ Placebo (N=225)	INTRON A/ Ribavirin (N=77)	INTRON A/ Placebo (N=76)	INTRON A/ Ribavirin (N=118)
Hemoglobin (g/dL)							
9.5 to 10.9	24	1	32	1	21	3	24
8.0 to 9.4	5	0	4	0	4	0	3
6.5 to 7.9	0	0	0	0.4	0	0	0
<6.5	0	0	0	0	0	0	0
Leukocytes (x 10^9/L)							
2.0 to 2.9	40	20	38	23	45	26	35
1.5 to 1.9	4	1	9	2	5	3	8
1.0 to 1.4	0.9	0	2	0	0	0	0
<1.0	0	0	0	0	0	0	0
Neutrophils (x 10^9/L)							
1.0 to 1.49	30	32	31	44	42	34	37
0.75 to 0.99	14	15	14	11	16	18	15
0.5 to 0.74	9	9	14	7	8	4	16
<0.5	11	8	11	5	5	8	3
Platelets (x 10^9/L)							
70 to 99	9	11	11	14	6	12	0.8
50 to 69	2	3	2	3	0	5	2
30 to 49	0	0.4	0	0.4	0	0	0
<30	0.9	0	1	0.9	0	0	0
Total Bilirubin (mg/dL)							
1.5 to 3.0	27	13	32	13	21	7	2
3.1 to 6.0	0.9	0.4	2	0	3	0	0
6.1 to 12.0	0	0	0.4	0	0	0	0
>12.0	0	0	0	0	0	0	0

6.2 Postmarketing Experiences

The following adverse reactions have been identified and reported during post approval use of ribavirin in combination with INTRON A or PegIntron. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System disorders
Pure red cell aplasia, aplastic anemia
Ear and Labyrinth disorders
Hearing disorder, vertigo
Respiratory, Thoracic and Mediastinal disorders
Pulmonary hypertension
Eye disorders
Serous retinal detachment
Endocrine disorders
Diabetes

7 DRUG INTERACTIONS

7.1 Didanosine

Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is coadministered with ribavirin, which could cause or worsen clinical toxicities; therefore, coadministration of ribavirin capsules and didanosine is contraindicated *[see Contraindications (4)]*. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials.

7.2 Nucleoside Analogues

Hepatic decompensation (some fatal) has occurred in cirrhotic HIV/HCV co-infected patients receiving combination antiretroviral therapy for HIV and interferon alpha and ribavirin. Patients receiving interferon with ribavirin and nucleoside reverse transcriptase inhibitors (NRTIs) should be closely monitored for treatment-associated toxicities, especially hepatic decompensation and anemia. Discontinuation of NRTIs should be considered as medically appropriate *(see labeling for individual NRTI product)*. Dose reduction or discontinuation of interferon, ribavirin, or both should also be considered if worsening clinical toxicities are observed, including hepatic decompensation (e.g., Child-Pugh greater than 6).

Ribavirin may antagonize the cell culture antiviral activity of stavudine and zidovudine against HIV. Ribavirin has been shown in cell culture to inhibit phosphorylation of lamivudine, stavudine, and zidovudine, which could lead to decreased antiretroviral activity. However, in a study with another pegylated interferon in combination with ribavirin, no pharmacokinetic (e.g., plasma concentrations or intracellular triphosphorylated active metabolite concentrations) or pharmacodynamic (e.g., loss of HIV/HCV virologic suppress) interaction was observed when ribavirin and lamivudine (n=18), stavudine (n=10), or zidovudine (n=6) were coadministered as part of a multidrug regimen in HIV/HCV co-infected subjects. Concomitant use of ribavirin with any of these drugs should be done with caution.

7.3 Drugs Metabolized by Cytochrome P-450

Results of *in vitro* studies using both human and rat liver microsome preparations indicated little or no cytochrome P-450 enzyme-mediated metabolism of ribavirin, with minimal potential for P-450 enzyme-based drug interactions.

No pharmacokinetic interactions were noted between INTRON A and ribavirin capsules in a multiple-dose pharmacokinetic study.

7.4 Azathioprine

The use of ribavirin for the treatment of chronic hepatitis C in patients receiving azathioprine has been reported to induce severe pancytopenia and may increase the risk of azathioprine-related myelotoxicity. Inosine monophosphate dehydrogenase (IMDH) is required for one of the metabolic pathways of azathioprine. Ribavirin is known to inhibit IMDH, thereby leading to accumulation of an azathioprine metabolite, 6-methylthioinosine monophosphate (6-MTITP), which is associated with myelotoxicity (neutropenia, thrombocytopenia, and anemia). Patients receiving azathioprine with ribavirin should have complete blood counts, including platelet counts, monitored weekly for the first month, twice monthly for the second and third months of treatment, then monthly or more frequently if dosage or other therapy changes are necessary *[see Warnings and Precautions (5.8)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Ribavirin is contraindicated for use in pregnant women and in men whose female partners are pregnant *[see Contraindications (4)]*. Based on animal data, ribavirin use in pregnancy may be associated with birth defects. Data from the Ribavirin Pregnancy Registry are insufficient to identify a drug-associated risk of birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*. Ribavirin is known to accumulate in intracellular components from where it is cleared very slowly. In animal studies, ribavirin exposure was shown to have teratogenic and/or embryocidal effects *(see Data)*.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Available data from the Ribavirin Pregnancy Registry on 88 live births from pregnancies in women directly exposed and 98 live births from pregnancies in women indirectly exposed (by a male partner) to ribavirin during pregnancy or during the 6 months prior to pregnancy show a higher rate of birth defects (9.09% and 6.12%, respectively) compared to a background birth defect rate of 2.72% in the Metropolitan Atlanta Congenital Defects Program (MACDP) birth defects surveillance system. No pattern of birth defects can be identified from these reports. The miscarriage rate was approximately 21%. The current sample size is insufficient for reaching definitive conclusions based on statistical analysis. Trends suggesting a common etiology or relationship with ribavirin exposure were not observed. Methodologic limitations of the Ribavirin Pregnancy Registry include the use of MACDP as the external comparator group. Limitations of using an external comparator include differences in methodology and populations, as well as confounding due to the underlying disease and comorbidities.

Animal Data

Embryotoxicity/teratogenicity studies with ribavirin were conducted in rats (oral doses of 0.3, 1 and 10 mg/kg on Gestation Days 6 to 15) and rabbits (oral dose of 0.1, 0.3 and 1 mg/kg on Gestation Days 6 to 18). Ribavirin demonstrated significant embryocidal and teratogenic effects at doses well below the recommended human dose in all animal species in which adequate studies have been conducted. Malformations of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tract were noted. The incidence and severity of teratogenic effects increased with escalation of the drug dose. Survival of fetuses and offspring was reduced *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

8.2 Lactation

Risk Summary

There are no data on the presence of ribavirin in human milk or the effects on the breastfed infant or milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ribavirin and any potential adverse effects on the breastfed infant from ribavirin or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Ribavirin may cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Ribavirin therapy should not be started until a report of a negative pregnancy test has been obtained immediately prior to planned initiation of treatment. Patients should have periodic pregnancy tests during treatment and during the 6-month period after treatment has been stopped *[see Warnings and Precautions (5.1)]*.

Contraception

Females of reproductive potential should use effective contraception during treatment and for 6 months post-therapy based on a multiple-dose half-life ($t_{1/2}$) of ribavirin of 12 days (e.g., 15 half-lives for ribavirin clearance from the body).

Male patients and their female partners should use effective contraception during treatment with ribavirin and for the 6-month post-therapy period *[see Warnings and Precautions (5.1)]*.

Infertility

Based on animal data, ribavirin may impair male fertility. In animal studies, these effects were mostly reversible within a few months after drug cessation *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of ribavirin in combination with PegIntron has not been established in pediatric patients below the age of 3 years. For treatment with ribavirin/INTRON A, evidence of disease progression, such as hepatic inflammation and fibrosis, as well as prognostic factors for response, HCV genotype and viral load should be considered when deciding to treat a pediatric patient. The benefits of treatment should be weighed against the observed safety findings.

Long-term follow-up data in pediatric subjects indicates that ribavirin in combination with PegIntron or with INTRON A may induce a growth inhibition that results in reduced height in some patients *[see Warnings and Precautions (5.9) and Adverse Reactions (6.1)]*.

Suicidal ideation or attempts occurred more frequently among pediatric patients, primarily adolescents, compared to adult patients (2.4% vs. 1%) during treatment and off-therapy follow-up *[see Warnings and Precautions (5.10)]*. As in adult patients, pediatric patients experienced other psychiatric adverse reactions (e.g., depression, emotional lability, somnolence), anemia, and neutropenia *[see Warnings and Precautions (5.2)]*.

8.5 Geriatric Use

Clinical trials of ribavirin combination therapy did not include sufficient numbers of subjects aged 65 and over to determine if they respond differently from younger subjects.

Ribavirin is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients often have decreased renal function, care should be taken in dose selection. Renal function should be monitored and dosage adjustments made accordingly. Ribavirin should not be used in patients with creatinine clearance less than 50 mL/min *[see Contraindications (4)]*.

In general, ribavirin capsules should be administered to elderly patients cautiously, starting at the lower end of the dosing range, reflecting the greater frequency of decreased hepatic and cardiac function, and of concomitant disease or other drug therapy. In clinical trials, elderly subjects had a higher frequency of anemia (67%) than younger patients (28%) *[see Warnings and Precautions (5.2)]*.

8.6 Organ Transplant Recipients

The safety and efficacy of INTRON A and PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been established. In a small (n=16) single-center, uncontrolled case experience, renal failure in renal allograft recipients receiving interferon alpha and ribavirin combination therapy was more frequent than expected from the center's previous experience with renal allograft recipients not receiving combination therapy. The relationship of the renal failure to renal allograft rejection is not clear.

8.7 HIV or HBV Co-infection

The safety and efficacy of PegIntron/ribavirin and INTRON A/ribavirin for the treatment of patients with HCV co-infected with HIV or HBV have not been established.

10 OVERDOSAGE

There is limited experience with overdosage. Acute ingestion of up to 20 g of ribavirin capsules, INTRON A ingestion of up to 120 million units, and subcutaneous doses of INTRON A up to 10 times the recommended doses have been reported. Primary effects that have been observed are increased incidence and severity of the adverse reactions related to the therapeutic use of INTRON A and ribavirin. However, hepatic enzyme abnormalities, renal failure, hemorrhage, and myocardial infarction have been reported with administration of single subcutaneous doses of INTRON A that exceed dosing recommendations.

There is no specific antidote for INTRON A or ribavirin overdose, and hemodialysis and peritoneal dialysis are not effective for treatment of overdose of these agents.

11 DESCRIPTION

Ribavirin, is a synthetic nucleoside analogue (purine analogue). The chemical name of ribavirin is 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide and has the following structural formula (see Figure 1).

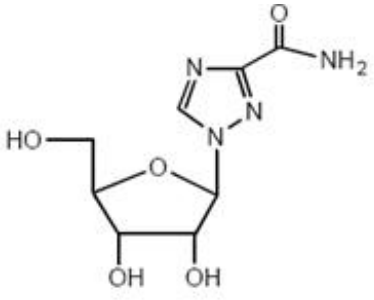

Figure 1: Structural Formula

Ribavirin USP is a white, crystalline powder. It is freely soluble in water and slightly soluble in anhydrous alcohol. The molecular formula is $C_8H_{12}N_4O_5$ and the molecular weight is 244.21.

Ribavirin capsules USP consist of a white to off-white granular powder in a white, opaque, gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline cellulose,

lactose monohydrate, povidone-K 30, and magnesium stearate. The capsule shell consists of titanium dioxide, sodium lauryl sulfate, and gelatin. The capsule is printed with edible ink containing black iron oxide.

Meets USP dissolution test 2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ribavirin is an anti-HCV agent *[see Microbiology (12.4)]*.

12.3 Pharmacokinetics

Single- and multiple-dose pharmacokinetic properties in adults are summarized in Table 11. Ribavirin was rapidly and extensively absorbed following oral administration. However, due to first-pass metabolism, the absolute bioavailability averaged 64% (44%). There was a linear relationship between dose and AUC_{tf} (AUC from time zero to last measurable concentration) following single doses of 200 to 1200 mg ribavirin. The relationship between dose and C_{max} was curvilinear, tending to asymptote above single doses of 400 to 600 mg.

Upon multiple oral dosing, based on AUC_{12hr}, a 6-fold accumulation of ribavirin was observed in plasma. Following oral dosing with 600 mg twice daily, steady-state was reached by approximately 4 weeks, with mean steady-state plasma concentrations of 2200 ng/mL (37%). Upon discontinuation of dosing, the mean half-life was 298 (30%) hours, which probably reflects slow elimination from nonplasma compartments.

Effect of Antacid on Absorption of Ribavirin: Coadministration of ribavirin capsules with an antacid containing magnesium, aluminum, and simethicone resulted in a 14% decrease in mean ribavirin AUC_{tf}. The clinical relevance of results from this single-dose study is unknown.

Table 11: Mean (% CV) Pharmacokinetic Parameters for Ribavirin When Administered Individually to Adults

Parameter	Ribavirin		
	Single-Dose 600 mg Oral Solution (N=14)	**Single-Dose 600 mg Capsules** (N=12)	**Multiple-Dose 600 mg Capsules twice daily** (N=12)
T_{max} (hr)	1.00 (34)	1.7 (46)*	3 (60)
C_{max} (ng/mL)	872 (42)	782 (37)	3680 (85)
AUC_{tf} (ng·hr/mL)	14,098 (38)	13,400 (48)	228,000 (25)
$T_{1/2}$ (hr)		43.6 (47)	298 (30)
Apparent Volume of Distribution (L)		2825 (9)†	
Apparent Clearance (L/hr)		38.2 (40)	
Absolute Bioavailability		64% (44)‡	

* N=11.
† Data obtained from a single-dose pharmacokinetic study using ^{14}C labeled ribavirin; N=5.
‡ N=6.

Tissue Distribution: Ribavirin transport into nonplasma compartments has been most extensively studied in red blood cells and has been identified to be primarily via an e_s-type equilibrative nucleoside transporter. This type of transporter is present on virtually all cell types and may account for the extensive volume of distribution. Ribavirin does not bind to plasma proteins.

Metabolism and Excretion: Ribavirin has two pathways of metabolism: (i) a reversible phosphorylation pathway in nucleated cells; and (ii) a degradative pathway involving deribosylation and amide hydrolysis to yield a triazole carboxylic acid metabolite. Ribavirin and its triazole carboxamide and triazole carboxylic acid metabolites are excreted renally. After oral administration of 600 mg of ^{14}C-ribavirin, approximately 61% and 12% of the radioactivity was eliminated in the urine and feces, respectively, in 336 hours. Unchanged ribavirin accounted for 17% of the administered dose.

Special Populations:

Renal Dysfunction

The pharmacokinetics of ribavirin were assessed after administration of a single oral dose (400 mg) of ribavirin to non-HCV-infected subjects with varying degrees of renal dysfunction. The mean AUC_{tf} value was threefold greater in subjects with creatinine clearance values between 10 to 30 mL/min when compared to control subjects (creatinine clearance greater than 90 mL/min). In subjects with creatinine clearance values between 30 to 60 mL/min, AUC_{tf} was twofold greater when compared to control subjects. The increased AUC_{tf} appears to be due to reduction of renal and nonrenal clearance in these subjects. Phase 3 efficacy trials included subjects with creatinine clearance values greater than 50 mL/min. The multiple-dose pharmacokinetics of ribavirin cannot be accurately predicted in patients with renal dysfunction. Ribavirin is not effectively removed by hemodialysis. Patients with creatinine clearance less than 50 mL/min should not be treated with ribavirin *[see Contraindications (4)]*.

Hepatic Dysfunction

The effect of hepatic dysfunction was assessed after a single oral dose of ribavirin (600 mg). The mean AUC_{tf} values were not significantly different in subjects with mild, moderate, or severe hepatic dysfunction (Child-Pugh Classification A, B, or C) when compared to control subjects. However, the mean C_{max} values increased with severity of hepatic dysfunction and was twofold greater in subjects with severe hepatic dysfunction when compared to control subjects.

Elderly Patients

Pharmacokinetic evaluations in elderly subjects have not been performed.

Gender

There were no clinically significant pharmacokinetic differences noted in a single-dose trial of 18 male and 18 female subjects.

Pediatric Patients

Multiple-dose pharmacokinetic properties for ribavirin capsules and INTRON A in pediatric subjects with chronic hepatitis C between 5 and 16 years of age are summarized in Table 12. The pharmacokinetics of ribavirin and INTRON A (dose-normalized) are similar in adults and pediatric subjects.

Complete pharmacokinetic characteristics of ribavirin oral solution have not been determined in pediatric subjects. Ribavirin C_{min} values were similar following administration of ribavirin oral

solution or ribavirin capsules during 48 weeks of therapy in pediatric subjects (3 to 16 years of age).

Table 12: Mean (% CV) Multiple-dose Pharmacokinetic Parameters for INTRON A and Ribavirin Capsules When Administered to Pediatric Subjects with Chronic Hepatitis C

Parameter	Ribavirin 15 mg/kg/day as 2 divided doses (N=17)	INTRON A 3 MIU/m^2 three times weekly (N=54)
T_{max} (hr)	1.9 (83)	5.9 (36)
C_{max} (ng/mL)	3275 (25)	51 (48)
AUC*	29,774 (26)	622 (48)
Apparent Clearance L/hr/kg	0.27 (27)	ND†

* AUC_{12} (ng·hr/mL) for ribavirin; AUC_{0-24} (IU·hr/mL) for INTRON A.
† ND=not done.

Note: numbers in parenthesis indicate % coefficient of variation.

A clinical trial in pediatric subjects with chronic hepatitis C between 3 and 17 years of age was conducted in which pharmacokinetics for PegIntron and ribavirin (capsules and oral solution) were evaluated. In pediatric subjects receiving body surface area-adjusted dosing of PegIntron at 60 mcg/m^2/week, the log transformed ratio estimate of exposure during the dosing interval was predicted to be 58% [90% CI: 141%, 177%] higher than observed in adults receiving 1.5 mcg/kg/week. The pharmacokinetics of ribavirin (dose-normalized) in this trial were similar to those reported in a prior study of ribavirin in combination with INTRON A in pediatric subjects and in adults.

Effect of Food on Absorption of Ribavirin

Both AUC_{tf} and C_{max} increased by 70% when ribavirin capsules were administered with a high-fat meal (841 kcal, 53.8 g fat, 31.6 g protein, and 57.4 g carbohydrate) in a single-dose pharmacokinetic study *[see Dosage and Administration (2)]*.

12.4 Microbiology

Mechanism of Action

The mechanism by which ribavirin contributes to its antiviral efficacy in the clinic is not fully understood. Ribavirin has direct antiviral activity in cell culture against many RNA viruses. Ribavirin increases the mutation frequency in the genomes of several RNA viruses and ribavirin triphosphate inhibits HCV polymerase in a biochemical reaction.

Antiviral Activity in Cell Culture

The antiviral activity of ribavirin in the HCV replicon is not well understood and has not been defined because of the cellular toxicity of ribavirin. Direct antiviral activity has been observed in cell culture of other RNA viruses. The anti-HCV activity of interferon was demonstrated in cell culture using self-replicating HCV RNA (HCV replicon cells) or HCV infection.

Resistance

HCV genotypes show wide variability in their response to pegylated recombinant human interferon/ribavirin therapy. Genetic changes associated with the variable response have not been identified.

Cross-resistance

There is no reported cross-resistance between pegylated/non-pegylated interferons and ribavirin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Ribavirin did not cause an increase in any tumor type when administered for 6 months in the transgenic p53 deficient mouse model at doses up to 300 mg/kg (estimated human equivalent of 25 mg/kg based on body surface area adjustment for a 60 kg adult; approximately 1.9 times the maximum recommended human daily dose). Ribavirin was noncarcinogenic when administered for 2 years to rats at doses up to 40 mg/kg (estimated human equivalent of 5.71 mg/kg based on body surface area adjustment for a 60 kg adult).

Mutagenesis

Ribavirin demonstrated increased incidences of mutation and cell transformation in multiple genotoxicity assays. Ribavirin was active in the Balb/3T3 *In Vitro* Cell Transformation Assay. Mutagenic activity was observed in the mouse lymphoma assay, and at doses of 20 to 200 mg/kg (estimated human equivalent of 1.67 to 16.7 mg/kg, based on body surface area adjustment for a 60 kg adult; 0.1 to 1 times the maximum recommended human 24-hour dose of ribavirin) in a mouse micronucleus assay. A dominant lethal assay in rats was negative, indicating that if mutations occurred in rats they were not transmitted through male gametes.

Impairment of Fertility

In studies in mice to evaluate the time course and reversibility of ribavirin-induced testicular degeneration at doses of 15 to 150 mg/kg/day (estimated human equivalent of 1.25 to 12.5 mg/kg/day, based on body surface area adjustment for a 60-kg adult; 0.1 to 0.8 times the maximum human 24-hour dose of ribavirin) administered for 3 or 6 months, abnormalities in sperm occurred. Upon cessation of treatment, recovery from ribavirin-induced testicular toxicity was mostly apparent within 1 or 2 spermatogenesis cycles.

13.2 Animal Toxicology and Pharmacology

Long-term studies in the mouse and rat [18 to 24 months; doses of 20 to 75 and 10 to 40 mg/kg/day, respectively (estimated human equivalent doses of 1.67 to 6.25 and 1.43 to 5.71 mg/kg/day, respectively, based on body surface area adjustment for a 60 kg adult; approximately 0.1 to 0.4 times the maximum human 24-hour dose of ribavirin)] have demonstrated a relationship between chronic ribavirin exposure and increased incidences of vascular lesions (microscopic hemorrhages) in mice. In rats, retinal degeneration occurred in controls, but the incidence was increased in ribavirin-treated rats.

In a study in which rat pups were dosed postnatally with ribavirin at doses of 10, 25, and 50 mg/kg/day, drug-related deaths occurred at 50 mg/kg (at rat pup plasma concentrations below human plasma concentrations at the human therapeutic dose) between study Days 13 and 48. Rat pups dosed from postnatal Days 7 through 63 demonstrated a minor, dose-related decrease in overall growth at all doses, which was subsequently manifested as slight decreases in body weight, crown-rump length, and bone length. These effects showed evidence of reversibility, and no histopathological effects on bone were observed. No ribavirin effects were observed regarding neurobehavioral or reproductive development.

14 CLINICAL STUDIES

Clinical Study 1 evaluated PegIntron monotherapy. See PegIntron labeling for information about this trial.

14.1 Ribavirin/PegIntron Combination Therapy

Adult Subjects

Study 2

A randomized trial compared treatment with two PegIntron/ribavirin regimens [PegIntron 1.5 mcg/kg subcutaneously once weekly/ribavirin 800 mg orally daily (in divided doses); PegIntron 1.5 mcg/kg subcutaneously once weekly for 4 weeks then 0.5 mcg/kg subcutaneously once weekly for 44 weeks/ribavirin 1000 or 1200 mg orally daily (in divided doses)] with INTRON A [3 MIU subcutaneously three times weekly/ribavirin 1000 or 1200 mg orally daily (in divided doses)] in 1,530 adults with chronic hepatitis C. Interferon-naïve subjects were treated for 48 weeks and followed for 24 weeks post-treatment. Eligible subjects had compensated liver disease, detectable HCV-RNA, elevated ALT, and liver histopathology consistent with chronic hepatitis.

Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment (see Table 13). The response rate to the PegIntron 1.5 mcg/kg and ribavirin 800 mg dose was higher than the response rate to INTRON A/ribavirin (see Table 13). The response rate to PegIntron 1.5→0.5 mcg/kg/ribavirin was essentially the same as the response to INTRON A/ ribavirin (data not shown).

Table 13: Rates of Response to Combination Treatment – Study 2

	PegIntron 1.5 mcg/kg once weekly Ribavirin 800 mg once daily	**INTRON A 3 MIU three times weekly Ribavirin 1000/1200 mg once daily**
Overall response*,†	52% (264/511)	46% (231/505)
Genotype 1	41% (141/348)	33% (112/343)
Genotype 2 to 6	75% (123/163)	73% (119/162)

* Serum HCV-RNA was measured with a research-based quantitative polymerase chain reaction assay by a central laboratory.
† Difference in overall treatment response (PegIntron/ribavirin vs. INTRON A/ribavirin) is 6% with 95% confidence interval of (0.18, 11.63) adjusted for viral genotype and presence of cirrhosis at baseline. Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment.

Subjects with viral genotype 1, regardless of viral load, had a lower response rate to PegIntron (1.5 mcg/kg)/ribavirin (800 mg) compared to subjects with other viral genotypes. Subjects with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 30% (78/256) compared to a response rate of 29% (71/247) with INTRON A/ ribavirin combination therapy.

Subjects with lower body weight tended to have higher adverse-reaction rates *[see Adverse Reactions (6.1)]* and higher response rates than subjects with higher body weights. Differences in response rates between treatment arms did not substantially vary with body weight.

Treatment response rates with PegIntron/ribavirin combination therapy were 49% in men and 56% in women. Response rates were lower in African American and Hispanic subjects and higher in Asians compared to Caucasians. Although African Americans had a higher proportion of poor prognostic

factors compared to Caucasians, the number of non-Caucasians studied (11% of the total) was insufficient to allow meaningful conclusions about differences in response rates after adjusting for prognostic factors in this trial.

Liver biopsies were obtained before and after treatment in 68% of subjects. Compared to baseline, approximately two-thirds of subjects in all treatment groups were observed to have a modest reduction in inflammation.

Study 3

In a large United States community-based trial, 4,913 subjects with chronic hepatitis C were randomized to receive PegIntron 1.5 mcg/kg subcutaneously once weekly in combination with a ribavirin dose of 800 to 1400 mg (weight-based dosing [WBD]) or 800 mg (flat) orally daily (in divided doses) for 24 or 48 weeks based on genotype. Response to treatment was defined as undetectable HCV-RNA (based on an assay with a lower limit of detection of 125 IU/mL) at 24 weeks post-treatment.

Treatment with PegIntron 1.5 mcg/kg and ribavirin 800 to 1400 mg resulted in a higher sustained virologic response compared to PegIntron in combination with a flat 800 mg daily dose of ribavirin. Subjects weighing greater than 105 kg obtained the greatest benefit with WBD, although a modest benefit was also observed in subjects weighing greater than 85 to 105 kg (see Table 14). The benefit of WBD in subjects weighing greater than 85 kg was observed with HCV genotypes 1 to 3. Insufficient data were available to reach conclusions regarding other genotypes. Use of WBD resulted in an increased incidence of anemia *[see Adverse Reactions (6.1)]*.

Table 14: SVR Rate by Treatment and Baseline Weight - Study 3

Treatment Group	Subject Baseline Weight			
	<65 kg (<143 lb)	**65 to 85 kg (143 to 188 lb)**	**>85 to 105 kg (>188 to 231 lb)**	**>105 kg (>231 lb)**
WBD*	50% (173/348)	45% (449/994)	42% (351/835)	47% (138/292)
Flat	51% (173/342)	44% (443/1011)	39% (318/819)	33% (91/272)

* *P*=0.01, primary efficacy comparison (based on data from subjects weighing 65 kg or higher at baseline and utilizing a logistic regression analysis that includes treatment [WBD or Flat], genotype and presence/absence of advanced fibrosis, in the model).

A total of 1,552 subjects weighing greater than 65 kg in Study 3 had genotype 2 or 3 and were randomized to 24 or 48 weeks of therapy. No additional benefit was observed with the longer treatment duration.

Study 4

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two PegIntron/ribavirin regimens [PegIntron 1.5 mcg/kg and 1 mcg/kg subcutaneously once weekly both in combination with ribavirin 800 to 1400 mg PO daily (in two divided doses)] and Pegasys 180 mcg subcutaneously once weekly in combination with Copegus 1000 to 1200 mg PO daily (in two divided doses) in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. In this trial, lack of early virologic response (undetectable HCV-RNA or greater than or equal to 2 $\log_{10}$ reduction from baseline) by treatment Week 12 was the criterion for discontinuation of treatment. SVR was defined as undetectable HCV-RNA (Roche COBAS TaqMan assay, a lower limit of quantitation of 27 IU/mL) at 24 weeks post-treatment (see Table 15).

Table 15: SVR Rate by Treatment – Study 4

% (number) of Subjects		
PegIntron 1.5 mcg/kg/Ribavirin	**PegIntron 1 mcg/kg/Ribavirin**	**Pegasys 180 mcg/Copegus**
40 (406/1019)	38 (386/1016)	41 (423/1035)

Overall SVR rates were similar among the three treatment groups. Regardless of treatment group, SVR rates were lower in subjects with poor prognostic factors. Subjects with poor prognostic factors randomized to PegIntron (1.5 mcg/kg)/ribavirin or Pegasys/Copegus, however, achieved higher SVR rates compared to similar subjects randomized to PegIntron 1 mcg/kg/ribavirin. For the PegIntron 1.5 mcg/kg and ribavirin dose, SVR rates for subjects with and without the following prognostic factors were as follows: cirrhosis (10% vs. 42%), normal ALT levels (32% vs. 42%), baseline viral load greater than 600,000 IU/mL (35% vs. 61%), 40 years of age and older (38% vs. 50%), and African American race (23% vs. 44%). In subjects with undetectable HCV-RNA at treatment Week 12 who received PegIntron (1.5 mcg/kg)/ribavirin, the SVR rate was 81% (328/407).

Study 5 - Ribavirin/PegIntron Combination Therapy in Prior Treatment Failures

In a noncomparative trial, 2,293 subjects with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were re-treated with PegIntron, 1.5 mcg/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Eligible subjects included prior nonresponders (subjects who were HCV-RNA positive at the end of a minimum 12 weeks of treatment) and prior relapsers (subjects who were HCV-RNA negative at the end of a minimum 12 weeks of treatment and subsequently relapsed after post-treatment follow-up). Subjects who were negative at Week 12 were treated for 48 weeks and followed for 24 weeks post-treatment. Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment (measured using a research-based test, limit of detection 125 IU/mL). The overall response rate was 22% (497/2293) (99% CI: 19.5, 23.9). Subjects with the following characteristics were less likely to benefit from re-treatment: previous nonresponse, previous pegylated interferon treatment, significant bridging fibrosis or cirrhosis, and genotype 1 infection.

The re-treatment sustained virologic response rates by baseline characteristics are summarized in Table 16.

Table 16: SVR Rates by Baseline Characteristics of Prior Treatment Failures - Study 5

HCV Genotype/Metavir Fibrosis Score	Overall SVR by Previous Response and Treatment			
	Nonresponder		Relapser	
	interferon alfa/ribavirin % (number of subjects)	peginterferon (2a and 2b combined)/ribavirin % (number of subjects)	interferon alfa/ribavirin % (number of subjects)	peginterferon (2a and 2b combined)/ribavirin % (number of subjects)
Overall	18 (158/903)	6 (30/476)	43 (130/300)	35 (113/344)
HCV 1	13 (98/761)	4 (19/431)	32 (67/208)	23 (56/243)
F2	18 (36/202)	6 (7/117)	42 (33/79)	32 (23/72)
F3	16 (38/233)	4 (4/112)	28 (16/58)	21 (14/67)
F4	7 (24/325)	4 (8/202)	26 (18/70)	18 (19/104)
HCV 2/3	49 (53/109)	36 (10/28)	67 (54/81)	57 (52/92)

F2	68 (23/34)	56 (5/9)	76 (19/25)	61 (11/18)
F3	39 (11/28)	38 (3/8)	67 (18/27)	62 (18/29)
F4	40 (19/47)	18 (2/11)	59 (17/29)	51 (23/45)
HCV 4	17 (5/29)	7 (1/15)	88 (7/8)	50 (4/8)

Achievement of an undetectable HCV-RNA at treatment Week 12 was a strong predictor of SVR. In this trial, 1,470 (64%) subjects did not achieve an undetectable HCV-RNA at treatment Week 12, and were offered enrollment into long-term treatment trials, due to an inadequate treatment response. Of the 823 (36%) subjects who were HCV-RNA undetectable at treatment Week 12, those infected with genotype 1 had an SVR of 48% (245/507), with a range of responses by fibrosis scores (F4-F2) of 39 to 55%. Subjects infected with genotype 2/3 who were HCV-RNA undetectable at treatment Week 12 had an overall SVR of 70% (196/281), with a range of responses by fibrosis scores (F4-F2) of 60 to 83%. For all genotypes, higher fibrosis scores were associated with a decreased likelihood of achieving SVR.

Pediatric Subjects

Previously untreated pediatric subjects 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were treated with ribavirin 15 mg/kg per day and PegIntron 60 mcg/m^2 once weekly for 24 or 48 weeks based on HCV genotype and baseline viral load. All subjects were to be followed for 24 weeks post-treatment. A total of 107 subjects received treatment, of which 52% were female, 89% were Caucasian, and 67% were infected with HCV Genotype 1. Subjects infected with Genotypes 1, 4 or Genotype 3 with HCV-RNA greater than or equal to 600,000 IU/mL received 48 weeks of therapy while those infected with Genotype 2 or Genotype 3 with HCV-RNA less than 600,000 IU/mL received 24 weeks of therapy. The trial results are summarized in Table 17.

Table 17: Sustained Virologic Response Rates by Genotype and Assigned Treatment Duration – Pediatric Trial

Genotype	All Subjects N=107	
	24 Weeks	48 Weeks
	Virologic Response N*,† (%)	Virologic Response N*,† (%)
All	26/27 (96.3)	44/80 (55.0)
1	-	38/72 (52.8)
2	14/15 (93.3)	-
3‡	12/12 (100)	2/3 (66.7)
4	-	4/5 (80.0)

* Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment.
† N=number of responders/number of subjects with given genotype and assigned treatment duration.
‡ Subjects with genotype 3 low viral load (less than 600,000 IU/mL) were to receive 24 weeks of treatment while those with genotype 3 and high viral load were to receive 48 weeks of treatment.

14.2 Ribavirin/INTRON A Combination Therapy

Adult Subjects

Previously Untreated Subjects

Adults with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) who were previously untreated with alpha interferon therapy were enrolled into two multicenter, double-blind trials (U.S. and international) and randomized to receive ribavirin capsules 1200 mg/day (1000 mg/day for subjects weighing less than or equal to 75 kg) and INTRON A 3 MIU three times weekly or INTRON A and placebo for 24 or 48 weeks followed by 24 weeks of off-therapy follow-up. The international trial did not contain a 24-week INTRON A and placebo treatment arm. The U.S. trial enrolled 912 subjects who, at baseline, were 67% male, 89% Caucasian with a mean Knodell HAI score (I+II+III) of 7.5, and 72% genotype 1. The international trial, conducted in Europe, Israel, Canada, and Australia, enrolled 799 subjects (65% male, 95% Caucasian, mean Knodell score 6.8, and 58% genotype 1).

Trial results are summarized in Table 18.

Table 18: Virologic and Histologic Responses: Previously Untreated Subjects*

	U.S. Trial				International Trial		
	24 weeks of treatment		48 weeks of treatment		24 weeks of treatment	48 weeks of treatment	
	INTRON A/Ribavirin (N=228)	INTRON A/Placebo (N=231)	INTRON A/Ribavirin (N=228)	INTRON A/Placebo (N=225)	INTRON A/Ribavirin (N=265)	INTRON A/Ribavirin (N=268)	INTRON A/Placebo (N=266)
Virologic Response							
Responder†	65 (29)	13 (6)	85 (37)	27 (12)	86 (32)	113 (42)	46 (17)
Nonresponder	147 (64)	194 (84)	110 (48)	168 (75)	158 (60)	120 (45)	196 (74)
Missing Data	16 (7)	24 (10)	33 (14)	30 (13)	21 (8)	35 (13)	24 (9)
Histologic Response							
Improvement‡	102 (45)	77 (33)	96 (42)	65 (29)	103 (39)	102 (38)	69 (26)
No improvement	77 (34)	99 (43)	61 (27)	93 (41)	85 (32)	58 (22)	111 (41)
Missing Data	49 (21)	55 (24)	71 (31)	67 (30)	77 (29)	108 (40)	86 (32)

* Number (%) of subjects.
†Defined as HCV-RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.
‡Defined as post-treatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of greater than or equal to 2 points.

Of subjects who had not achieved HCV-RNA below the limit of detection of the research-based assay by Week 24 of ribavirin/INTRON A treatment, less than 5% responded to an additional 24 weeks of combination treatment.

Among subjects with HCV Genotype 1 treated with ribavirin/INTRON A therapy who achieved HCV-RNA below the detection limit of the research-based assay by 24 weeks, those randomized to 48 weeks of treatment had higher virologic responses compared to those in the 24-week treatment group. There was no observed increase in response rates for subjects with HCV non-genotype 1 randomized to ribavirin/INTRON A therapy for 48 weeks compared to 24 weeks.

Relapse Subjects

Subjects with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) who had relapsed following one or two courses of interferon therapy (defined as abnormal serum ALT levels) were enrolled into two multicenter, double-blind trials (U.S. and international) and randomized to receive ribavirin 1200 mg/day (1000 mg/day for subjects weighing ≤75 kg) and INTRON A 3 MIU three times weekly or INTRON A and placebo for 24 weeks followed by 24 weeks of off-therapy follow-up. The U.S. trial enrolled 153 subjects who, at baseline, were 67% male, 92% Caucasian with a mean Knodell HAI score (I+II+III) of 6.8, and 58% genotype 1. The international trial, conducted in Europe, Israel, Canada, and Australia, enrolled 192 subjects (64% male, 95% Caucasian, mean Knodell score 6.6, and 56% genotype 1). Trial results are summarized in Table 19.

Table 19: Virologic and Histologic Responses: Relapse Subjects*

	U.S. Trial		International Trial	
	INTRON A/ Ribavirin (N=77)	**INTRON A/ Placebo** (N=76)	**INTRON A/ Ribavirin** (N=96)	**INTRON A/ Placebo** (N=96)
Virologic Response				
Responder†	33 (43)	3 (4)	46 (48)	5 (5)
Nonresponder	36 (47)	66 (87)	45 (47)	91 (95)
Missing Data	8 (10)	7 (9)	5 (5)	0 (0)
Histologic Response				
Improvement‡	38 (49)	27 (36)	49 (51)	30 (31)
No improvement	23 (30)	37 (49)	29 (30)	44 (46)
Missing Data	16 (21)	12 (16)	18 (19)	22 (23)

* Number (%) of subjects.
† Defined as HCV-RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.
‡Defined as post-treatment (end of follow-up) minus pretreatment liver biopsy Knodell HAI score (I+II+III) improvement of greater than or equal to 2 points.

Virologic and histologic responses were similar among male and female subjects in both the previously untreated and relapse trials.

Pediatric Subjects

Pediatric subjects 3 to 16 years of age with compensated chronic hepatitis C and detectable HCV-RNA (assessed by a central laboratory using a research-based RT-PCR assay) were treated with ribavirin 15 mg/kg per day and INTRON A 3 MIU/m^2 three times weekly for 48 weeks followed by 24 weeks of off-therapy follow-up. A total of 118 subjects received treatment, of which 57% were male, 80% Caucasian, and 78% genotype 1. Subjects less than 5 years of age received ribavirin oral solution and those 5 years of age or older received either ribavirin oral solution or capsules.

Trial results are summarized in Table 20.

Table 20: Virologic Response: Previously Untreated Pediatric Subjects*

	INTRON A 3 MIU/m^2 three times weekly/Ribavirin 15 mg/kg/day

Overall Response† (N=118)	54 (46)
Genotype 1 (N=92)	33 (36)
Genotype non-1 (N=26)	21 (81)

* Number (%) of subjects.
† Defined as HCV-RNA below limit of detection using a research-based RT-PCR assay at end of treatment and during follow-up period.

Subjects with viral genotype 1, regardless of viral load, had a lower response rate to INTRON A/ribavirin combination therapy compared to subjects with genotype non-1, 36% vs. 81%. Subjects with both poor prognostic factors (genotype 1 and high viral load) had a response rate of 26% (13/50).

16 HOW SUPPLIED/STORAGE AND HANDLING

Ribavirin Capsules USP, 200 mg are white/white, size '1' hard gelatin capsule filled with white to off-white granular powder and imprinted with 'E' on white cap and '81' on white body with black ink.

Bottles of 42	NDC 65862-290-42
Bottles of 56	NDC 65862-290-56
Bottles of 70	NDC 65862-290-70
Bottles of 84	NDC 65862-290-84
Bottles of 180	NDC 65862-290-18
Bottles of 500	NDC 65862-290-05

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Anemia

The most common adverse experience occurring with ribavirin capsules is anemia, which may be severe *[see Warnings and Precautions (5.2) and Adverse Reactions (6)]*. Advise patients that laboratory evaluations are required prior to starting therapy and periodically thereafter *[see Dosage and Administration (2.4)]*. Advise patients to be well hydrated, especially during the initial stages of treatment.

Embryo-Fetal Toxicity

Inform females of reproductive potential and pregnant women that ribavirin capsules may cause birth defects, miscarriage, and stillbirth. Advise females of reproductive potential that they must have a pregnancy test prior to initiating treatment and periodically during therapy. Advise females of reproductive potential and male patients with female partners of reproductive potential to use effective contraception during treatment with ribavirin and for 6 months post therapy. Advise patients to notify the physician immediately in the event of a pregnancy *[see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.3)]*.

Missed Dose

Inform patients that in the event a dose is missed, the missed dose should be taken as soon as possible during the same day. Patients should not double the next dose. Advise patients to contact their healthcare provider if they have questions.

Dental and Periodontal Disorders

Advise patients to brush their teeth thoroughly twice daily and have regular dental examinations. If vomiting occurs, advise patients to rinse out their mouth thoroughly afterwards *[see Warnings and Precautions (5.7)]*.

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Dispense with Medication Guide available at: www.aurobindousa.com/product-medication-guides

MEDICATION GUIDE

Ribavirin Capsules USP
(rye'' ba vye' rin)

What is the most important information I should know about ribavirin capsules?

1. **Ribavirin capsules may cause birth defects, miscarriage or death of your unborn baby. Do not take ribavirin capsules if you or your sexual partner is pregnant or plan to become pregnant. Do not become pregnant during treatment or within 6 months after stopping treatment with ribavirin capsules.** You must use effective birth control during treatment with ribavirin capsules and for 6 months after stopping treatment.
- Females must have a pregnancy test before starting ribavirin capsules, during treatment with ribavirin capsules, and for 6 months after the last dose of ribavirin capsules.
- **If you or your female sexual partner becomes pregnant during treatment with ribavirin capsules or within 6 months after you stop taking ribavirin capsules, tell your healthcare provider right away.**

2. **Ribavirin capsules may cause a significant drop in your red blood cell count and cause anemia in some cases. Anemia has been associated with worsening of heart problems, and in rare cases can cause a heart attack and death.** Tell your healthcare provider if you have ever had any heart problems. Ribavirin capsules may not be right for you. **Get medical help right away if you experience chest pain.**

3. **Do not take ribavirin capsules alone to treat chronic hepatitis C infection.** Ribavirin capsules should be used in combination with **either interferon alfa-2b or peginterferon alfa-2b** to treat chronic hepatitis C infection.

What are ribavirin capsules?

Ribavirin capsules are a medicine used with either interferon alfa-2b or peginterferon alfa-2b to treat chronic (lasting a long time) hepatitis C infection in people 3 years and older with liver disease.

It is not known if ribavirin capsules use for longer than 1 year is safe and will work.

It is not known if ribavirin capsules use in children younger than 3 years old is safe and will work.

Who should not take ribavirin capsules?

See "What is the most important information I should know about ribavirin capsules?"

Do not take ribavirin capsules if you have:

- ever had serious allergic reactions to the ingredients in ribavirin capsules. See the end of this Medication Guide for a complete list of ingredients.
- certain types of hepatitis (autoimmune hepatitis).
- certain blood disorders (hemoglobinopathies).
- severe kidney disease.
- taken or currently take didanosine.

Talk to your healthcare provider before taking ribavirin capsules if you have any of these conditions.

What should I tell my healthcare provider before taking ribavirin capsules?

Before you take ribavirin capsules, tell your healthcare provider if you have or ever had:

- treatment for hepatitis C that did not work for you
- breathing problems. Ribavirin capsules may cause or worsen breathing problems you already have.
- vision problems. Ribavirin capsules may cause eye problems or worsen eye problems you already have. You should have an eye exam before you start treatment with ribavirin capsules.
- certain blood disorders such as anemia (low red blood cell count)
- high blood pressure, heart problems, or have had a heart attack. Your healthcare provider should check your blood and heart before you start treatment with ribavirin capsules.
- thyroid problems
- liver problems other than hepatitis C infection
- human immunodeficiency virus (HIV) or any immunity problems
- mental health problems, including depression and thoughts of hurting yourself or others
- kidney problems
- an organ transplant
- diabetes. Ribavirin capsules may make your diabetes worse or harder to treat.
- any other medical condition
- are breastfeeding. It is not known if ribavirin passes into your breast milk. You and your healthcare provider should decide if you will take ribavirin capsules or breastfeed.

Tell your healthcare provider about all the medicines you take, including prescription medicines, vitamins, and herbal supplements. Ribavirin capsules may affect the way other medicines work.

Especially tell your healthcare provider if you take didanosine or a medicine that contains azathioprine.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take ribavirin capsules?

- Take ribavirin capsules exactly as your healthcare provider tells you. Your healthcare provider will tell you how much ribavirin capsules to take and when to take them.
- Take ribavirin capsules with food.
- Take ribavirin capsules whole. Do not open, break, or crush ribavirin capsules before swallowing. If you cannot swallow ribavirin capsules whole, tell your healthcare provider.

- If you miss a dose of ribavirin capsules, take the missed dose as soon as possible during the same day. Do not double the next dose. If you have questions about what to do, call your healthcare provider.
- If you take too much ribavirin, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of ribavirin capsules?

Ribavirin capsules may cause serious side effects, including:

See "What is the most important information I should know about ribavirin capsules?"

- **Swelling and irritation of your pancreas (pancreatitis).** Symptoms may include: stomach pain, nausea, vomiting, or diarrhea.
- **Serious breathing problems.** Difficulty breathing may be a sign of a serious lung infection (pneumonia) that can lead to death.
- **Serious eye problems** that may lead to vision loss or blindness.
- **Dental problems.** Brush your teeth well 2 times each day. Get regular dental exams. If you vomit at any time during treatment with ribavirin capsules, rinse out your mouth well.
- **Severe blood disorders.** You may have an increased risk of developing severe blood disorders when ribavirin capsules is used in combination with pegylated alpha interferons and azathioprine. Your healthcare provider should do blood tests during your treatment with ribavirin capsules in combination with pegylated alpha interferon and azathioprine to check you for these problems.

- **Growth problems in children.** Weight loss and slowed growth are common in children during combination treatment with ribavirin capsules and peginterferon alfa-2b or interferon alfa-2b. Most children will go through a growth spurt and gain weight after treatment stops. Some children may not reach the height that they were expected to have before treatment. Talk to your healthcare provider if you are concerned about your child's growth during treatment with ribavirin capsules and peginterferon alfa-2b or with ribavirin capsules and interferon alfa-2b.
- **Severe depression.**
- **Thoughts of hurting yourself or others, and suicide attempts.** Adults and children who take ribavirin capsules, especially teenagers, are more likely to have suicidal thoughts or attempt to hurt themselves while taking ribavirin capsules. Call your healthcare provider right away or go to the nearest hospital emergency room if you have new or worse depression or thoughts about hurting yourself or others or dying.

The most common side effects of ribavirin capsules in adults include:

- flu-like symptoms - feeling tired or weak, headache, shaking chills along with high temperature (fever), nausea, and muscle aches
- mood changes, feeling irritable

The most common side effects of ribavirin capsules in children include:

- fever
- headache
- a decrease in blood cells that fight infection (neutropenia)
- tiredness
- decreased appetite
- vomiting

These are not all the possible side effects of ribavirin capsules. For more information ask your healthcare provider or pharmacist.

Call your healthcare provider if you have any side effect that bothers you or that does not go away, and for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ribavirin capsules?

- Store **ribavirin capsules** between 15° to 30°C (59° to 86°F).

Keep ribavirin capsules and all medicines out of the reach of children.

General information about the safe and effective use of ribavirin capsules.

It is not known if treatment with ribavirin capsules will cure hepatitis C virus infections or prevent cirrhosis, liver failure, or liver cancer that can be caused by hepatitis C virus infections. It is not known if taking ribavirin capsules will prevent you from infecting another person with the hepatitis C virus.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ribavirin capsules for a condition for which it was not prescribed. Do not give ribavirin capsules to other people, even if they have the same symptoms that you have. They may harm them.

You can ask your pharmacist or healthcare provider for information about ribavirin capsules that is written for health professionals.

What are the ingredients in ribavirin capsules?

Active ingredient: ribavirin

Inactive ingredients: microcrystalline cellulose, lactose monohydrate, povidone-K 30, and magnesium stearate. The capsule shell consists of titanium dioxide, sodium lauryl sulfate, and gelatin. The capsule is printed with edible ink containing black iron oxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

For more information, call Aurobindo Pharma USA, Inc. at 1-866-850-2876.

Dispense with Medication Guide available at: www.aurobindousa.com/product-medication-guides

Distributed by:
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Manufactured by:
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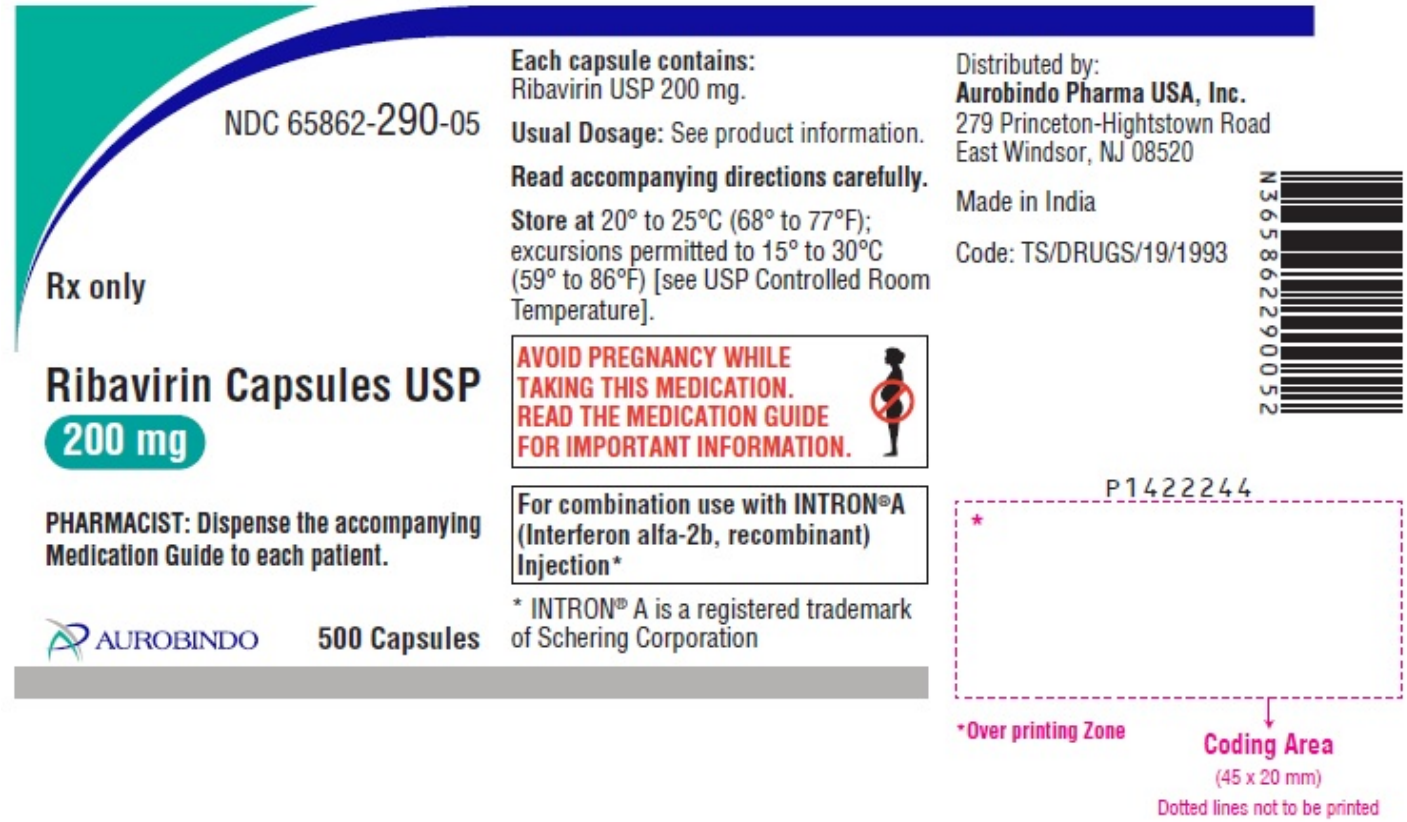
Hyderabad-500 038, India

Revised: 02/2020

PACKAGE LABEL-PRINCIPAL DISPLAY PANEL - 200 mg (500 Capsules Bottle)

NDC 65862-290-05

Rx only
Ribavirin Capsules USP
200 mg
PHARMACIST: Dispense the accompanying
Medication Guide to each patient.
AUROBINDO 500 Capsules



RIBAVIRIN

ribavirin capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:65862-290
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
RIBAVIRIN (UNII: 49717AWG6K) (RIBAVIRIN - UNII:49717AWG6K)	RIBAVIRIN	200 mg

Inactive Ingredients	
Ingredient Name	**Strength**
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
POVIDONE K30 (UNII: U725QWY32X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
GELATIN, UNSPECIFIED (UNII: 2G86QN327L)	
FERROSOFERRIC OXIDE (UNII: XM0M87F357)	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	CAPSULE	**Size**	19mm
Flavor		**Imprint Code**	E;81
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:65862-290-42	42 in 1 BOTTLE; Type 0: Not a Combination Product	09/17/2009	
2	NDC:65862-290-56	56 in 1 BOTTLE; Type 0: Not a Combination Product	09/17/2009	
3	NDC:65862-290-70	70 in 1 BOTTLE; Type 0: Not a Combination Product	09/17/2009	
4	NDC:65862-290-84	84 in 1 BOTTLE; Type 0: Not a Combination Product	09/17/2009	
5	NDC:65862-290-18	180 in 1 BOTTLE; Type 0: Not a Combination Product	09/17/2009	
6	NDC:65862-290-05	500 in 1 BOTTLE; Type 0: Not a Combination Product	09/17/2009	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA079117	09/17/2009	

Labeler - Aurobindo Pharma Limited (650082092)

Establishment

Name	Address	ID/FEI	Business Operations
Aurobindo Pharma Limited		918917642	ANALYSIS(65862-290) , MANUFACTURE(65862-290)

Revised: 2/2020 Aurobindo Pharma Limited

STUDY PROTOCOL

The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)

Study No: CCB-CRISIS-01

Version Date: 01 May 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

TABLE OF CONTENTS

LIST OF FIGURES

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
EHR	Electronic health record
ESR	Erythrocyte Sedimentation Rate
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
US	United States
XMP	Xanthosine-5’ phosphate
WHO	World Health Organization

Abbreviation	Definition
WOCBP	Women of childbearing potential

2 SYNOPSIS

CCB-CRISIS-01 SYNOPSIS	
IND	149291
Title	The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)
Protocol	CCB-CRISIS-01
Investigational Product and Dosage	Subjects will be randomized in a 1:2 ratio to either standard of care (SOC) alone, or SOC + brequinar. Brequinar is available as 100 mg oral capsules. Five once daily doses of brequinar 100 mg are to be administered on Study Days 1 – 5 for those assigned to the SOC + brequinar group. Treatment assignment will be randomized, open label.
Primary Objective	● To determine the safety and tolerability of SOC and SOC plus brequinar in hospitalized COVID-19 subjects.
Secondary Objectives	● To determine the rates of/changes in clinical status measures listed through Day 15: – Hospitalization status – Duration of hospitalization – NEWS2 Score ● Mortality through Day 29
Exploratory Objectives	• To determine the change in SARS-CoV-2 nasopharyngeal viral load through Day 15 ● To determine the change in inflammatory markers through Day 15 ● To determine the change in DHO levels through Day 15 ● To determine the change in brequinar concentration levels through Day 7
Design	This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive SOC per institutional guidelines for treatment of patients with COVID-19 infection. In addition to SOC, the brequinar group will receive brequinar 100 mg once daily for 5 days. Subjects will have a Screening Visit followed as soon as possible with Study Day 1 (Day 1 may take place on the same day if entry criteria data are available). Study

	procedures are presented in detail in the procedures section, see below. Subjects will be followed through Day 15. Mortality will be assessed at Day 29. See below for instructions regarding hospital discharge prior to Day 15. Hematology and chemistry results and study information such as NEWS2 criteria are to be collected using the available EHR data as much as possible to avoid extra procedures for the study.
Sample Size:	Approximately 24 subjects will be randomized to either standard of care or standard of care plus brequinar in a 1:2 ratio (approximately 8 assigned to standard of care and 16 subjects on brequinar).
Number of Sites:	1 - 8
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 and at least one of the following co-morbidities by subject history or present in the institution's electronic health record: hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease (COPD) or asthma, cardiovascular disease (coronary artery disease or congestive heart failure), liver cirrhosis, age > 65, BMI > 30. 3. If discharged from the hospital prior to Study Day 15 or if follow up is needed for study drug-related adverse event, willing to go to an outpatient laboratory for a laboratory sample as well as a contact (phone call or other digital media) on Study Days 7 and 15 and contact only on Day 29. 4. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay. 5. Life expectancy > 48h in the opinion of the investigator. 6. Hospitalized (in patient with expected duration ≥ 24 hours) 7. 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 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.

	8. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of brequinar. 9. ≤ 10 days since first COVID-19 symptom as determined by treating clinician. 10. Platelets ≥100,000 cell/mm^3
Exclusion Criteria:	1. In intensive care unit (ICU) or equivalent level of care or expected to require ICU level of care within next 24 hours. 2. 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 3. Active malignancy other than squamous cell carcinoma; anticancer treatment such as chemotherapy or radiation therapy within the past month. 4. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test. 5. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide), tacrolimus, sirolimus, or pre-existing prednisone at higher than 20 mg daily (ongoing or within 2 weeks of study entry).
Treatment	All subjects will receive standard of care (SOC) per institutional guidelines. Subjects will be randomly assigned to SOC alone or SOC plus brequinar 100 mg daily x 5 days.
Procedures	**Screening Visit (Since hospital admission)** Results of these procedures must be available in the EHR and completed since hospital admission. Obtain the subject's written informed consent (be sure to note time of consent), then collect baseline information. Collect information from EHR. Do not perform study-specific procedures for data available from EHR. • Demographics (height, weight, date of birth, gender, race, ethnicity). • Recent (within one year unless ongoing), relevant medical/surgical history and concomitant medications. • Date of first symptom. • Record any clinically significant abnormal physical examination findings. • Ensure EHR has negative pregnancy test result for women of childbearing potential (WOCBP). • Record any adverse events that occurred since signing the ICF. • Record any new or changed concomitant medications since signing the ICF. • Hematology/chemistry from EHR for Inclusion/Exclusion criteria check.

	• Polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay for SARS-CoV-2 infection (may utilize test results from external laboratory to meet entry criteria provided such results are accurately documented and can be confirmed). • Confirm subject meets all inclusion and no exclusion criteria. **Treatment** The treatment period is up to 5 days: standard of care alone (SOC) or SOC + brequinar 100 mg daily x 5 days. Data points such as NEWS2 Assessments and safety labs are to be collected from the EHR, a separate visit by study staff is not to be performed. Give the first dose of brequinar as soon as possible after randomization. See below regarding hospital discharge prior to Day 15. **Days 1 – 7 (8 AM ± 8 hours):** • If Day 1 is different date from Screening, confirm subject continues to meet all inclusion and no exclusion criteria. • Randomize subject and record the time and date of randomization. • Review Progress Notes and medication records to collect any new or ongoing adverse events or new or changed concomitant medications since previous visit (may be omitted on Day 1 if Screening visit is conducted on same day as Study Day 1). Repeat on Day 7. • Collect SOC hematology/chemistry results from EHR on Day 1 (pre-dose) and Day 7 (may be omitted for Day 1 if Screening visit conducted on same date as Study Day 1). Ensure that Day 1 samples are obtained prior to first dose of study drug, if applicable. • Days 1 (pre-dose), 3, 5, 7: – Collect NEWS2 Assessments from EHR. – Collect results for inflammatory markers from EHR for those analyzed locally; collect, process and ship samples for DHO/brequinar PK and cytokine panel to be analyzed at the central laboratory per the Laboratory Manual. – Collect, process, and ship nasopharyngeal viral load samples. – Record hospitalization status (hospitalized, hospitalized in ICU, discharged); subject must be hospitalized Day 1 to meet inclusion criteria, do not record again. • Dispense study medication (Days 1 through 5 if in brequinar group). Keep the brequinar study drug administration interval to 24h as much as possible. Record date and time of study drug administration. • Drug accountability Day 7 ± 2 days. Note: If discharge occurs prior to Day 5 for subjects in the brequinar group, the subject will take one final dose on the day of discharge.

	Final Visit Day 15 (8 AM ± 2 days) • Review Progress Notes and medication records to collect information for any new adverse events or changes in ongoing adverse events or new or changed concomitant medications since Day 7 (collect from EHR if subject still hospitalized, otherwise by phone or other digital media). • Collect SOC hematology/chemistry results from EHR if subject still hospitalized. • Collect results for inflammatory markers from EHR for those analyzed locally; collect and process samples for DHO and cytokine panel to be analyzed at the central laboratory on. • Collect and process nasopharyngeal viral load samples. • Record hospitalization status (hospitalized, hospitalized in ICU, discharged). • Collect NEWS2 Assessments from EHR. • If the subject is being discharged prior to Day 15, follow procedures below. **Day 29 (8 AM ± 3 Days)** • Determine survival status from EHR if available or by telephone/digital media per institutional guidelines. <u>Hospital Discharge Before Day 15 (Brequinar Treatment Group Only)</u> For subjects in the brequinar treatment group, if the subject is discharged from the hospital prior to Day 5 the subject is to take a final dose on the day of discharge. If the subject is discharged from the hospital on Days 2 or 4 or 6, ensure hematology and chemistry sample has been obtained prior to discharge and collect these results on the appropriate EDC page. Following discharge, the subject is to return to the research facility for the Days 7 and 15 visits if able and permitted. If discharge occurs on Days 10, 11, or 12, ensure a hematology/chemistry sample has been obtained prior to discharge and record these results on the appropriate EDC page. Following discharge, the subject is to return to the research facility for the Day 15 visit if able and permitted. If discharge occurs on Days 13, 14 or 15, complete the Day 15 Final Visit activities. No further visits are required unless follow up is needed for a study drug-related AE or an SAE; the Day 29 mortality assessment is still to take place. If the subject is unable or not permitted to return for planned study visits, the visit activities will be conducted by contacting the subject (phone or other digital media) except for the lab draw. The hematology/chemistry sample will be obtained via outpatient laboratory. Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF. A subject is considered completed the study if

	they have assessments through Day 15, whether conducted in the hospital or contacted via phone or other digital media.
Safety/ Tolerability	**Safety/Tolerability** Adverse events will be collected from the time of informed consent through Day 15. After Day 15, collect/record only Serious Adverse Events (SAEs) or those judged by the Investigator or designated person to be related to study drug, including but not limited to potential hematologic toxicities. Post-randomization adverse events will be those with an onset after the date and time of randomization.
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, safety laboratory data, and NEWS2 Assessments. Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of post randomization adverse events, defined as AEs 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, NEWS2 Criteria, and other clinical measures will be summarized using appropriate descriptive statistics.

STUDY PERSONNEL

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3 INTRODUCTION

3.1 Background

3.2 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]).

3.2.1 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]).

3.3 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.

3.4 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.

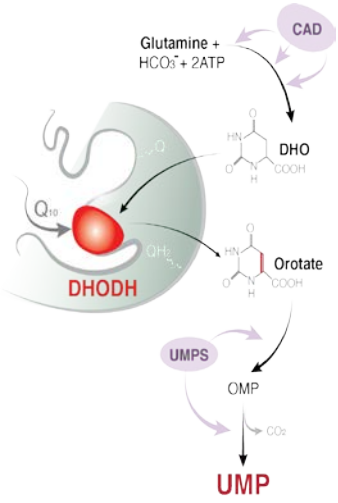

Figure 3-1. DHODH is a mitochondrial enzyme that catalyzes the 4th step of pyrimidine synthesis; it is completely essential for the generation of UMP.

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]).

3.5 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]).

3.6 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 CRISIS trial will study standard of care (SOC) and SOC with 5 days of DHODH inhibition. 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.

3.6.1 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 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 reassuring the safety of this regimen (see Brequinar IB [5]).

3.6.2 Risk/Benefit of Brequinar

As presented in the Brequinar IB [5], an extensive database exists with more than 800 cancer patients 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. Brequinar has also been utilized at lower doses than used in the cancer studies in 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. While no DHODHi has been tested to date in the clinic for infection with SARS-CoV-2 and no brequinar safety information is available in treatment of this disease, DHODHi therapy in the context of trials for patients with cancer has the expected safety side-effects of mucositis and bone marrow suppression. 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 mucositis and only 1 (2.6%) episode of mild thrombocytopenia. The 100 mg per day dose proposed for administration in this study should be safe and well tolerated.

The possible 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. As discussed above, inhibition of DHODH is expected to reduce the ability of the virus to replicate and it is for this reason that study CCB-CRISIS-01 will administer brequinar to patients with COVID-19.

3.7 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration of 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.

COVID-19 patients are at higher risk of complications and poor outcomes when their infection is combined with comorbidities including hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease (COPD) or asthma, cardiovascular disease (coronary artery disease or congestive heart failure), liver cirrhosis, age > 65, and BMI > 30 [15]. Therefore, participants in this protocol must have at least one of these comorbidities in order to justify that the risks of potential and known toxicities associated with brequinar are outweighed by the potential benefits in this higher risk population.

In addition to ensuring a higher risk population, a comprehensive safety monitoring plan will be utilized in this study to assess the ongoing safety and well-being of participants (see Section 10.6).

3.8 Possible Interactions with Concomitant Medical Treatments

While not previously tested in patients with viral infections, brequinar has been administered to subjects taking a variety of concomitant medications that are typical in severely ill cancer patients. 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. Brequinar has also been used concomitantly with antibiotics, antifungals and other critical care medications.

There is no experience with brequinar for treatment of SARS-CoV-2 and other severe viral infections and no formal interaction studies have been conducted.

3.8.1 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).

3.9 Steps to be Taken to Control or Mitigate Risks

All subjects will be treated in a hospital setting by highly experienced infectious disease or other critical care specialists and other qualified staff familiar with the treatment of severe viral infections and their complications.

Subjects in the Brequinar Treatment Group

If the subject is in the brequinar treatment group and is being discharged prior to completing the study, ensure a hematology/chemistry sample is obtained prior to discharge on the day of discharge. The subject is to return to the research facility for the Days 7 and 15 visits if able and permitted. If unable or not permitted to return to the research facility due to COVID-19 restrictions,

the remaining visit activities except for the lab draw will be conducted by phone or other digital media. The lab draw will be performed by an outpatient laboratory at a designated facility. Lab draws for any outpatient visits for the Day 7 and 15 visits are limited to safety labs (hematology and chemistry). Additional outpatient laboratory or study visits are to be conducted as needed for follow up of adverse events including hematologic toxicities.

4 TRIAL OBJECTIVES

4.1 Primary Objective

- To determine the safety and tolerability of standard of care (SOC and SOC plus brequinar in hospitalized COVID-19 subjects.

4.2 Secondary Objectives

The secondary objectives of this study are:

- To determine the changes in clinical status measures listed through Day 15:
  - Hospitalization status
  - Duration of hospitalization
  - National Early Warning System 2 Score (NEWS2) Score
- To determine survival status through Day 29

4.3 EXPLORATORY OBJECTIVES

- To determine the change in SARS-CoV-2 nasopharyngeal viral load through Day 15
- To determine the change in inflammatory markers through Day 15
- To determine the change in dihydroorotate dehydrogenase (DHO) through Day 15
- To determine the change in brequinar concentration levels through Day 7

5 TRIAL DESIGN

This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive standard of care per institutional guidelines for treatment of patients with SARS-CoV-2 infection. In addition to standard of care, the brequinar group will receive brequinar 100 mg once daily for 5 days.

The Massachusetts General Hospital (MGH) COVID-19 Treatment Guidance is provided in Appendix D Section 15.4. This guidance provides an example of standard of care instructions for treatment of COVID-19. The guidance is provided as informational only, it is not required that this guidance be used for treatment as standards of care may differ between institutions.

Subjects will have a Screening Visit followed as soon as possible with Study Day 1 (Day 1 may take place on the same day if entry criteria data are available). Study procedures are presented in detail in Section 8. Subjects will be followed through Day 15, with mortality assessed via a phone call/other digital media acceptable to institution on Day 29.

If the subject is being discharged prior to Day 7, see Section 8.4.

It is understood that some assessments may not be conducted if the subject is unable to return to the clinic after discharge due to restricted travel. If an assessment is missed due to after hospital discharge, e.g., samples or blood draws, this will not be counted as a protocol deviation. Any of the study visits may be conducted via telephone if the subject has been discharged from the hospital and is not permitted to or is unable to return to the hospital/clinic for these visits.

Information is to be collected using the electronic health record (EHR) whenever possible. It is not required to perform study-specific laboratory assessments, NEWS 2 assessments, etc. separately for study purposes.

6 TRIAL ENDPOINTS

6.1 Primary Endpoint

- Safety/tolerability measured by rates of post randomization adverse events and hematology/chemistry safety labs.

6.2 Secondary Endpoints

- Rates of/changes to the below clinical status measures through Day 15.
  - Hospitalization status
  - Duration of hospitalization in days
  - NEWS2 Assessments Days 1, 3, 5, 7, and Day 15 for hospitalized subjects.
- Mortality through Day 29

6.3 EXPLORATORY Endpoints

- SARS-CoV-2 nasopharyngeal viral load: Day 1 (pre-dose), Days 3, 5, 7, and 15
- Inflammatory markers (to be specified in the Laboratory Manual, may include but are not limited to erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), D-dimer, serum ferritin, and fibrinogen, procalcitonin, IL-6, IL-5, IL-2, IFN-ɣ, final list to be determined) on Day 1 pre-dose, D3, D5, D7, D15 or at frequency per institutional standard of care. The markers are to be tested locally when possible; requested tests as listed in the Laboratory Manual that are not analyzed locally are to be shipped to the central laboratory for analysis.
- DHO concentration levels through Day 15.
- Brequinar concentration levels through Day 7

7 TRIAL POPULATION

7.1 Number of Subjects

Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 24 subjects have completed the study. Subjects will be randomized to either standard of care or standard of care plus brequinar or in a 1:2: ratio (approximately 8 subjects assigned to standard of care alone and approximately 16 subjects on standard of care plus brequinar).

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 and at least one of the following co-morbidities by subject history or present in the institution's electronic health record: hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease (COPD) or asthma, cardiovascular disease (coronary artery disease or congestive heart failure), liver cirrhosis, age > 65, BMI > 30.
3. If discharged from the hospital prior to Study Day 15 or if follow up is needed for study drug-related adverse event, willing to go to an outpatient laboratory to obtain a laboratory sample as well as a contact (phone call or other digital media) on Study Days 7 and 15 and contact only on Day 29.
4. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other Food and Drug Administration (FDA)-cleared commercial or public health assay.
5. Life expectancy > 48h in the opinion of the investigator.
6. Hospitalized (in patient with expected duration ≥ 24 hours)
7. 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 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.
8. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of brequinar.
9. ≤ 10 days since first COVID-19 symptom as determined by treating clinician.
10. Platelets ≥100,000 cell/mm^3.

7.3 Exclusion Criteria

1. In intensive care unit (ICU) or equivalent level of care or expected to require ICU level of care within next 24 hours.

2. 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.
3. Active malignancy other than squamous cell carcinoma; anticancer treatment such as chemotherapy or radiation therapy within the past month.
4. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test.
5. Treatment with another DHODH inhibitor (e.g., leflunomide or teriflunomide), tacrolimus, sirolimus, or pre-existing prednisone at higher than 20 mg daily (ongoing or within 2 weeks of study entry).

7.4 Inclusion of Women and Minorities

Adult men and women of all races and ethnic groups are eligible for this trial.

8 STUDY TREATMENTS

8.1 Description of Study Medications

8.1.1 Brequinar

Brequinar will be supplied as 100 mg capsules. Dosing will be a single 5-day course of brequinar 100 mg once daily for 5 doses. The initial brequinar dose (Day 1) should be administered as soon as possible based on study drug availability from the investigational pharmacy.

8.2 Treatment Administration

This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive standard of care (SOC) per institutional guidelines for SARS-CoV-2 infection. Subjects will be randomly assigned in a 1:2 ratio to standard of care alone or standard of care plus brequinar.

8.2.1 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE).

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 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 (Study 785-001 [16], 785-003 [17], and 785-005 [18]) with five consecutive days of intravenous (IV) brequinar dosing and 168 subjects, there were no toxic deaths. For subjects from these three studies who were treated with a dose of 100 mg or below (as will be dosed in CCB-CRISIS-01), 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 [19], 785-031 [20] , and 785-034 [21]), 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 15 (or longer if needed to follow up study drug-related adverse events). Mortality is assessed via a phone call or other digital media at Day 29.

After treatment, participants will be monitored through at least Study Day 15 (or longer if needed to follow study drug-related AEs/SAEs). Participants may discontinue from the study by withdrawing consent at any time or for any reason as presented in Section 9.7.

8.4 Hospital Discharge Prior to Study Day 15

For subjects in the brequinar treatment group, if the subject is discharged from the hospital prior to Day 5 the subject is to take a final dose on the day of discharge.

If the subject is discharged from the hospital on Days 2 or 4 or 6, ensure hematology/chemistry sample has been obtained prior to discharge and collect these results on the appropriate EDC page. Following discharge, the subject is to return to the research facility for the Days 7 and 15 visits if able and permitted.

If discharge occurs on Days 10, 11, or 12, ensure a hematology/chemistry sample has been obtained prior to discharge and record these results on the appropriate EDC page. Following discharge, the subject is to return to the research facility for the Day 15 visit if able and permitted.

If discharge occurs on Days 13, 14 or 15, complete the Day 15 Final Visit activities. No further visits are required unless follow up is needed for a study drug-related AE or an SAE; the Day 29 mortality assessment is still to take place.

If the subject is unable or not permitted to return for planned study visits, the visit activities will be conducted by contacting the subject (phone or other digital media) except for the lab draw. The lab draw will be completed at an outpatient laboratory.

Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF. A subject is considered completed the study if they have assessments through Day 15, whether conducted in the hospital or contacted via phone or other digital media.

8.5 Concomitant Medication/Treatment

Record the name, 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. The use of other DHODH inhibitors is not permitted during the study including leflunomide or teriflunomide (see Section 8.8).

8.6 Treatment Compliance

Compliance will be assessed by reviewing the subject's EHR and other 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

Each brequinar bottle/dispensing container for subject use will be labeled with at least the following information:

For Clinical Trial Use Only
Study Number: CCB-CRISIS-01
Contents: Brequinar 100 mg capsules
For oral use only. Take with approximately 8 ounces water.
Subject Number: XX-XXXX
Treatment Duration: As directed
Clinical Batch Number: XXXXXXX
Expiration Date: TBD
Storage: Store at controlled room temperature
Study Sponsor: Clear Creek Bio, Inc., 585 Massachusetts Avenue, 4th Floor, Cambridge MA 02139
Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

8.7.3 Blinding and Randomization

The trial will be conducted in an open-label manner with random assignment to standard of care or standard of care plus brequinar. The brequinar capsules will be provided to each participating institution in bulk to be dispensed by the institution's pharmacist for each subject. Randomization assignments will be provided by the sponsor.

8.7.4 Unblinding/Expectedness

It is not necessary to break the blind for this open label study as the treatment will be known for each subject.

Expectedness will be determined by establishing whether the 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, used and discarded. It must be clear from the records whether the subject received study medication or was assigned to standard of care. 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.

8.8 Prohibited Medications

Treatment is prohibited with another DHODH inhibitor (e.g., leflunomide and teriflunomide), tacrolimus, sirolimus, or pre-existing prednisone at higher than 20 mg daily (ongoing or within 2 weeks of study entry).

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 telephone or other digital media. Study information is to be collected from the EHR as much as possible such as NEWS2 Assessments, height, weight, hematology/chemistry, from Progress Notes for AEs, and from medication records for new or changed concomitant medications. Visits to an outpatient laboratory post hospital discharge may be required if subjects are not able or permitted to return for follow up study visits.

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), 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.

Signed written informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to signing the informed consent but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. An original signed informed consent form will be subject to review by the Sponsor; a copy will be given to the subject and a copy will be filed with the subject's medical notes.

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.

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

NEWS2 Assessments, laboratory assessments, SARS-CoV-2 testing, and other observations will be conducted by experienced personnel throughout the study based on the Schedule of Events. The majority of study information is to be collected from the EHR. Phone calls or other digital media and outpatient visits for hematology/chemistry samples may be required to complete some study assessments if the subject is discharged prior to Study Day 15.

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 (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST), bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium), lactate dehydrogenase (LDH).

Inflammatory markers including D-dimer, ferritin, CRP, ESR, troponin, fibrinogen, and procalcitonin may be collected locally if available by the Institution. Additional inflammatory markers will be collected and analyzed by a central laboratory, as specified in the Laboratory Manual. A sample is to be collected for DHO and brequinar pharmacokinetics at the timepoints specified in the Laboratory Manual.

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

Nasopharyngeal swabs for SARS-CoV-2 viral load, inflammatory markers, and DHO samples will be collected Days 1, 3, 5, 7, and 15 (collection instructions available in the supplied Laboratory Manual).

NEWS2 Criteria are available in Appendix C Section 15.3.

Hospitalization status is to be recorded as hospitalized not in ICU, hospitalized in ICU, or discharged.

9.5 Study Conduct

Screening Visit (Since hospital admission)

These procedures must be completed since hospital admission and prior to starting dosing. Obtain the subject's written informed consent (be sure to note time of consent), then collect baseline information from the EHR. Do not perform study specific procedures for data available from the EHR. For Screening/Day 1 use the EHR results closest to the visit to confirm subject eligibility.

- Demographics (date of birth, gender, race, ethnicity, height and weight).
- Recent (within one year unless ongoing), relevant medical/surgical history and concomitant medications.
- Date of first symptom.
- Record any new or changed adverse events and new or changed concomitant medications since signing the ICF.
- Record any clinically significant abnormal physical examination findings as recorded in EHR.
- Hematology/chemistry from EHR.
- Ensure negative pregnancy test result is present in the EHR for women of childbearing potential (WOCBP).

- Polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay for SARS-CoV-2 infection (may utilize test results from external laboratory to meet entry criteria provided such results are accurately documented and can be confirmed).
- Confirm subject meets all inclusion and no exclusion criteria.

Treatment

The treatment period is up to 5 days: standard of care alone (SOC) or SOC + brequinar 100 mg daily for 5 days. Data points such as NEWS2 Assessments are to be collected from the EHR when possible, a separate visit by study staff is not to be conducted. The first dose of brequinar is to be given as soon as possible depending on availability of investigational pharmacy staff. If the subject is discharged from the hospital prior to Day 15, see Section 8.4 for how and when to conduct study assessments.

It is understood that some assessments may not be conducted if the subject is unable to return to the clinic after discharge due to restricted travel or if the study visit cannot be conducted remotely; this will not be counted as a protocol deviation. Collect information from the EHR, medication records and Progress Notes whenever possible

Days 1 - 7 (8 AM ± 8 hours)

- If Day 1 is different date from Screening, confirm subject continues to meet all inclusion and no exclusion criteria.
- Randomize the subject (record date and time of randomization).
- Review Progress Notes and medication records to collect any new or changes to ongoing adverse events or new or changed concomitant medications since previous visit (may be omitted on Day 1 if Screening visit was conducted on same day as Study Day 1). Repeat on Day 7.
- Collect SOC hematology/chemistry results from the EHR on Day 1 (pre-dose) and Day 7 (may be omitted for Day 1 if Screening visit conducted on same date as Study Day 1). Ensure that Day 1 samples are obtained prior to first dose of study drug, if applicable.
- Days 1 (pre-dose), 3, 5, 7:
  - Collect NEWS2 Assessments from the EHR.
  - Collect results for inflammatory markers from EHR for those analyzed locally; collect, process and ship samples for DHO/brequinar PK and cytokine panel to be analyzed at the central laboratory per the Laboratory Manual.
  - Collect and process SARS-CoV-2 nasopharyngeal viral load samples.
  - Record hospitalization status (hospitalized, hospitalized in ICU, discharged) (Day 1 already recorded as part of Inclusion criteria, do not record again).
- Dispense study medication (Days 1 through 5 if in brequinar group) and record date and time of brequinar administration. Keep the drug administration interval as close as possible to 24h. Ensure Day 1 labs are drawn prior to first brequinar dose on Day 1. If a subject taking brequinar is discharged prior to Day 5, administer final dose on day of discharge. Do not give subject study drug to take home.

- Drug accountability Day 7 ± 2 days.

Final Visit Day 15 (8 AM ± 2 days) or Hospital Discharge Day if earlier than Day 15

- Review Progress Notes and the medication record to collect information for any adverse events or new concomitant medications since Day 7 (from EHR if subject still hospitalized, otherwise by phone or other digital media).
- Collect results for SOC hematology/chemistry from the EHR if subject still hospitalized.
- Collect inflammatory markers from EHR for those analyzed locally; collect samples for DHO and cytokine panel to be analyzed at the central laboratory if subject still hospitalized.
- Collect NEWS2 Assessments from the EHR.
- Collect nasopharyngeal viral load sample.
- Collect hospital status (hospitalized, hospitalized in ICU, discharged).

Day 29 (8 AM ± 3 days)

- Determine survival status from EHR if available or contact the subject by phone call/digital media as acceptable to the institution.

If the subject is being discharged before Day 15, follow the procedures outlined in Section 8.4.

9.5.1 Unscheduled Visits

Unscheduled visits and tests to assess AEs/SAEs are permitted as needed providing the AE related to study drug or SAE onset occurs within two (2) weeks after the final study dose.

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. Provided that activities are carried out within the identified windows it will not be necessary to file a protocol deviation. It is understood that some scheduled study assessments may not be able to be conducted if the subject is unable to return to the clinic after discharge due to COVID-19 restricted travel; it is also understood that crowded hospital conditions/lack of personnel may make it impossible to carry out all requested study procedures; this will not be counted as a protocol deviation. The Day 7 and 15 visits are to be conducted via telephone if the subject has been discharged from the hospital with lab draws for subjects in the brequinar treatment group as described in Section 8.4.

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 be withdrawn from the study 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 evaluations for subjects who withdraw from the study 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).

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 15. After Day 15, collect/record only Serious Adverse Events (SAEs) or those judged 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.

Any serious adverse events (SAEs) experienced after 30 days post the last dose of study drug should only be reported to the sponsor if the investigator suspects a causal relationship to the 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, or require therapy.

Death due to disease progression should not be reported as an SAE. Report death from disease progression on the appropriate electronic data capture form.

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 progression of the disease under study.

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 descriptions and grading scales found in the revised National Cancer Institute (NCI) Common Terminology *Criteria for Adverse Events (CTCAE) version 4.03* will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html)*.

10.1 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.

10.2 Classification of Severity

The descriptions and grading scales found in the revised NCI CTCAE version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria. The CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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.

10.3 Serious Adverse Event (SAE) Reporting

The regulatory definition of an SAE is any untoward medical occurrence or effect that at any dose:

- 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, or
- is a congenital anomaly / birth defect;
- all other events that are 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 the studied indication, 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;
- Note that 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 is not an SAE.

Death due to disease progression is considered to be an Expected event in patients with severe SARS-CoV-2 infection and does not require reporting on an expedited basis.

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 the Sponsor contact until the event has subsided or, in case of permanent impairment, it stabilizes, and the overall clinical outcome has been ascertained.

SAE REPORTING EMAIL: Safety-CCB-CRISIS-01@prosoftclinical.com

Medical Monitor:

Sharon Levy, MD	Telephone:	O: (484) 320-2062

Sponsor Representative:

Barbara Powers, MSN, Ph.D.	Telephone:	M: 484-686-0545
	Email:	bpowers@clearcreekbio.com

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

10.4 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 Medical Monitor 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 is to 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 the Medical Monitor/Sponsor. Follow-up information is to be subsequently communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs are to 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 knowledge by the Medical Monitor/Sponsor.

The Medical Monitor/Sponsor or designee must 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.

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

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as 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-up with 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.

10.6 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 initially be hospitalized as in-patients and will be under the care of highly qualified infectious disease, critical care, and associated medical personnel. As is standard of care for moderately to severely ill in-patients, daily samples will be obtained for hematology assessments including complete blood count with full differential (WBC, RBC, hemoglobin, hematocrit, platelet count, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils). Any clinically significant out-of-range laboratory values will be assessed by hospital staff in a timely manner and treatment needs addressed as appropriate. 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 Clear Creek Medical Monitor will assess the available hematology data on a weekly 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, the Sponsor, and the Medical Monitor. In addition, the Data Safety Monitoring Board 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.

Subjects who are discharged from the hospital before Day 7 will have follow up contacts with study staff (phone calls or other digital media) on Days 7, 15 and 29. Early discharge subjects in the brequinar treatment group will also have samples for safety labs (hematology and chemistry) obtained either at the research facility or at an outpatient laboratory on Study Days 7 ± 2 and 15 ± 2. The safety laboratory results are to be initially assessed in real time by the Principal Investigator or designated person and the Medical Monitor. 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-hospital assessments and phone call visits will specifically ask about possible hematologic toxicity including any evidence of the list below. Early discharge 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.

10.7 Data Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be established to provide independent oversight to this trial. The primary responsibility of the DSMB 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 DSMB will be detailed in a separate DSMB charter. The DSMB 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 DSMB Chair will advise the Sponsor that the study be stopped, the design changed, or that the study may continue per protocol.

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 analyses will be based on the ITT population, which is defined as all randomized subjects.

11.2 Safety Analyses

Safety and tolerability will be assessed in terms of AEs, SAEs, NEWS2 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 NEWS2 Assessments will be summarized using appropriate descriptive statistics.

11.3 Efficacy Analyses

Efficacy will be assessed in terms of mortality, hospitalization status and duration, NEWS2 score, viral load (plasma and nasopharyngeal), and inflammatory markers.

11.4 DHO and Brequinar Concentration Levels

DHO and brequinar concentrations levels will be summarized using descriptive statistics.

11.5 Sample Size Considerations

Formal sample size calculations are not applicable for this phase 1a, open label study. Up to 24 subjects are planned to be entered in this trial. Additional subjects may be enrolled following data review.

11.6 Randomization

A randomization scheme will be provided by the Sponsor to ensure subjects are randomly assigned to SOC or SOC + brequinar in a 1:2 ratio.

11.7 Pooling of Study Centers

Not applicable to this small, early phase study.

11.8 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.

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) 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.

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19. Study DUP 785-022 Clinical Study Report (on file with Clear Creek)
20. Study DUP 785-031 Clinical Study Report (on file with Clear Creek)
21. Study DUP 785-034 Clinical Study Report (on file with Clear Creek)

15 APPENDICES

15.1 Appendix A: CCB-CRISIS-01 Schedule of Events

CCB-CRISIS-01 Schedule of Events **Procedures**	**Screen**	**D1**	**D2 - D7 (± 8 hours)**	**Final Visit D15 (± 2 days)**	**F/U Phone Call 2 weeks/ Survival (± 3 days)**
Informed Consent	X				
AE/Concomitant Medications	X	X	D7	X	
Medical history / History of current illness	X				
Demographics, collect Height and weight	X				
Check for Physical Exam abnormalities	X				
Pregnancy Test (urine or serum)	X				
Hematology/Chemistry	X	X (pre-dose)	D7	X	
Inflammatory Markers*		X (pre-dose)	D3, D5, D7	X	
DHO/brequinar PK Sample Collection & Processing		X (pre-dose)	D3, D5, D7	X (DHO only)	
Swab collection for nasopharyngeal viral load		X (pre-dose)	D3, D5, D7	X	
Clinical SARS-CoV-2 testing RT-PCR	X				
Hospital Status			D3, D5, D7	X	
NEWS2 Assessments		X	D3, D5, D7	X	
Dispense Study Medication if assigned to brequinar		X	D2 – 5		
Drug Accountability			D7		
Survival Assessment Day 29					X

Collect information from available electronic health record (EHR), Progress Notes, and medication records; a special visit by research staff is not to be performed. Hematology, Results for Chemistry and available inflammatory markers analyzed locally are to be obtained from the EHR; do not draw another set of labs. Missed samples due to hospital staff too busy or for technical reasons unable to obtain samples will not be counted as protocol deviations.

Note that any visits other than Screening/Day 1 may be conducted via telephone or digital media. Missed samples/assessments when phone visits occur will not be counted as protocol deviations.

*Inflammatory markers are to be collected from the EHR when available; otherwise process and ship samples to the central laboratory per the Laboratory Manual. DHO and brequinar samples will also be sent to the central laboratory.

Note that if the subject is discharged before Day 15, ensure safety laboratory samples for hematology and chemistry are obtained prior to discharge and on an outpatient basis per Section 8.4.

15.2 Appendix B: Investigator's Statement and Agreement

STUDY NUMBER: CCB-CRISIS-01

STUDY TITLE: The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19).

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:** _____

Site Address:

_____

_____

15.3 Appendix C: National Early Warning Score (NEWS2)

Chart 1: The NEWS scoring system

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Use SpO_2 Scale 2 if target range is 88 – 92%, e.g., in hypercapnic respiratory failure.

National Early Warning System Score (NEWS) 2 Royal College of Physicians 2017 [14]

15.4 Appendix D: Massachusetts General Hospital COVID-19 Treatment Guidance.

Recommended daily labs: • CBC with diff • CMP • CPK (creatine kinase)	If Clinically Indicated: • Blood cultures • For acute kidney injury- urinalysis and spot urine protein creatinine • Procalcitonin • IL-6
Recommended repeated labs q 2-3 days: • D-dimer • Ferritin/CRP/ESR • LDH • Troponin • Baseline ECG	Radiology: • Chest X-ray at admission
Viral Serologies: • HBV serologies (sAb, cAb, sAg) • HCV antibody • HIV ½ Ab/Ag	

Risk Factors for COVID-19 Progression:

Epidemiological - Category 1	
Age > 65	Vital Signs – Category 2
Pre-existing pulmonary disease	Respiratory Rate > 24 breaths per minute
Chronic kidney disease	Heart rate > 125 beats per minute
Diabetes with A1c > 7.6%	Sp02 ≤ 93%
History of hypertension	
History of cardiovascular disease	Labs – Category 3
Obesity (BMI > 30)	D-dimer > 1000 ng/mL
Use of biologics	CRP > 100
History of transplant or other immunosuppression	LDH > 245 U/L
HIV, CD4 cell count < 200 or unknown CD4 count	Elevated troponin
	Admission absolute lymphocyte count < 0.8
	Ferritin > 500 µg/L

STUDY PROTOCOL

The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)

Study No: CCB-CRISIS-01

Version Date: 05 JUNE 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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DHODH is a mitochondrial enzyme that catalyzes the 4th step of pyrimidine synthesis; it is completely essential for the generation of UMP.

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
DSMB	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-01 SYNOPSIS	
IND	149291
Title	The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)
Protocol	CCB-CRISIS-01
Rationale	Brequinar is a potent DHODH inhibitor that has been studied in more than 1,000 cancer, psoriasis, and organ transplant patients. 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. 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 primary dose-limiting adverse effects have included thrombocytopenia and mucositis. The CRISIS trial will study standard of care (SOC) and SOC with 5 days of DHODH inhibition. 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. 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. Brequinar has not been previously tested as an anti-viral.
Investigational Product and Dosage	Subjects will be randomized in a 1:2 ratio to either standard of care (SOC) alone, or SOC + brequinar. Brequinar is available as 100 mg oral capsules. Five once daily doses of brequinar 100 mg are to be administered on Study Days 1 – 5 for those assigned to the SOC + brequinar group.

	Treatment assignment will be randomized, open label.
Primary Objective	● To determine the safety and tolerability of SOC and SOC plus brequinar in hospitalized COVID-19 subjects.
Secondary Objectives	● To determine the rates of/changes in clinical status measures listed through Day 15: – Hospitalization status – Duration of hospitalization – NEWS2 Score ● Mortality through Day 29
Exploratory Objectives	• To determine the change in SARS-CoV-2 nasopharyngeal viral load through Day 15 ● To determine the change in inflammatory markers through Day 15 ● To determine the change in DHO levels through Day 15 ● To determine the change in brequinar concentration levels through Day 7
Design	This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive SOC per institutional guidelines for treatment of patients with COVID-19 infection. In addition to SOC, the brequinar group will receive brequinar 100 mg once daily for 5 days. Subjects will have a Screening Visit followed as soon as possible with Study Day 1 (Day 1 may take place on the same day if entry criteria data are available). Study procedures are presented in detail in the procedures section, see below. Subjects will be followed through Day 15. Mortality will be assessed at Day 29. See below for instructions regarding hospital discharge prior to Day 15. Hematology and chemistry results and study information such as NEWS2 criteria are to be collected using the available EHR data as much as possible to avoid extra procedures for the study.
Sample Size:	Approximately 24 subjects will be randomized to either standard of care or standard of care plus brequinar in a 1:2 ratio (approximately 8 assigned to standard of care and 16 subjects on brequinar).
Number of Sites:	1 - 8
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 and at least one of the following co-morbidities by subject history or present in the institution's electronic health record: hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease (COPD) or asthma, cardiovascular disease (coronary artery disease or congestive heart failure), liver cirrhosis, age > 65, BMI > 30. 3. If discharged from the hospital prior to Study Day 15 or if follow up is needed for study drug-related adverse event, willing to go to an outpatient laboratory for a laboratory sample as well as a contact (phone call or other digital media) on Study Days 7 and 15 and contact only on Day 29. 4. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay. 5. Hospitalized (in patient with expected duration ≥ 24 hours) 6. 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 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. 7. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of brequinar. 8. ≤ 10 days since first COVID-19 symptom as determined by treating clinician. 9. COVID-19 symptoms of severity mild (fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea), moderate (any symptom of mild illness or shortness of breath with exertion), or severe (any symptom of moderate illness or shortness of breath at rest, or respiratory distress). 10. COVID-19 signs of severity mild (no clinical signs), moderate (respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute) or severe (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300)

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. Active malignancy other than squamous cell carcinoma; anticancer treatment such as chemotherapy or radiation therapy within the past month. 3. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test. 4. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide), tacrolimus, sirolimus, or pre-existing prednisone at higher than 20 mg daily (ongoing or within 2 weeks of study entry). 5. Platelets ≤150,000 cell/mm^3. 6. Hemoglobin < 12 gm/dL 7. Absolute neutrophil count < 1500 cells/mm^3 8. Renal dysfunction, i.e., creatinine clearance < 50 mL/min 9. AST and/or ALT > 1.5 ULN, or total bilirubin > ULN 10. History of bleeding disorders or recent surgery in the six weeks preceding enrollment 11. Concomitant use of agents known to cause thrombocytopenia 12. Concomitant use of corticosteroids, regardless of dose; or use of corticosteroids at any dose in the two weeks preceding enrollment. 13. History of gastrointestinal ulcer, or history of gastrointestinal bleeding. 14. History of hepatitis B and/or C infection, active liver disease and/or cirrhosis. 15. History of known cardiovascular disease including unstable angina, myocardial infarction, uncontrolled arrythmias, and heart failure. 16. Baseline COVID-19 severity characterized as "Critical" based on the FDA Guidance "COVID-19: Developing Drugs and Biological Products for the Treatment or Prevention (https://www.fda.gov/media/137926/download). Evidence of critical illness defined by at least one of the following: 1. Respiratory failure based on resource utilization requiring at least one of the following: 1. Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies

	may not be able to be administered in setting of resource limitation) 2. Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors) 17. Multi-organ dysfunction/failure.
Treatment	All subjects will receive standard of care (SOC) per institutional guidelines. Subjects will be randomly assigned to SOC alone or SOC plus brequinar 100 mg daily x 5 days.
Stopping Criteria	Individual Criteria: • Participants who develop a Grade 3 symptomatic 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 symptomatic 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. Study-Level Stopping Criteria: The study is to be stopped as shown below: • If ≥ 4 subjects on the brequinar treatment arm develop the same Grade 3 or 4 adverse event or symptomatic laboratory abnormality • If ≥ 8 subjects on the brequinar treatment arm develop any Grade 3 or 4 adverse event or symptomatic laboratory abnormality.
DSMB	A Data Safety Monitoring Board (DSMB) will meet periodically to review the safety and scientific conduct of the study. At a minimum, the DSMB is to review adverse events and safety laboratory assessments after the first six subjects complete Day 5 of treatment, and again after the first 12 subjects complete Day 5 of treatment.
Procedures	**Screening Visit (Since hospital admission)** Results of these procedures must be available in the EHR and completed since hospital admission. Obtain the subject's written informed consent (be sure to note time of consent), then collect baseline information. Collect information from EHR. Do not perform study-specific procedures for data available from EHR. • Demographics (height, weight, date of birth, gender, race, ethnicity). • Recent (within one year unless ongoing), relevant medical/surgical history and concomitant medications.

	• Date of first symptom. • Record any clinically significant abnormal physical examination findings. • Ensure EHR has negative pregnancy test result for women of childbearing potential (WOCBP). • Record any adverse events that occurred since signing the ICF. • Record any new or changed concomitant medications since signing the ICF. Concomitant medications information is to include the medication, dosage, and duration of administration. • Hematology/chemistry from EHR for Inclusion/Exclusion criteria check. • Polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay for SARS-CoV-2 infection (may utilize test results from external laboratory to meet entry criteria provided such results are accurately documented and can be confirmed). • Confirm subject meets all inclusion and no exclusion criteria. **Treatment** The treatment period is up to 5 days: standard of care alone (SOC) or SOC + brequinar 100 mg daily x 5 days. Data points such as NEWS2 Assessments and safety labs are to be collected from the EHR, a separate visit by study staff is not to be performed. Give the first dose of brequinar as soon as possible after randomization. See below regarding hospital discharge prior to Day 15. **Days 1 – 7 (8 AM ± 8 hours):** • If Day 1 is different date from Screening, confirm subject continues to meet all inclusion and no exclusion criteria. • Randomize subject and record the time and date of randomization. • Review Progress Notes and medication records to collect any new or ongoing adverse events or new or changed concomitant medications since previous visit (may be omitted on Day 1 if Screening visit is conducted on same day as Study Day 1). Repeat daily through hospital discharge. • Collect SOC hematology/chemistry results from EHR on Day 1 (pre-dose) (may be omitted for Day 1 if Screening visit conducted on same date as Study Day 1) then daily through Day 7 or until the clinician decides daily testing is no longer necessary. Ensure that Day 1 samples are obtained prior to first dose of study drug, if applicable. • Days 1 (pre-dose), 3, 5, 7: – Collect NEWS2 Assessments from EHR. – Collect results for inflammatory markers from EHR for those analyzed locally; collect, process and ship samples for

	DHO/brequinar PK and cytokine panel to be analyzed at the central laboratory per the Laboratory Manual. – Collect, process, and ship nasopharyngeal viral load samples. – Record hospitalization status (hospitalized, hospitalized in ICU, discharged); subject must be hospitalized Day 1 to meet inclusion criteria, do not record again. • Dispense study medication (Days 1 through 5 if in brequinar group). Keep the brequinar study drug administration interval to 24h as much as possible. Record date and time of study drug administration. • Drug accountability Day 7 ± 2 days. Note: If discharge occurs prior to Day 5 for subjects in the brequinar group, the subject will take one final dose on the day of discharge. **Final Visit Day 15** (8 AM ± 2 days) • Review Progress Notes and medication records to collect information for any new adverse events or changes in ongoing adverse events or new or changed concomitant medications since Day 7 (collect from EHR if subject still hospitalized, otherwise by phone or other digital media). • Collect SOC hematology/chemistry results from EHR if subject still hospitalized. • Collect results for inflammatory markers from EHR for those analyzed locally; collect and process samples for DHO and cytokine panel to be analyzed at the central laboratory on. • Collect and process nasopharyngeal viral load samples. • Record hospitalization status (hospitalized, hospitalized in ICU, discharged). • Collect NEWS2 Assessments from EHR. • If the subject is being discharged prior to Day 15, follow procedures below. **Day 29 (8 AM ± 3 Days)** • Determine survival status from EHR if available or by telephone/digital media per institutional guidelines. <u>Hospital Discharge Before Day 15 (Brequinar Treatment Group Only)</u> For subjects in the brequinar treatment group, if the subject is discharged from the hospital prior to Day 5 the subject is to take a final dose on the day of discharge. If the subject is discharged from the hospital prior to Day 7, ensure hematology/chemistry sample has been obtained prior to discharge and collect these results on the appropriate EDC page. Following discharge, the subject is to return to the research facility for the Days 7 and 15 visits if able and permitted.

	If discharge occurs on Days 10, 11, or 12, ensure a hematology/chemistry sample has been obtained prior to discharge and record these results on the appropriate EDC page. Following discharge, the subject is to return to the research facility for the Day 15 visit if able and permitted. If discharge occurs on Days 13, 14 or 15, complete the Day 15 Final Visit activities. No further visits are required unless follow up is needed for a study drug-related AE or an SAE; the Day 29 mortality assessment is still to take place. If the subject is unable or not permitted to return for planned study visits, the visit activities will be conducted by contacting the subject (phone or other digital media) except for the lab draw. The hematology/chemistry sample will be obtained via outpatient laboratory. Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF. A subject is considered completed the study if they have assessments through Day 15, whether conducted in the hospital or contacted via phone or other digital media.
Safety/ Tolerability	**Safety/Tolerability** Adverse events will be collected from the time of informed consent through Day 15. After Day 15, collect/record only Serious Adverse Events (SAEs) or those judged by the Investigator or designated person to be related to study drug, including but not limited to potential hematologic toxicities. Post-randomization adverse events will be those with an onset after the date and time of randomization. Subjects who develop Grade 3 or 4 toxicities are to be re-evaluated every 2 days, as feasible, until the toxicity returns to Grade $\leq$ 2 severity.
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, safety laboratory data, and NEWS2 Assessments. Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of post randomization adverse events, defined as AEs 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, NEWS2 Criteria, and other clinical measures will be summarized using appropriate descriptive statistics.

STUDY PERSONNEL

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3 INTRODUCTION

3.1 Background

3.2 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]).

3.2.1 Coronavirus Biology

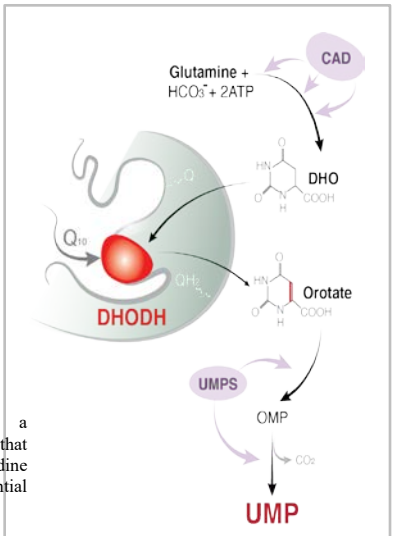
Coronaviruses, like other RNA-based viruses, do not have the machinery to synthesize their own nucleotides and thus depend upon the host intracellular pool of nucleotides for viral replication. In essence, viruses steal the host RNA building blocks, and without these building blocks they are unable to 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]).

3.3 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.

3.4 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 mitochondrial enzyme that catalyzes the 4th step of pyrimidine synthesis and is absolutely essential for the generation of UMP.

Figure 3-1.

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]).

3.5 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]).

3.6 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 CRISIS trial will study standard of care (SOC) and SOC with 5 days of DHODH inhibition. 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.

3.6.1 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 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 reassuring the safety of this regimen (see Brequinar IB [5]).

3.6.2 Risk/Benefit of Brequinar

As presented in the Brequinar IB [5], an extensive database exists with more than 800 cancer patients 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. Brequinar has also been utilized at lower doses than used in the cancer studies in 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. While no DHODHi has been tested to date in the clinic for infection with SARS-CoV-2 and no brequinar safety information is available in treatment of this disease, DHODHi therapy in the context of trials for patients with cancer has the expected safety side-effects of mucositis and bone marrow suppression. 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 mucositis and only 1 (2.6%) episode of mild thrombocytopenia. The 100 mg per day dose proposed for administration in this study should be safe and well tolerated.

The possible 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. As discussed above, inhibition of DHODH is expected to reduce the ability of the virus to replicate and it is for this reason that study CCB-CRISIS-01 will administer brequinar to patients with COVID-19.

3.7 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration of 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.

COVID-19 patients are at higher risk of complications and poor outcomes when their infection is combined with comorbidities including hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease (COPD) or asthma, cardiovascular disease (coronary artery disease or congestive heart failure), liver cirrhosis, age > 65, and BMI > 30 [15]. Therefore, participants in this protocol must have at least one of these comorbidities in order to justify that the risks of potential and known toxicities associated with brequinar are outweighed by the potential benefits in this higher risk population.

In addition to ensuring a higher risk population, 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).

3.8 Possible Interactions with Concomitant Medical Treatments

While not previously tested in patients with viral infections, brequinar has been administered to subjects taking a variety of concomitant medications that are typical in severely ill cancer patients. 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. Brequinar has also been used concomitantly with antibiotics, antifungals and other critical care medications.

There is no experience with brequinar for treatment of SARS-CoV-2 and other severe viral infections and no formal interaction studies have been conducted.

3.8.1 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).

3.9 Steps to be Taken to Control or Mitigate Risks

All subjects will be treated in a hospital setting by highly experienced infectious disease or other critical care specialists and other qualified staff familiar with the treatment of severe viral infections and their complications.

Subjects in the Brequinar Treatment Group

If the subject is in the brequinar treatment group and is being discharged prior to completing the study, ensure a hematology/chemistry sample is obtained prior to discharge on the day of discharge. The subject is to return to the research facility for the Days 7 and 15 visits if able and permitted. If unable or not permitted to return to the research facility due to COVID-19 restrictions,

the remaining visit activities except for the lab draw will be conducted by phone or other digital media. The lab draw will be performed by an outpatient laboratory at a designated facility. Lab draws for any outpatient visits for the Day 7 and 15 visits are limited to safety labs (hematology and chemistry). Additional outpatient laboratory or study visits are to be conducted as needed for follow up of adverse events including hematologic toxicities.

4 TRIAL OBJECTIVES

4.1 Primary Objective

- To determine the safety and tolerability of standard of care (SOC and SOC plus brequinar in hospitalized COVID-19 subjects.

4.2 Secondary Objectives

The secondary objectives of this study are:

- To determine the changes in clinical status measures listed through Day 15:
  - Hospitalization status
  - Duration of hospitalization
  - National Early Warning System 2 Score (NEWS2) Score
- To determine survival status through Day 29

4.3 EXPLORATORY OBJECTIVES

- To determine the change in SARS-CoV-2 nasopharyngeal viral load through Day 15
- To determine the change in inflammatory markers through Day 15
- To determine the change in dihydroorotate dehydrogenase (DHO) through Day 15
- To determine the change in brequinar concentration levels through Day 7

5 TRIAL DESIGN

This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive standard of care per institutional guidelines for treatment of patients with SARS-CoV-2 infection. In addition to standard of care, the brequinar group will receive brequinar 100 mg once daily for 5 days.

The Massachusetts General Hospital (MGH) COVID-19 Treatment Guidance is provided in Appendix D Section 15.4. This guidance provides an example of standard of care instructions for treatment of COVID-19. The guidance is provided as informational only, it is not required that this guidance be used for treatment as standards of care may differ between institutions.

Subjects will have a Screening Visit followed as soon as possible with Study Day 1 (Day 1 may take place on the same day if entry criteria data are available). Study procedures are presented in detail in Section 8. Subjects will be followed through Day 15, with mortality assessed via a phone call/other digital media acceptable to institution on Day 29.

If the subject is being discharged prior to Day 7, see Section 8.5.

It is understood that some assessments may not be conducted if the subject is unable to return to the clinic after discharge due to restricted travel. If an assessment is missed due to after hospital discharge, e.g., samples or blood draws, this will not be counted as a protocol deviation. Any of the study visits may be conducted via telephone if the subject has been discharged from the hospital and is not permitted to or is unable to return to the hospital/clinic for these visits.

Information is to be collected using the electronic health record (EHR) whenever possible. It is not required to perform study-specific laboratory assessments, NEWS 2 assessments, etc. separately for study purposes.

6 TRIAL ENDPOINTS

6.1 Primary Endpoint

- Safety/tolerability measured by rates of post randomization adverse events and hematology/chemistry safety labs.

6.2 Secondary Endpoints

- Rates of/changes to the below clinical status measures through Day 15.
  - Hospitalization status
  - Duration of hospitalization in days
  - NEWS2 Assessments Days 1, 3, 5, 7, and Day 15 for hospitalized subjects.
- Mortality through Day 29

6.3 EXPLORATORY Endpoints

- SARS-CoV-2 nasopharyngeal viral load: Day 1 (pre-dose), Days 3, 5, 7, and 15
- Inflammatory markers (to be specified in the Laboratory Manual, may include but are not limited to erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), D-dimer, serum ferritin, and fibrinogen, procalcitonin, IL-6, IL-5, IL-2, IFN-ɣ, final list to be determined) on Day 1 pre-dose, D3, D5, D7, D15 or at frequency per institutional standard of care. The markers are to be tested locally when possible; requested tests as listed in the Laboratory Manual that are not analyzed locally are to be shipped to the central laboratory for analysis.
- DHO concentration levels through Day 15.
- Brequinar concentration levels through Day 7

7 TRIAL POPULATION

7.1 Number of Subjects

Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 24 subjects have completed the study. Subjects will be randomized to either standard of care or standard of care plus brequinar or in a 1:2: ratio (approximately 8 subjects assigned to standard of care alone and approximately 16 subjects on standard of care plus brequinar).

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 and at least one of the following co-morbidities by subject history or present in the institution's electronic health record: hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease (COPD) or asthma, cardiovascular disease (coronary artery disease or congestive heart failure), liver cirrhosis, age > 65, BMI > 30.
3. If discharged from the hospital prior to Study Day 15 or if follow up is needed for study drug-related adverse event, willing to go to an outpatient laboratory to obtain a laboratory sample as well as a contact (phone call or other digital media) on Study Days 7 and 15 and contact only on Day 29.
4. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other Food and Drug Administration (FDA)-cleared commercial or public health assay.
5. Hospitalized (in patient with expected duration ≥ 24 hours)
6. 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 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.
7. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of brequinar.
8. ≤ 10 days since first COVID-19 symptom as determined by treating clinician.
9. COVID-19 symptoms of severity mild (fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea), moderate (any symptom of mild illness or shortness of breath with exertion), or severe (any symptom of moderate illness or shortness of breath at rest, or respiratory distress). [22].

10. COVID-19 signs of severity mild (no clinical signs), moderate (respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute) or severe (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300) [22].

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. Active malignancy other than squamous cell carcinoma; anticancer treatment such as chemotherapy or radiation therapy within the past month.
3. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test.
4. Treatment with another DHODH inhibitor (e.g., leflunomide or teriflunomide), tacrolimus, sirolimus, or pre-existing prednisone at higher than 20 mg daily (ongoing or within 2 weeks of study entry).
5. Platelets ≤150,000 cell/mm^3.
6. Hemoglobin < 12 gm/dL
7. Absolute neutrophil count < 1500 cells/mm^3
8. Renal dysfunction, i.e., creatinine clearance < 50 mL/min
9. AST and/or ALT > 1.5 ULN, or total bilirubin > ULN
10. History of bleeding disorders or recent surgery in the six weeks preceding enrollment
11. Concomitant use of agents known to cause thrombocytopenia
12. Concomitant use of corticosteroids, regardless of dose; or use of corticosteroids at any dose in the two weeks preceding enrollment.
13. History of gastrointestinal ulcer, or history of gastrointestinal bleeding.
14. History of hepatitis B and/or C infection, active liver disease and/or cirrhosis.
15. History of known cardiovascular disease including unstable angina, myocardial infarction, uncontrolled arrythmias, and heart failure.
16. Baseline COVID-19 severity characterized as “Critical” based on the FDA Guidance “COVID-19: Developing Drugs and Biological Products for the Treatment or Prevention (https://www.fda.gov/media/137926/download). Evidence of critical illness defined by at least one of the following:
    a. Respiratory failure based on resource utilization requiring at least one of the following:
        i. Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical

diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies may not be able to be administered in setting of resource limitation)

b. Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)

c. Multi-organ dysfunction/failure. See [22].

7.4 Inclusion of Women and Minorities

Adult men and women of all races and ethnic groups are eligible for this trial.

8 STUDY TREATMENTS

8.1 Description of Study Medications

8.1.1 Brequinar

Brequinar will be supplied as 100 mg capsules. Dosing will be a single 5-day course of brequinar 100 mg once daily for 5 doses. The initial brequinar dose (Day 1) should be administered as soon as possible based on study drug availability from the investigational pharmacy.

8.2 Treatment Administration

This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive standard of care (SOC) per institutional guidelines for SARS-CoV-2 infection. Subjects will be randomly assigned in a 1:2 ratio to standard of care alone or standard of care plus brequinar.

8.2.1 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE).

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 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 (Study 785-001 [16], 785-003 [17], and 785-005 [18]) with five consecutive days of intravenous (IV) brequinar dosing and 168 subjects, there were no toxic deaths. For subjects from these three studies who were treated with a dose of 100 mg or below (as will be dosed in CCB-CRISIS-01), 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 [19], 785-031 [20] , and 785-034 [21]), 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 15 (or longer if needed to follow up study drug-related adverse events). Mortality is assessed via a phone call or other digital media at Day 29.

After treatment, participants will be monitored through at least Study Day 15 (or longer if needed to follow study drug-related AEs/SAEs). 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 symptomatic 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 symptomatic 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

Following assessment by the Data Safety Monitoring Board (DSMB, see Section 10.9), the study is to be stopped as shown below:

- If ≥ 4 subjects on the brequinar treatment arm develop the same Grade 3 or 4 adverse event or symptomatic laboratory abnormality
- If ≥ 8 subjects on the brequinar treatment arm develop any Grade 3 or 4 adverse event or symptomatic laboratory abnormality.

8.5 Hospital Discharge Prior to Study Day 15

For subjects in the brequinar treatment group, if the subject is discharged from the hospital prior to Day 5 the subject is to take a final dose on the day of discharge.

If the subject is discharged from the hospital prior to Day 7, ensure hematology/chemistry sample has been obtained prior to discharge and collect these results on the appropriate EDC page. Following discharge, the subject is to return to the research facility for the Days 7 and 15 visits if able and permitted.

If discharge occurs on Days 10, 11, or 12, ensure a hematology/chemistry sample has been obtained prior to discharge and record these results on the appropriate EDC page. Following discharge, the subject is to return to the research facility for the Day 15 visit if able and permitted.

If discharge occurs on Days 13, 14 or 15, complete the Day 15 Final Visit activities. No further visits are required unless follow up is needed for a study drug-related AE or an SAE; the Day 29 mortality assessment is still to take place.

If the subject is unable or not permitted to return for planned study visits, the visit activities will be conducted by contacting the subject (phone or other digital media) except for the lab draw. The lab draw will be completed at an outpatient laboratory when feasible.

Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF. A subject is considered completed the study if they have assessments through Day 15, whether conducted in the hospital or contacted via phone or other digital media.

8.6 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 8.9.

8.7 Treatment Compliance

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

8.8 Storage, Stability, Labeling and Packaging

8.8.1 Storage and Stability

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

8.8.2 Labeling and Packaging

Each brequinar bottle/dispensing container for subject use will be labeled with at least the following information:

For Clinical Trial Use Only

Study Number: CCB-CRISIS-01

Contents: Brequinar 100 mg capsules

For oral use only. Take with approximately 8 ounces water.

Subject Number: XX-XXXX

Treatment Duration: As directed

Clinical Batch Number: XXXXXXX

Expiration Date: TBD

Storage: Store at controlled room temperature

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

Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

8.8.3 Blinding and Randomization

The trial will be conducted in an open-label manner with random assignment to standard of care or standard of care plus brequinar. The brequinar capsules will be provided to each participating institution in bulk to be dispensed by the institution's pharmacist for each subject. Randomization assignments will be provided by the sponsor.

8.8.4 Unblinding/Expectedness

It is not necessary to break the blind for this open label study as the treatment will be known for each subject.

Expectedness will be determined by establishing whether the 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.

8.8.5 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, used and discarded. It must be clear from the records whether the subject received study medication or was assigned to standard of care. 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.

8.9 Prohibited Medications

Treatment is prohibited with another DHODH inhibitor (e.g., leflunomide and teriflunomide), tacrolimus, sirolimus, or pre-existing prednisone at higher than 20 mg daily (ongoing or within 2 weeks of study entry). Treatment is prohibited with agents known to cause thrombocytopenia. Concomitant use of corticosteroids, regardless of dose or use or corticosteroids at any dose in the two weeks preceding enrollment is also prohibited.

8.10 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 telephone or other digital media. Study information is to be collected from the EHR as much as possible such as NEWS2 Assessments, height, weight, hematology/chemistry, from Progress Notes for AEs, and from medication records for new or changed concomitant medications. Visits to an outpatient laboratory post hospital discharge may be required if subjects are not able or permitted to return for follow up study visits.

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). Remdesivir may be used in this clinical trial as a component of standard of care of patients hospitalized with severe disease in settings where remdesivir is available via the Emergency Use Authorization (EUA).

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), 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.

Signed written informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to signing the informed consent but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. An original signed informed consent form will be subject to review by the Sponsor; a copy will be given to the subject and a copy will be filed with the subject's medical notes.

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.

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

NEWS2 Assessments, laboratory assessments, SARS-CoV-2 testing, and other observations will be conducted by experienced personnel throughout the study based on the Schedule of Events. The majority of study information is to be collected from the EHR. Phone calls or other digital media and outpatient visits for hematology/chemistry samples may be required to complete some study assessments if the subject is discharged prior to Study Day 15.

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), bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium), lactate dehydrogenase (LDH).

Inflammatory markers including D-dimer, ferritin, CRP, ESR, troponin, fibrinogen, and procalcitonin may be collected locally if available by the Institution. Additional inflammatory markers will be collected and analyzed by a central laboratory, as specified in the Laboratory Manual. A sample is to be collected for DHO and brequinar pharmacokinetics at the timepoints specified in the Laboratory Manual.

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

If urinalysis is clinically indicated, collect results from the EHR.

Nasopharyngeal swabs for SARS-CoV-2 viral load, inflammatory markers, and DHO samples will be collected Days 1, 3, 5, 7, and 15 (standardized collection instructions available in the supplied Laboratory Manual; please use the same nostril each time). Samples may be banked for future retrospective analyses.

NEWS2 Criteria are available in Appendix C Section 15.3.

Hospitalization status is to be recorded as hospitalized not in ICU, hospitalized in ICU, or discharged.

9.5 Study Conduct

Screening Visit (Since hospital admission)

These procedures must be completed since hospital admission and prior to starting dosing. Obtain the subject's written informed consent (be sure to note time of consent), then collect baseline information from the EHR. Do not perform study specific procedures for data available from the EHR. For Screening/Day 1 use the EHR results closest to the visit to confirm subject eligibility.

- Demographics (date of birth, gender, race, ethnicity, height and weight).
- Recent (within one year unless ongoing), relevant medical/surgical history and concomitant medications.
- Date of first symptom.
- Record any new or changed adverse events and new or changed concomitant medications since signing the ICF.
- Record any clinically significant abnormal physical examination findings as recorded in EHR.
- Hematology/chemistry from EHR.

- Ensure negative pregnancy test result is present in the EHR for women of childbearing potential (WOCBP).
- Polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay for SARS-CoV-2 infection (may utilize test results from external laboratory to meet entry criteria provided such results are accurately documented and can be confirmed).
- Confirm subject meets all inclusion and no exclusion criteria.

Treatment

The treatment period is up to 5 days: standard of care alone (SOC) or SOC + brequinar 100 mg daily for 5 days. Data points such as NEWS2 Assessments are to be collected from the EHR when possible, a separate visit by study staff is not to be conducted. The first dose of brequinar is to be given as soon as possible depending on availability of investigational pharmacy staff. If the subject is discharged from the hospital prior to Day 15, see Section 8.5 for how and when to conduct study assessments.

It is understood that some assessments may not be conducted if the subject is unable to return to the clinic after discharge due to restricted travel or if the study visit cannot be conducted remotely; this will not be counted as a protocol deviation. Collect information from the EHR, medication records and Progress Notes whenever possible

Days 1 - 7 (8 AM ± 8 hours)

- If Day 1 is different date from Screening, confirm subject continues to meet all inclusion and no exclusion criteria.
- Randomize the subject (record date and time of randomization).
- Review Progress Notes and medication records to collect any new or changes to ongoing adverse events or new or changed concomitant medications since previous visit (may be omitted on Day 1 if Screening visit was conducted on same day as Study Day 1). Repeat daily until discharge.
- Collect SOC hematology/chemistry results from the EHR beginning on Day 1 (pre-dose) (may be omitted for Day 1 if Screening visit conducted on same date as Study Day 1) then daily through Day 7 or until the clinician decides daily testing is no longer necessary. Ensure that Day 1 samples are obtained prior to first dose of study drug, if applicable.
- Days 1 (pre-dose), 3, 5, 7:
  - Collect NEWS2 Assessments from the EHR.
  - Collect results for inflammatory markers from EHR for those analyzed locally; collect, process and ship samples for DHO/brequinar PK and cytokine panel to be analyzed at the central laboratory per the Laboratory Manual.
  - Collect and process SARS-CoV-2 nasopharyngeal viral load samples.
  - Record hospitalization status (hospitalized, hospitalized in ICU, discharged) (Day 1 already recorded as part of Inclusion criteria, do not record again).
- Dispense study medication (Days 1 through 5 if in brequinar group) and record date and time of brequinar administration. Keep the drug administration interval as close as possible

to 24 hours. Ensure Day 1 labs are drawn prior to first brequinar dose on Day 1. If a subject taking brequinar is discharged prior to Day 5, administer final dose on day of discharge. Do not give subject study drug to take home.

- Drug accountability Day 7 ± 2 days.

Final Visit Day 15 (8 AM ± 2 days) or Hospital Discharge Day if earlier than Day 15

- Review Progress Notes and the medication record to collect information for any adverse events or new concomitant medications since Day 7 (from EHR if subject still hospitalized, otherwise by phone or other digital media).
- Collect results for SOC hematology/chemistry from the EHR if subject still hospitalized.
- Collect inflammatory markers from EHR for those analyzed locally; collect samples for DHO and cytokine panel to be analyzed at the central laboratory if subject still hospitalized.
- Collect NEWS2 Assessments from the EHR.
- Collect nasopharyngeal viral load sample.
- Collect hospital status (hospitalized, hospitalized in ICU, discharged).

Day 29 (8 AM ± 3 days)

- Determine survival status from EHR if available or contact the subject by phone call/digital media as acceptable to the institution.

If the subject is being discharged before Day 15, follow the procedures outlined in Section 8.5.

9.5.1 Unscheduled Visits

Unscheduled visits and tests to assess AEs/SAEs are permitted as needed providing the AE related to study drug or SAE onset occurs within two (2) weeks after the final study dose.

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. Provided that activities are carried out within the identified windows it will not be necessary to file a protocol deviation. It is understood that some scheduled study assessments may not be able to be conducted if the subject is unable to return to the clinic after discharge due to COVID-19 restricted travel; it is also understood that crowded hospital conditions/lack of personnel may make it impossible to carry out all requested study procedures; this will not be counted as a protocol deviation. The Day 7 and 15 visits are to be conducted via telephone if the subject has been discharged from the hospital with lab draws for subjects in the brequinar treatment group as described in Section 8.5.

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 be withdrawn from the study 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 evaluations for subjects who withdraw from the study 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).

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 15. After Day 15, collect/record only Serious Adverse Events (SAEs) or those judged 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.

Any serious adverse events (SAEs) experienced after 30 days post the last dose of study drug should only be reported to the sponsor if the investigator suspects a causal relationship to the 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, or require therapy.

Death due to disease progression should not be reported as an SAE. Report death from disease progression on the appropriate electronic data capture form.

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 progression of the disease under study.

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 descriptions and grading scales found in the revised National Cancer Institute (NCI) Common Terminology *Criteria for Adverse Events (CTCAE) version 4.03* will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html)*.

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 descriptions and grading scales found in the revised NCI CTCAE version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria. The CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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:

- 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, or
- is a congenital anomaly / birth defect;
- all other events that are 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 the studied indication, 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;
- Note that 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 is not an SAE.

Death due to disease progression is considered to be an Expected event in patients with severe SARS-CoV-2 infection and does not require reporting on an expedited basis.

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 the Sponsor contact until the event has subsided or, in case of permanent impairment, it stabilizes, and the overall clinical outcome has been ascertained.

SAE REPORTING EMAIL: Safety-CCB-CRISIS-01@prosoftclinical.com

Medical Monitor:

Sharon Levy, MD	Telephone:	O: (484) 320-2062

Sponsor Representative:

Barbara Powers, MSN, Ph.D.	Telephone:	M: 484-686-0545
	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 Medical Monitor 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 is to 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 the Medical Monitor/Sponsor. Follow-up information is to be subsequently communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs are to 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 knowledge by the Medical Monitor/Sponsor.

The Medical Monitor/Sponsor or designee must 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 the Sponsor Contact 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 pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should also be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as 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-up with 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 initially be hospitalized as in-patients and will be under the care of highly qualified infectious disease, critical care, and associated medical personnel. As is standard of care for moderately to severely ill in-patients, daily samples will be obtained for hematology assessments including complete blood count with full differential (WBC, RBC, hemoglobin, hematocrit, platelet count, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils). Any clinically significant out-of-range laboratory values will be assessed by hospital staff in a timely manner and treatment needs addressed as appropriate. 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 Clear Creek Medical Monitor will assess the available hematology data on a weekly 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, the Sponsor, and the Medical Monitor. In addition, the Data Safety Monitoring Board 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.

Subjects who are discharged from the hospital before Day 7 will have follow up contacts with study staff (phone calls or other digital media) on Days 7, 15 and 29. Early discharge subjects in the brequinar treatment group will also have samples for safety labs (hematology and chemistry) obtained either at the research facility or at an outpatient laboratory on Study Days 7 ± 2 and 15 ± 2. The safety laboratory results are to be initially assessed in real time by the Principal Investigator or designated person and the Medical Monitor. 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-hospital assessments and phone call visits will specifically ask about possible hematologic toxicity including any evidence of the list below. Early discharge 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 Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be established to provide independent oversight to this trial. The primary responsibility of the DSMB 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 DSMB will be detailed in a separate DSMB charter. The DSMB 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 DSMB Chair will advise the Sponsor that the study be stopped, the design changed, or that the study may continue per protocol.

10.9.1 DSMB Safety Review Schedule

The DSMB is to review adverse events and safety laboratory assessments after the first six subjects complete Day 5 of treatment, and again after the first 12 subjects complete Day 5 of treatment.

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 analyses will be based on the ITT population, which is defined as all randomized subjects.

11.2 Safety Analyses

Safety and tolerability will be assessed in terms of AEs, SAEs, NEWS2 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 NEWS2 Assessments will be summarized using appropriate descriptive statistics.

11.3 Efficacy Analyses

Efficacy will be assessed in terms of mortality, hospitalization status and duration, NEWS2 score, viral load (plasma and nasopharyngeal), and inflammatory markers.

11.4 DHO and Brequinar Concentration Levels

DHO and brequinar concentrations levels will be summarized using descriptive statistics.

11.5 Sample Size Considerations

Formal sample size calculations are not applicable for this phase 1a, open label study. Up to 24 subjects are planned to be entered in this trial. Additional subjects may be enrolled following data review.

11.6 Randomization

A randomization scheme will be provided by the Sponsor to ensure subjects are randomly assigned to SOC or SOC + brequinar in a 1:2 ratio.

11.7 Pooling of Study Centers

Not applicable to this small, early phase study.

11.8 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.

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) 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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21. Study DUP 785-034 Clinical Study Report (on file with Clear Creek)
22. 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-01 Schedule of Events

CCB-CRISIS-01 Schedule of Events **Procedures**	**Screen**	**D1**	**D2 - D7 (± 8 hours)**	**Final Visit D15 (± 2 days)**	**F/U Phone Call 2 weeks/ Survival (± 3 days)**
Informed Consent	X				
AE/Concomitant Medications (daily until discharge)	X	X	D1-7	X	
Medical history / History of current illness	X				
Demographics, collect Height and weight	X				
Check for Physical Exam abnormalities	X				
Pregnancy Test (urine or serum)	X				
Hematology/Chemistry	X	X (pre-dose)	D1-7	X	
Inflammatory Markers*		X (pre-dose)	D3, D5, D7	X	
DHO/brequinar PK Sample Collection & Processing		X (pre-dose)	D3, D5, D7	X (DHO only)	
Swab collection for nasopharyngeal viral load		X (pre-dose)	D3, D5, D7	X	
Clinical SARS-CoV-2 testing RT-PCR	X				
Hospital Status			D3, D5, D7	X	
NEWS2 Assessments		X	D3, D5, D7	X	
Dispense Study Medication if assigned to brequinar		X	D2 – 5		
Drug Accountability			D7		
Survival Assessment Day 29					X

Collect information from available electronic health record (EHR), Progress Notes, and medication records; a special visit by research staff is not to be performed. Results for Hematology, Chemistry and available inflammatory markers analyzed locally are to be obtained from the EHR; do not draw another set of labs. Missed samples due to hospital staff too busy or for technical reasons unable to obtain samples will not be counted as protocol deviations. Record urinalysis results if urinalysis is clinically indicated and results are available in the EHR.

Note that any visits other than Screening/Day 1 may be conducted via telephone or digital media. Missed samples/assessments when phone visits occur will not be counted as protocol deviations.

*Inflammatory markers are to be collected from the EHR when available; otherwise process and ship samples to the central laboratory per the Laboratory Manual. DHO and brequinar samples will also be sent to the central laboratory.

Note that if the subject is discharged before Day 15, ensure safety laboratory samples for hematology and chemistry are obtained prior to discharge and on an outpatient basis when feasible per Section 8.5.

15.2 Appendix B: Investigator's Statement and Agreement

STUDY NUMBER: CCB-CRISIS-01

STUDY TITLE: The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19).

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:** _____

Site Address:

_____

_____

15.3 Appendix C: National Early Warning Score (NEWS2)

Chart 1: The NEWS scoring system

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Use SpO_2 Scale 2 if target range is 88 – 92%, e.g., in hypercapnic respiratory failure.

National Early Warning System Score (NEWS) 2 Royal College of Physicians 2017 [14].

15.4 Appendix D: Massachusetts General Hospital COVID-19 Treatment Guidance.

Recommended daily labs: • CBC with diff • CMP • CPK (creatine kinase)	If Clinically Indicated: • Blood cultures • For acute kidney injury- urinalysis and spot urine protein creatinine • Procalcitonin • IL-6
Recommended repeated labs q 2-3 days: • D-dimer • Ferritin/CRP/ESR • LDH • Troponin • Baseline ECG	Radiology: • Chest X-ray at admission
Viral Serologies: • HBV serologies (sAb, cAb, sAg) • HCV antibody • HIV ½ Ab/Ag	

Risk Factors for COVID-19 Progression:

Epidemiological - Category 1	
Age > 65	Vital Signs – Category 2
Pre-existing pulmonary disease	Respiratory Rate > 24 breaths per minute
Chronic kidney disease	Heart rate > 125 beats per minute
Diabetes with A1c > 7.6%	Sp02 ≤ 93%
History of hypertension	
History of cardiovascular disease	Labs – Category 3
Obesity (BMI > 30)	D-dimer > 1000 ng/mL
Use of biologics	CRP > 100
History of transplant or other immunosuppression	LDH > 245 U/L
HIV, CD4 cell count < 200 or unknown CD4 count	Elevated troponin
	Admission absolute lymphocyte count < 0.8
	Ferritin > 500 µg/L

STUDY PROTOCOL

The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)

Study No: CCB-CRISIS-01

Version Date: 06 JULY 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

TABLE OF CONTENTS

LIST OF FIGURES

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
DSMB	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-01 SYNOPSIS	
IND	149291
Title	The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)
Protocol	CCB-CRISIS-01
Rationale	Brequinar is a potent DHODH inhibitor that has been studied in more than 1,000 cancer, psoriasis, and organ transplant patients. 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. 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 primary dose-limiting adverse effects have included thrombocytopenia and mucositis. The CRISIS trial will study standard of care (SOC) and SOC with 5 days of DHODH inhibition. 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. 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. Brequinar has not been previously tested as an anti-viral.
Investigational Product and Dosage	Subjects will be randomized in a 1:2 ratio to either standard of care (SOC) alone, or SOC + brequinar. Brequinar is available as 100 mg oral capsules. Five once daily doses of brequinar 100 mg are to be administered on Study Days 1 – 5 for those assigned to the SOC + brequinar group.

	Treatment assignment will be randomized, open label.
Primary Objective	● To determine the safety and tolerability of SOC and SOC plus brequinar in hospitalized COVID-19 subjects.
Secondary Objectives	● To determine the rates of/changes in clinical status measures listed through Day 15: – Hospitalization status – Duration of hospitalization – NEWS2 Score ● Mortality through Day 29
Exploratory Objectives	• To determine the change in SARS-CoV-2 nasopharyngeal viral load through Day 15 ● To determine the change in inflammatory markers through Day 15 ● To determine the change in DHO levels through Day 15 ● To determine the change in brequinar concentration levels through Day 7
Design	This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive SOC per institutional guidelines for treatment of patients with COVID-19 infection. In addition to SOC, the brequinar group will receive brequinar 100 mg once daily for 5 days. Subjects will have a Screening Visit followed as soon as possible with Study Day 1 (Day 1 may take place on the same day if entry criteria data are available). Study procedures are presented in detail in the procedures section, see below. Subjects will be followed through Day 15. Mortality will be assessed at Day 29. See below for instructions regarding hospital discharge prior to Day 15. Hematology and chemistry results and study information such as NEWS2 criteria are to be collected using the available EHR data as much as possible to avoid extra procedures for the study.
Sample Size:	Approximately 24 subjects will be randomized to either standard of care or standard of care plus brequinar in a 1:2 ratio (approximately 8 assigned to standard of care and 16 subjects on brequinar).
Number of Sites:	1 - 8
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. If discharged from the hospital prior to Study Day 15 or if follow up is needed for study drug-related adverse event, willing to go to an outpatient laboratory for a laboratory sample as well as a contact (phone call or other digital media) on Study Days 7 and 15 and contact only on Day 29. 4. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay. 5. Hospitalized (in patient with expected duration ≥ 24 hours) 6. 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. 7. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of brequinar. 8. ≤ 10 days since first COVID-19 symptom as determined by treating clinician. 9. COVID-19 symptoms of severity mild (fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea), moderate (any symptom of mild illness or shortness of breath with exertion), or severe (any symptom of moderate illness or shortness of breath at rest, or respiratory distress). 10. COVID-19 signs of severity mild (no clinical signs), moderate (respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute) or severe (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300)
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. Active malignancy other than squamous cell carcinoma; anticancer treatment such as chemotherapy or radiation therapy within the past month.

	3. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test. 4. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide), tacrolimus, sirolimus. 5. Platelets ≤150,000 cell/mm^3. 6. Hemoglobin < 12 gm/dL 7. Absolute neutrophil count < 1500 cells/mm^3 8. Renal dysfunction, i.e., creatinine clearance < 30 mL/min 9. AST and/or ALT > 1.5 ULN, or total bilirubin > ULN 10. History of bleeding disorders or recent surgery in the six weeks preceding enrollment 11. Concomitant use of agents known to cause bone marrow suppression leading to thrombocytopenia 12. History of gastrointestinal ulcer, or history of gastrointestinal bleeding. 13. History of hepatitis B and/or C infection, active liver disease and/or cirrhosis. 14. 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). 15. Baseline COVID-19 severity characterized as "Critical" based on the FDA Guidance "COVID-19: Developing Drugs and Biological Products for the Treatment or Prevention (https://www.fda.gov/media/137926/download). Evidence of critical illness defined by at least one of the following: 1. Respiratory failure based on resource utilization requiring at least one of the following: 1. Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies may not be able to be administered in setting of resource limitation) 2. Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors) 16. Multi-organ dysfunction/failure.

Treatment	All subjects will receive standard of care (SOC) per institutional guidelines. Subjects will be randomly assigned to SOC alone or SOC plus brequinar 100 mg daily x 5 days.
Stopping Criteria	Individual Criteria: • Participants who develop a Grade 3 symptomatic 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 symptomatic 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. Study-Level Stopping Criteria: The study is to be stopped as shown below: • If ≥ 4 subjects on the brequinar treatment arm develop the same Grade 3 or 4 adverse event or symptomatic laboratory abnormality • If ≥ 8 subjects on the brequinar treatment arm develop any Grade 3 or 4 adverse event or symptomatic laboratory abnormality.
DSMB	A Data Safety Monitoring Board (DSMB) will meet periodically to review the safety and scientific conduct of the study. At a minimum, the DSMB is to review adverse events and safety laboratory assessments after the first six subjects complete Day 5 of treatment, and again after the first 12 subjects complete Day 5 of treatment.
Procedures	**Screening Visit (Since hospital admission)** Results of these procedures must be available in the EHR and completed since hospital admission. Obtain the subject's written informed consent (be sure to note time of consent), then collect baseline information. Collect information from EHR. Do not perform study-specific procedures for data available from EHR. • Demographics (height, weight, date of birth, gender, race, ethnicity). • Recent (within one year unless ongoing), relevant medical/surgical history and concomitant medications. • Date of first symptom. • Record any clinically significant abnormal physical examination findings. • Ensure EHR has negative pregnancy test result for women of childbearing potential (WOCBP).

	• Record any adverse events that occurred since signing the ICF. • Record any new or changed concomitant medications since signing the ICF. Concomitant medications information is to include the medication, dosage, and duration of administration. • Hematology/chemistry from EHR for Inclusion/Exclusion criteria check. • Polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay for SARS-CoV-2 infection (may utilize test results from external laboratory to meet entry criteria provided such results are accurately documented and can be confirmed). • Confirm subject meets all inclusion and no exclusion criteria. **Treatment** The treatment period is up to 5 days: standard of care alone (SOC) or SOC + brequinar 100 mg daily x 5 days. Data points such as NEWS2 Assessments and safety labs are to be collected from the EHR, a separate visit by study staff is not to be performed. Give the first dose of brequinar as soon as possible after randomization. See below regarding hospital discharge prior to Day 15. **Days 1 – 7 (8 AM ± 8 hours):** • If Day 1 is different date from Screening, confirm subject continues to meet all inclusion and no exclusion criteria. • Randomize subject and record the time and date of randomization. • Review Progress Notes and medication records to collect any new or ongoing adverse events or new or changed concomitant medications since previous visit (may be omitted on Day 1 if Screening visit is conducted on same day as Study Day 1). Repeat daily through hospital discharge. • Collect SOC hematology/chemistry results from EHR on Day 1 (pre-dose) (may be omitted for Day 1 if Screening visit conducted on same date as Study Day 1) then daily through Day 7 or until the clinician decides daily testing is no longer necessary. Ensure that Day 1 samples are obtained prior to first dose of study drug, if applicable. • Days 1 (pre-dose), 3, 5, 7: – Collect NEWS2 Assessments from EHR. – Collect results for inflammatory markers from EHR for those analyzed locally; collect, process and ship samples for DHO/brequinar PK and cytokine panel to be analyzed at the central laboratory per the Laboratory Manual. – Collect, process, and ship nasopharyngeal viral load samples. – Record hospitalization status (hospitalized, hospitalized in ICU, discharged); subject must be hospitalized Day 1 to meet inclusion criteria, do not record again.

	• Dispense study medication (Days 1 through 5 if in brequinar group). Keep the brequinar study drug administration interval to 24h as much as possible. Record date and time of study drug administration. • Drug accountability Day 7 ± 2 days. Note: If discharge occurs prior to Day 5 for subjects in the brequinar group, the subject will take one final dose on the day of discharge. **Final Visit Day 15** (8 AM ± 2 days) • Review Progress Notes and medication records to collect information for any new adverse events or changes in ongoing adverse events or new or changed concomitant medications since Day 7 (collect from EHR if subject still hospitalized, otherwise by phone or other digital media). • Collect SOC hematology/chemistry results from EHR if subject still hospitalized. • Collect results for inflammatory markers from EHR for those analyzed locally; collect and process samples for DHO and cytokine panel to be analyzed at the central laboratory on. • Collect and process nasopharyngeal viral load samples. • Record hospitalization status (hospitalized, hospitalized in ICU, discharged). • Collect NEWS2 Assessments from EHR. • If the subject is being discharged prior to Day 15, follow procedures below. **Day 29 (8 AM ± 3 Days)** • Determine survival status from EHR if available or by telephone/digital media per institutional guidelines. <u>Hospital Discharge Before Day 15 (Brequinar Treatment Group Only)</u> For subjects in the brequinar treatment group, if the subject is discharged from the hospital prior to Day 5 the subject is to take a final dose on the day of discharge. If the subject is discharged from the hospital prior to Day 7, ensure hematology/chemistry sample has been obtained prior to discharge and collect these results on the appropriate EDC page. Following discharge, the subject is to return to the research facility for the Days 7 and 15 visits if able and permitted. If discharge occurs on Days 10, 11, or 12, ensure a hematology/chemistry sample has been obtained prior to discharge and record these results on the appropriate EDC page. Following discharge, the subject is to return to the research facility for the Day 15 visit if able and permitted. If discharge occurs on Days 13, 14 or 15, complete the Day 15 Final Visit activities. No further visits are required unless follow up is needed for a study drug-related AE or an SAE; the Day 29 mortality assessment is still to take place.

	If the subject is unable or not permitted to return for planned study visits, the visit activities will be conducted by contacting the subject (phone or other digital media) except for the lab draw. The hematology/chemistry sample will be obtained via outpatient laboratory. Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF. A subject is considered completed the study if they have assessments through Day 15, whether conducted in the hospital or contacted via phone or other digital media.
Safety/ Tolerability	**Safety/Tolerability** Adverse events will be collected from the time of informed consent through Day 15. After Day 15, collect/record only Serious Adverse Events (SAEs) or those judged by the Investigator or designated person to be related to study drug, including but not limited to potential hematologic toxicities. Post-randomization adverse events will be those with an onset after the date and time of randomization. Subjects who develop Grade 3 or 4 toxicities are to be re-evaluated every 2 days, as feasible, until the toxicity returns to Grade ≤ 2 severity.
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, safety laboratory data, and NEWS2 Assessments. Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of post randomization adverse events, defined as AEs 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, NEWS2 Criteria, and other clinical measures will be summarized using appropriate descriptive statistics.

STUDY PERSONNEL

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3 INTRODUCTION

3.1 Background

3.2 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]).

3.2.1 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]).

3.3 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.

3.4 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.

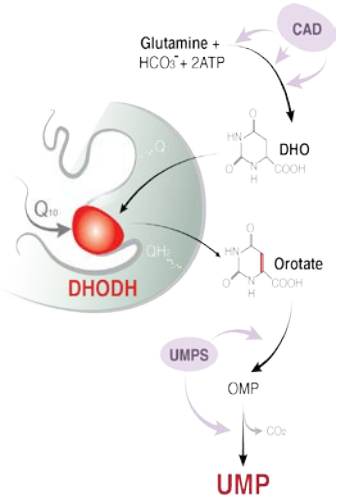

Figure 3-1. DHODH is a mitochondrial enzyme that catalyzes the 4th step of pyrimidine synthesis; it is completely essential for the generation of UMP.

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]).

3.5 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]).

3.6 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 CRISIS trial will study standard of care (SOC) and SOC with 5 days of DHODH inhibition. 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.

3.6.1 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 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 reassuring the safety of this regimen (see Brequinar IB [5]).

3.6.2 Risk/Benefit of Brequinar

As presented in the Brequinar IB [5], an extensive database exists with more than 800 cancer patients 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. Brequinar has also been utilized at lower doses than used in the cancer studies in 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. While no DHODHi has been tested to date in the clinic for infection with SARS-CoV-2 and no brequinar safety information is available in treatment of this disease, DHODHi therapy in the context of trials for patients with cancer has the expected safety side-effects of mucositis and bone marrow suppression. 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 mucositis and only 1 (2.6%) episode of mild thrombocytopenia. The 100 mg per day dose proposed for administration in this study should be safe and well tolerated.

The possible 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. As discussed above, inhibition of DHODH is expected to reduce the ability of the virus to replicate and it is for this reason that study CCB-CRISIS-01 will administer brequinar to patients with COVID-19.

3.7 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration of 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.

COVID-19 patients are at higher risk of complications and poor outcomes when their infection is combined with comorbidities including hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease (COPD) or asthma, cardiovascular disease (coronary artery disease or congestive heart failure), liver cirrhosis, age > 65, and BMI > 30 [15]. Therefore, participants in this protocol must have at least one of these comorbidities in order to justify that the risks of potential and known toxicities associated with brequinar are outweighed by the potential benefits in this higher risk population.

In addition to ensuring a higher risk population, 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).

3.8 Possible Interactions with Concomitant Medical Treatments

While not previously tested in patients with viral infections, brequinar has been administered to subjects taking a variety of concomitant medications that are typical in severely ill cancer patients. 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. Brequinar has also been used concomitantly with antibiotics, antifungals and other critical care medications.

There is no experience with brequinar for treatment of SARS-CoV-2 and other severe viral infections and no formal interaction studies have been conducted.

3.8.1 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).

3.9 Steps to be Taken to Control or Mitigate Risks

All subjects will be treated in a hospital setting by highly experienced infectious disease or other critical care specialists and other qualified staff familiar with the treatment of severe viral infections and their complications.

Subjects in the Brequinar Treatment Group

If the subject is in the brequinar treatment group and is being discharged prior to completing the study, ensure a hematology/chemistry sample is obtained prior to discharge on the day of discharge. The subject is to return to the research facility for the Days 7 and 15 visits if able and permitted. If unable or not permitted to return to the research facility due to COVID-19 restrictions,

the remaining visit activities except for the lab draw will be conducted by phone or other digital media. The lab draw will be performed by an outpatient laboratory at a designated facility. Lab draws for any outpatient visits for the Day 7 and 15 visits are limited to safety labs (hematology and chemistry). Additional outpatient laboratory or study visits are to be conducted as needed for follow up of adverse events including hematologic toxicities.

4 TRIAL OBJECTIVES

4.1 Primary Objective

- To determine the safety and tolerability of standard of care (SOC and SOC plus brequinar in hospitalized COVID-19 subjects.

4.2 Secondary Objectives

The secondary objectives of this study are:

- To determine the changes in clinical status measures listed through Day 15:
  - Hospitalization status
  - Duration of hospitalization
  - National Early Warning System 2 Score (NEWS2) Score
- To determine survival status through Day 29

4.3 EXPLORATORY OBJECTIVES

- To determine the change in SARS-CoV-2 nasopharyngeal viral load through Day 15
- To determine the change in inflammatory markers through Day 15
- To determine the change in dihydroorotate dehydrogenase (DHO) through Day 15
- To determine the change in brequinar concentration levels through Day 7

5 TRIAL DESIGN

This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive standard of care per institutional guidelines for treatment of patients with SARS-CoV-2 infection. In addition to standard of care, the brequinar group will receive brequinar 100 mg once daily for 5 days.

The Massachusetts General Hospital (MGH) COVID-19 Treatment Guidance is provided in Appendix D Section 15.4. This guidance provides an example of standard of care instructions for treatment of COVID-19. The guidance is provided as informational only, it is not required that this guidance be used for treatment as standards of care may differ between institutions.

Subjects will have a Screening Visit followed as soon as possible with Study Day 1 (Day 1 may take place on the same day if entry criteria data are available). Study procedures are presented in detail in Section 8. Subjects will be followed through Day 15, with mortality assessed via a phone call/other digital media acceptable to institution on Day 29.

If the subject is being discharged prior to Day 7, see Section 8.5.

It is understood that some assessments may not be conducted if the subject is unable to return to the clinic after discharge due to restricted travel. If an assessment is missed due to after hospital discharge, e.g., samples or blood draws, this will not be counted as a protocol deviation. Any of the study visits may be conducted via telephone if the subject has been discharged from the hospital and is not permitted to or is unable to return to the hospital/clinic for these visits.

Information is to be collected using the electronic health record (EHR) whenever possible. It is not required to perform study-specific laboratory assessments, NEWS 2 assessments, etc. separately for study purposes.

6 TRIAL ENDPOINTS

6.1 Primary Endpoint

- Safety/tolerability measured by rates of post randomization adverse events and hematology/chemistry safety labs.

6.2 Secondary Endpoints

- Rates of/changes to the below clinical status measures through Day 15.
  - Hospitalization status
  - Duration of hospitalization in days
  - NEWS2 Assessments Days 1, 3, 5, 7, and Day 15 for hospitalized subjects.
- Mortality through Day 29

6.3 EXPLORATORY Endpoints

- SARS-CoV-2 nasopharyngeal viral load: Day 1 (pre-dose), Days 3, 5, 7, and 15
- Inflammatory markers (to be specified in the Laboratory Manual, may include but are not limited to erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), D-dimer, serum ferritin, and fibrinogen, procalcitonin, IL-6, IL-5, IL-2, IFN-ɣ, final list to be determined) on Day 1 pre-dose, D3, D5, D7, D15 or at frequency per institutional standard of care. The markers are to be tested locally when possible; requested tests as listed in the Laboratory Manual that are not analyzed locally are to be shipped to the central laboratory for analysis.
- DHO concentration levels through Day 15.
- Brequinar concentration levels through Day 7

7 TRIAL POPULATION

7.1 Number of Subjects

Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 24 subjects have completed the study. Subjects will be randomized to either standard of care or standard of care plus brequinar or in a 1:2: ratio (approximately 8 subjects assigned to standard of care alone and approximately 16 subjects on standard of care plus brequinar).

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. If discharged from the hospital prior to Study Day 15 or if follow up is needed for study drug-related adverse event, willing to go to an outpatient laboratory to obtain a laboratory sample as well as a contact (phone call or other digital media) on Study Days 7 and 15 and contact only on Day 29.
4. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other Food and Drug Administration (FDA)-cleared commercial or public health assay.
5. Hospitalized (in patient with expected duration ≥ 24 hours)
6. 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.
7. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of brequinar.
8. ≤ 10 days since first COVID-19 symptom as determined by treating clinician.
9. COVID-19 symptoms of severity mild (fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea), moderate (any symptom of mild illness or shortness of breath with exertion), or severe (any symptom of moderate illness or shortness of breath at rest, or respiratory distress). [22].
10. COVID-19 signs of severity mild (no clinical signs), moderate (respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute) or severe (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300) [22].

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. Active malignancy other than squamous cell carcinoma; anticancer treatment such as chemotherapy or radiation therapy within the past month.
3. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test.
4. Treatment with another DHODH inhibitor (e.g., leflunomide or teriflunomide), tacrolimus, sirolimus.
5. Platelets ≤150,000 cell/mm^3.
6. Hemoglobin < 12 gm/dL
7. Absolute neutrophil count < 1500 cells/mm^3
8. Renal dysfunction, i.e., creatinine clearance < 30 mL/min
9. AST and/or ALT > 1.5 ULN, or total bilirubin > ULN
10. History of bleeding disorders or recent surgery in the six weeks preceding enrollment
11. Concomitant use of agents known to cause bone marrow suppression leading to thrombocytopenia
12. History of gastrointestinal ulcer, or history of gastrointestinal bleeding.
13. History of hepatitis B and/or C infection, active liver disease and/or cirrhosis.
14. 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).
15. Baseline COVID-19 severity characterized as "Critical" based on the FDA Guidance "COVID-19: Developing Drugs and Biological Products for the Treatment or Prevention (https://www.fda.gov/media/137926/download). Evidence of critical illness defined by at least one of the following:
    a. Respiratory failure based on resource utilization requiring at least one of the following:
        i. Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies may not be able to be administered in setting of resource limitation)
    b. Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)

16. Multi-organ dysfunction/failure. See [22].

7.4 Inclusion of Women and Minorities

Adult men and women of all races and ethnic groups are eligible for this trial.

8 STUDY TREATMENTS

8.1 Description of Study Medications

8.1.1 Brequinar

Brequinar will be supplied as 100 mg capsules. Dosing will be a single 5-day course of brequinar 100 mg once daily for 5 doses. The initial brequinar dose (Day 1) should be administered as soon as possible based on study drug availability from the investigational pharmacy.

8.2 Treatment Administration

This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive standard of care (SOC) per institutional guidelines for SARS-CoV-2 infection. Subjects will be randomly assigned in a 1:2 ratio to standard of care alone or standard of care plus brequinar. The brequinar dosing interval should be 24h ± 6h. Therefore, a subject being discharged less than 18 hours after the previous brequinar dose should not dose on the day of discharge. If possible, the subject should wait to be discharged until reaching at least 18 hours after the previous dose, then dose and be discharged.

8.2.1 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE).

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 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 (Study 785-001 [16], 785-003 [17], and 785-005 [18]) with five consecutive days of intravenous (IV) brequinar dosing and 168 subjects, there were no toxic deaths. For subjects from these three studies who were treated with a dose of 100 mg or below (as will be dosed in CCB-CRISIS-01), 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 [19], 785-031 [20] , and 785-034 [21]), 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 15 (or longer if needed to follow up study drug-related adverse events). Mortality is assessed via a phone call or other digital media at Day 29.

After treatment, participants will be monitored through at least Study Day 15 (or longer if needed to follow study drug-related AEs/SAEs). 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 symptomatic 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 symptomatic 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

Following assessment by the Data Safety Monitoring Board (DSMB, see Section 10.9), the study is to be stopped as shown below:

- If ≥ 4 subjects on the brequinar treatment arm develop the same Grade 3 or 4 adverse event or symptomatic laboratory abnormality
- If ≥ 8 subjects on the brequinar treatment arm develop any Grade 3 or 4 adverse event or symptomatic laboratory abnormality.

8.5 Hospital Discharge Prior to Study Day 15

For subjects in the brequinar treatment group, if the subject is discharged from the hospital prior to Day 5 the subject is to take a final dose on the day of discharge.

If the subject is discharged from the hospital prior to Day 7, ensure hematology/chemistry sample has been obtained prior to discharge and collect these results on the appropriate EDC page.

Following discharge, the subject is to return to the research facility for the Days 7 and 15 visits if able and permitted.

If discharge occurs on Days 10, 11, or 12, ensure a hematology/chemistry sample has been obtained prior to discharge and record these results on the appropriate EDC page. Following discharge, the subject is to return to the research facility for the Day 15 visit if able and permitted.

If discharge occurs on Days 13, 14 or 15, complete the Day 15 Final Visit activities. No further visits are required unless follow up is needed for a study drug-related AE or an SAE; the Day 29 mortality assessment is still to take place.

If the subject is unable or not permitted to return for planned study visits, the visit activities will be conducted by contacting the subject (phone or other digital media) except for the lab draw. The lab draw will be completed at an outpatient laboratory when feasible.

Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF. A subject is considered completed the study if they have assessments through Day 15, whether conducted in the hospital or contacted via phone or other digital media.

8.6 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 8.9.

8.7 Treatment Compliance

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

8.8 Storage, Stability, Labeling and Packaging

8.8.1 Storage and Stability

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

8.8.2 Labeling and Packaging

Each brequinar bottle/dispensing container for subject use will be labeled with at least the following information:

For Clinical Trial Use Only
Study Number: CCB-CRISIS-01
Contents: Brequinar 100 mg capsules
For oral use only. Take with approximately 8 ounces water.
Subject Number: XX-XXXX
Treatment Duration: As directed
Clinical Batch Number: XXXXXXX
Expiration Date: TBD
Storage: Store at controlled room temperature
Study Sponsor: Clear Creek Bio, Inc., 585 Massachusetts Avenue, 4th Floor, Cambridge MA 02139
Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

8.8.3 Blinding and Randomization

The trial will be conducted in an open-label manner with random assignment to standard of care or standard of care plus brequinar. The brequinar capsules will be provided to each participating institution in bulk to be dispensed by the institution's pharmacist for each subject. Randomization assignments will be provided by the sponsor.

8.8.4 Unblinding/Expectedness

It is not necessary to break the blind for this open label study as the treatment will be known for each subject.

Expectedness will be determined by establishing whether the 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.

8.8.5 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, used and discarded. It must be clear from the records whether the subject received study medication or was assigned to standard of care. 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.

8.9 Prohibited Medications

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

8.10 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 telephone or other digital media. Study information is to be collected from the EHR as much as possible such as NEWS2 Assessments, height, weight, hematology/chemistry, from Progress Notes for AEs, and from medication records for new or changed concomitant medications. Visits to an outpatient laboratory post hospital discharge may be required if subjects are not able or permitted to return for follow up study visits.

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). Remdesivir may be used in this clinical trial as a component of standard of care of patients hospitalized with severe disease in settings where remdesivir is available via the Emergency Use Authorization (EUA).

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), 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.

Signed written informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to signing the informed consent but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. An original signed informed consent form will be subject to review by the Sponsor; a copy will be given to the subject and a copy will be filed with the subject's medical notes.

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.

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

NEWS2 Assessments, laboratory assessments, SARS-CoV-2 testing, and other observations will be conducted by experienced personnel throughout the study based on the Schedule of Events. The majority of study information is to be collected from the EHR. Phone calls or other digital media and outpatient visits for hematology/chemistry samples may be required to complete some study assessments if the subject is discharged prior to Study Day 15.

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), bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium), lactate dehydrogenase (LDH).

Inflammatory markers including D-dimer, ferritin, CRP, ESR, troponin, fibrinogen, and procalcitonin may be collected locally if available by the Institution. Additional inflammatory markers will be collected and analyzed by a central laboratory, as specified in the Laboratory Manual. A sample is to be collected for DHO and brequinar pharmacokinetics at the timepoints specified in the Laboratory Manual.

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

If urinalysis is clinically indicated, collect results from the EHR.

Nasopharyngeal swabs for SARS-CoV-2 viral load, inflammatory markers, and DHO samples will be collected Days 1, 3, 5, 7, and 15 (standardized collection instructions available in the supplied Laboratory Manual; please use the same nostril each time). Samples may be banked for future retrospective analyses.

NEWS2 Criteria are available in Appendix C Section 15.3.

Hospitalization status is to be recorded as hospitalized not in ICU, hospitalized in ICU, or discharged.

9.5 Study Conduct

Screening Visit (Since hospital admission)

These procedures must be completed since hospital admission and prior to starting dosing. Obtain the subject's written informed consent (be sure to note time of consent), then collect baseline information from the EHR. Do not perform study specific procedures for data available from the EHR. For Screening/Day 1 use the EHR results closest to the visit to confirm subject eligibility.

- Demographics (date of birth, gender, race, ethnicity, height and weight).
- Recent (within one year unless ongoing), relevant medical/surgical history and concomitant medications.
- Date of first symptom.
- Record any new or changed adverse events and new or changed concomitant medications since signing the ICF.
- Record any clinically significant abnormal physical examination findings as recorded in EHR.
- Hematology/chemistry from EHR.

- Ensure negative pregnancy test result is present in the EHR for women of childbearing potential (WOCBP).
- Polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay for SARS-CoV-2 infection (may utilize test results from external laboratory to meet entry criteria provided such results are accurately documented and can be confirmed).
- Confirm subject meets all inclusion and no exclusion criteria.

Treatment

The treatment period is up to 5 days: standard of care alone (SOC) or SOC + brequinar 100 mg daily for 5 days. Data points such as NEWS2 Assessments are to be collected from the EHR when possible, a separate visit by study staff is not to be conducted. The first dose of brequinar is to be given as soon as possible depending on availability of investigational pharmacy staff. If the subject is discharged from the hospital prior to Day 15, see Section 8.5 for how and when to conduct study assessments.

It is understood that some assessments may not be conducted if the subject is unable to return to the clinic after discharge due to restricted travel or if the study visit cannot be conducted remotely; this will not be counted as a protocol deviation. Collect information from the EHR, medication records and Progress Notes whenever possible

Days 1 - 7 (8 AM ± 8 hours)

- If Day 1 is different date from Screening, confirm subject continues to meet all inclusion and no exclusion criteria.
- Randomize the subject (record date and time of randomization).
- Review Progress Notes and medication records to collect any new or changes to ongoing adverse events or new or changed concomitant medications since previous visit (may be omitted on Day 1 if Screening visit was conducted on same day as Study Day 1). Repeat daily until discharge.
- Collect SOC hematology/chemistry results from the EHR beginning on Day 1 (pre-dose) (may be omitted for Day 1 if Screening visit conducted on same date as Study Day 1) then daily through Day 7 or until the clinician decides daily testing is no longer necessary. Ensure that Day 1 samples are obtained prior to first dose of study drug, if applicable.
- Days 1 (pre-dose), 3, 5, 7:
  - Collect NEWS2 Assessments from the EHR.
  - Collect results for inflammatory markers from EHR for those analyzed locally; collect, process and ship samples for DHO/brequinar PK and cytokine panel to be analyzed at the central laboratory per the Laboratory Manual.
  - Collect and process SARS-CoV-2 nasopharyngeal viral load samples.
  - Record hospitalization status (hospitalized, hospitalized in ICU, discharged) (Day 1 already recorded as part of Inclusion criteria, do not record again).
- Dispense study medication (Days 1 through 5 if in brequinar group) and record date and time of brequinar administration. Keep the drug administration interval as close as possible

to 24 hours. Ensure Day 1 labs are drawn prior to first brequinar dose on Day 1. If a subject taking brequinar is discharged prior to Day 5, administer final dose on day of discharge. Do not give subject study drug to take home.

- Drug accountability Day 7 ± 2 days.

Final Visit Day 15 (8 AM ± 2 days) or Hospital Discharge Day if earlier than Day 15

- Review Progress Notes and the medication record to collect information for any adverse events or new concomitant medications since Day 7 (from EHR if subject still hospitalized, otherwise by phone or other digital media).
- Collect results for SOC hematology/chemistry from the EHR if subject still hospitalized.
- Collect inflammatory markers from EHR for those analyzed locally; collect samples for DHO and cytokine panel to be analyzed at the central laboratory if subject still hospitalized.
- Collect NEWS2 Assessments from the EHR.
- Collect nasopharyngeal viral load sample.
- Collect hospital status (hospitalized, hospitalized in ICU, discharged).

Day 29 (8 AM ± 3 days)

- Determine survival status from EHR if available or contact the subject by phone call/digital media as acceptable to the institution.

If the subject is being discharged before Day 15, follow the procedures outlined in Section 8.5.

9.5.1 Unscheduled Visits

Unscheduled visits and tests to assess AEs/SAEs are permitted as needed providing the AE related to study drug or SAE onset occurs within two (2) weeks after the final study dose.

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. Provided that activities are carried out within the identified windows it will not be necessary to file a protocol deviation. It is understood that some scheduled study assessments may not be able to be conducted if the subject is unable to return to the clinic after discharge due to COVID-19 restricted travel; it is also understood that crowded hospital conditions/lack of personnel may make it impossible to carry out all requested study procedures; this will not be counted as a protocol deviation. The Day 7 and 15 visits are to be conducted via telephone if the subject has been discharged from the hospital with lab draws for subjects in the brequinar treatment group as described in Section 8.5.

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 be withdrawn from the study 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 evaluations for subjects who withdraw from the study 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).

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 15. After Day 15, collect/record only Serious Adverse Events (SAEs) or those judged 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.

Any serious adverse events (SAEs) experienced after 30 days post the last dose of study drug should only be reported to the sponsor if the investigator suspects a causal relationship to the 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, or require therapy.

Death due to disease progression should not be reported as an SAE. Report death from disease progression on the appropriate electronic data capture form.

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 progression of the disease under study.

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 descriptions and grading scales found in the revised National Cancer Institute (NCI) Common Terminology *Criteria for Adverse Events (CTCAE) version 4.03* will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html)*.

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 descriptions and grading scales found in the revised NCI CTCAE version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria. The CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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:

- 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, or
- is a congenital anomaly / birth defect;
- all other events that are 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 the studied indication, 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;
- Note that 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 is not an SAE.

Death due to disease progression is considered to be an Expected event in patients with severe SARS-CoV-2 infection and does not require reporting on an expedited basis.

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 the Sponsor contact until the event has subsided or, in case of permanent impairment, it stabilizes, and the overall clinical outcome has been ascertained.

SAE REPORTING EMAIL: Safety-CCB-CRISIS-01@prosoftclinical.com

Medical Monitor:

Sharon Levy, MD	Telephone:	O: (484) 320-2062

Sponsor Representative:

Barbara Powers, MSN, Ph.D.	Telephone:	M: 484-686-0545
	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 Medical Monitor 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 is to 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 the Medical Monitor/Sponsor. Follow-up information is to be subsequently communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs are to 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 knowledge by the Medical Monitor/Sponsor.

The Medical Monitor/Sponsor or designee must 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 the Sponsor Contact 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 pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should also be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as 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-up with 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 initially be hospitalized as in-patients and will be under the care of highly qualified infectious disease, critical care, and associated medical personnel. As is standard of care for moderately to severely ill in-patients, daily samples will be obtained for hematology assessments including complete blood count with full differential (WBC, RBC, hemoglobin, hematocrit, platelet count, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils). Any clinically significant out-of-range laboratory values will be assessed by hospital staff in a timely manner and treatment needs addressed as appropriate. 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 Clear Creek Medical Monitor will assess the available hematology data on a weekly 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, the Sponsor, and the Medical Monitor. In addition, the Data Safety Monitoring Board 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.

Subjects who are discharged from the hospital before Day 7 will have follow up contacts with study staff (phone calls or other digital media) on Days 7, 15 and 29. Early discharge subjects in the brequinar treatment group will also have samples for safety labs (hematology and chemistry) obtained either at the research facility or at an outpatient laboratory on Study Days 7 ± 2 and 15 ± 2. The safety laboratory results are to be initially assessed in real time by the Principal Investigator or designated person and the Medical Monitor. 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-hospital assessments and phone call visits will specifically ask about possible hematologic toxicity including any evidence of the list below. Early discharge 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 Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be established to provide independent oversight to this trial. The primary responsibility of the DSMB 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 DSMB will be detailed in a separate DSMB charter. The DSMB 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 DSMB Chair will advise the Sponsor that the study be stopped, the design changed, or that the study may continue per protocol.

10.9.1 DSMB Safety Review Schedule

The DSMB is to review adverse events and safety laboratory assessments after the first six subjects complete Day 5 of treatment, and again after the first 12 subjects complete Day 5 of treatment.

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 analyses will be based on the ITT population, which is defined as all randomized subjects.

11.2 Safety Analyses

Safety and tolerability will be assessed in terms of AEs, SAEs, NEWS2 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 NEWS2 Assessments will be summarized using appropriate descriptive statistics.

11.3 Efficacy Analyses

Efficacy will be assessed in terms of mortality, hospitalization status and duration, NEWS2 score, viral load (plasma and nasopharyngeal), and inflammatory markers.

11.4 DHO and Brequinar Concentration Levels

DHO and brequinar concentrations levels will be summarized using descriptive statistics.

11.5 Sample Size Considerations

Formal sample size calculations are not applicable for this phase 1a, open label study. Up to 24 subjects are planned to be entered in this trial. Additional subjects may be enrolled following data review.

11.6 Randomization

A randomization scheme will be provided by the Sponsor to ensure subjects are randomly assigned to SOC or SOC + brequinar in a 1:2 ratio.

11.7 Pooling of Study Centers

Not applicable to this small, early phase study.

11.8 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.

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) 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.

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21. Study DUP 785-034 Clinical Study Report (on file with Clear Creek)
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15 APPENDICES

15.1 Appendix A: CCB-CRISIS-01 Schedule of Events

CCB-CRISIS-01 Schedule of Events **Procedures**	**Screen**	**D1**	**D2 - D7 (± 8 hours)**	**Final Visit D15 (± 2 days)**	**F/U Phone Call 2 weeks/ Survival (± 3 days)**
Informed Consent	X				
AE/Concomitant Medications (daily until discharge)	X	X	D1-7	X	
Medical history / History of current illness	X				
Demographics, collect Height and weight	X				
Check for Physical Exam abnormalities	X				
Pregnancy Test (urine or serum)	X				
Hematology/Chemistry	X	X (pre-dose)	D1-7	X	
Inflammatory Markers*		X (pre-dose)	D3, D5, D7	X	
DHO/brequinar PK Sample Collection & Processing		X (pre-dose)	D3, D5, D7	X (DHO only)	
Swab collection for nasopharyngeal viral load		X (pre-dose)	D3, D5, D7	X	
Clinical SARS-CoV-2 testing RT-PCR	X				
Hospital Status			D3, D5, D7	X	
NEWS2 Assessments		X	D3, D5, D7	X	
Dispense Study Medication if assigned to brequinar		X	D2 – 5		
Drug Accountability			D7		
Survival Assessment Day 29					X

Collect information from available electronic health record (EHR), Progress Notes, and medication records; a special visit by research staff is not to be performed. Results for Hematology, Chemistry and available inflammatory markers analyzed locally are to be obtained from the EHR; do not draw another set of labs. Missed samples due to hospital staff too busy or for technical reasons unable to obtain samples will not be counted as protocol deviations. Record urinalysis results if urinalysis is clinically indicated and results are available in the EHR.

Note that any visits other than Screening/Day 1 may be conducted via telephone or digital media. Missed samples/assessments when phone visits occur will not be counted as protocol deviations.

*Inflammatory markers are to be collected from the EHR when available; otherwise process and ship samples to the central laboratory per the Laboratory Manual. DHO and brequinar samples will also be sent to the central laboratory.

Note that if the subject is discharged before Day 15, ensure safety laboratory samples for hematology and chemistry are obtained prior to discharge and on an outpatient basis when feasible per Section 8.5.

15.2 Appendix B: Investigator's Statement and Agreement

STUDY NUMBER: CCB-CRISIS-01

STUDY TITLE: The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19).

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: _____

Site Address:

_____

_____

15.3 Appendix C: National Early Warning Score (NEWS2)

Chart 1: The NEWS scoring system

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Use SpO_2 Scale 2 if target range is 88 – 92%, e.g., in hypercapnic respiratory failure.

National Early Warning System Score (NEWS) 2 Royal College of Physicians 2017 [14].

15.4 Appendix D: Massachusetts General Hospital COVID-19 Treatment Guidance.

Recommended daily labs: • CBC with diff • CMP • CPK (creatine kinase)	If Clinically Indicated: • Blood cultures • For acute kidney injury- urinalysis and spot urine protein creatinine • Procalcitonin • IL-6
Recommended repeated labs q 2-3 days: • D-dimer • Ferritin/CRP/ESR • LDH • Troponin • Baseline ECG	Radiology: • Chest X-ray at admission
Viral Serologies: • HBV serologies (sAb, cAb, sAg) • HCV antibody • HIV ½ Ab/Ag	

Risk Factors for COVID-19 Progression:

Epidemiological - Category 1	
Age > 65	Vital Signs – Category 2
Pre-existing pulmonary disease	Respiratory Rate > 24 breaths per minute
Chronic kidney disease	Heart rate > 125 beats per minute
Diabetes with A1c > 7.6%	Sp02 ≤ 93%
History of hypertension	
History of cardiovascular disease	Labs – Category 3
Obesity (BMI > 30)	D-dimer > 1000 ng/mL
Use of biologics	CRP > 100
History of transplant or other immunosuppression	LDH > 245 U/L
HIV, CD4 cell count < 200 or unknown CD4 count	Elevated troponin
	Admission absolute lymphocyte count < 0.8
	Ferritin > 500 µg/L

STUDY PROTOCOL

The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)

Study No: CCB-CRISIS-01

Version Date: 31 JULY 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
DSMB	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-01 SYNOPSIS	
IND	149291
Title	The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)
Protocol	CCB-CRISIS-01
Rationale	Brequinar is a potent DHODH inhibitor that has been studied in more than 1,000 cancer, psoriasis, and organ transplant patients. 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. 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 primary dose-limiting adverse effects have included thrombocytopenia and mucositis. The CRISIS trial will study standard of care (SOC) and SOC with 5 days of DHODH inhibition. 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. 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. Brequinar has not been previously tested as an anti-viral.
Investigational Product and Dosage	Subjects will be randomized in a 1:2 ratio to either standard of care (SOC) alone, or SOC + brequinar. Brequinar is available as 100 mg oral capsules. Five once daily doses of brequinar 100 mg are to be administered on Study Days 1 – 5 for those assigned to the SOC + brequinar group.

	Treatment assignment will be randomized, open label.
Primary Objective	● To determine the safety and tolerability of SOC and SOC plus brequinar in hospitalized COVID-19 subjects.
Secondary Objectives	● To determine the rates of/changes in clinical status measures listed through Day 15: – Hospitalization status – Duration of hospitalization – NEWS2 Score ● Mortality through Day 29
Exploratory Objectives	• To determine the change in SARS-CoV-2 nasopharyngeal viral load through Day 15 ● To determine the change in inflammatory markers through Day 15 ● To determine the change in DHO levels through Day 15 ● To determine the change in brequinar concentration levels through Day 7
Design	This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive SOC per institutional guidelines for treatment of patients with COVID-19 infection. In addition to SOC, the brequinar group will receive brequinar 100 mg once daily for 5 days. Subjects will have a Screening Visit followed as soon as possible with Study Day 1 (Day 1 may take place on the same day if entry criteria data are available). Study procedures are presented in detail in the procedures section, see below. Subjects will be followed through Day 15. Mortality will be assessed at Day 29. See below for instructions regarding hospital discharge prior to Day 15. Hematology and chemistry results and study information such as NEWS2 criteria are to be collected using the available EHR data as much as possible to avoid extra procedures for the study.
Sample Size:	Approximately 24 subjects will be randomized to either standard of care or standard of care plus brequinar in a 1:2 ratio (approximately 8 assigned to standard of care and 16 subjects on brequinar).
Number of Sites:	1 - 8
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. If discharged from the hospital prior to Study Day 15 or if follow up is needed for study drug-related adverse event, willing to go to an outpatient facility if feasible or be in contact with the study team (phone call or other digital media) for remaining study assessments. 4. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay. 5. Hospitalized (in patient with expected duration ≥ 24 hours) 6. 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. 7. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of brequinar. 8. ≤ 10 days since first COVID-19 symptom as determined by treating clinician. 9. COVID-19 symptoms of severity mild (fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea), moderate (any symptom of mild illness or shortness of breath with exertion), or severe (any symptom of moderate illness or shortness of breath at rest, or respiratory distress). 10. COVID-19 signs of severity mild (no clinical signs), moderate (respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute) or severe (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300)
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. Active malignancy other than squamous cell carcinoma; anticancer treatment such as chemotherapy or radiation therapy within the past month.

	3. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test. 4. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide), tacrolimus, sirolimus. 5. Platelets ≤150,000 cell/mm^3. 6. Hemoglobin < 12 gm/dL 7. Absolute neutrophil count < 1500 cells/mm^3 8. Renal dysfunction, i.e., creatinine clearance < 30 mL/min 9. AST and/or ALT > 1.5 ULN, or total bilirubin > ULN 10. History of bleeding disorders or recent surgery in the six weeks preceding enrollment 11. Concomitant use of agents known to cause bone marrow suppression leading to thrombocytopenia 12. History of gastrointestinal ulcer, or history of gastrointestinal bleeding. 13. History of hepatitis B and/or C infection, active liver disease and/or cirrhosis. 14. 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). 15. Baseline COVID-19 severity characterized as "Critical" based on the FDA Guidance "COVID-19: Developing Drugs and Biological Products for the Treatment or Prevention (https://www.fda.gov/media/137926/download). Evidence of critical illness defined by at least one of the following: 1. Respiratory failure based on resource utilization requiring at least one of the following: 1. Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies may not be able to be administered in setting of resource limitation) 2. Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors) 16. Multi-organ dysfunction/failure.

Treatment	All subjects will receive standard of care (SOC) per institutional guidelines. Subjects will be randomly assigned to SOC alone or SOC plus brequinar 100 mg daily x 5 days.
Stopping Criteria	Individual Criteria: • Participants who develop a Grade 3 symptomatic 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 symptomatic 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. Study-Level Stopping Criteria: The study is to be stopped as shown below: • If ≥ 4 subjects on the brequinar treatment arm develop the same Grade 3 or 4 adverse event or symptomatic laboratory abnormality • If ≥ 8 subjects on the brequinar treatment arm develop any Grade 3 or 4 adverse event or symptomatic laboratory abnormality.
DSMB	A Data Safety Monitoring Board (DSMB) will meet periodically to review the safety and scientific conduct of the study. At a minimum, the DSMB is to review adverse events and safety laboratory assessments after the first six subjects complete Day 5 of treatment, and again after the first 12 subjects complete Day 5 of treatment.
Procedures	**Screening Visit (Since hospital admission)** Results of these procedures must be available in the EHR and completed since hospital admission. Obtain the subject's written informed consent (be sure to note time of consent), then collect baseline information. Collect information from EHR. Do not perform study-specific procedures for data available from EHR. • Demographics (height, weight, date of birth, gender, race, ethnicity). • Recent (within one year unless ongoing), relevant medical/surgical history and concomitant medications. • Date of first symptom. • Record any clinically significant abnormal physical examination findings. • Ensure EHR has negative pregnancy test result for women of childbearing potential (WOCBP).

	• Record any adverse events that occurred since signing the ICF. • Record any new or changed concomitant medications since signing the ICF. Concomitant medications information is to include the medication, dosage, and duration of administration. • Hematology/chemistry from EHR for Inclusion/Exclusion criteria check. • Polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay for SARS-CoV-2 infection (may utilize test results from external laboratory to meet entry criteria provided such results are accurately documented and can be confirmed). • Confirm subject meets all inclusion and no exclusion criteria. **Treatment** The treatment period is up to 5 days: standard of care alone (SOC) or SOC + brequinar 100 mg daily x 5 days. Data points such as NEWS2 Assessments and safety labs are to be collected from the EHR, a separate visit by study staff is not to be performed. Give the first dose of brequinar as soon as possible after randomization. See below regarding hospital discharge prior to Day 15. **Days 1 – 7 (8 AM ± 8 hours):** • If Day 1 is different date from Screening, confirm subject continues to meet all inclusion and no exclusion criteria. • Randomize subject and record the time and date of randomization. • Review Progress Notes and medication records to collect any new or ongoing adverse events or new or changed concomitant medications since previous visit (may be omitted on Day 1 if Screening visit is conducted on same day as Study Day 1). Repeat daily through hospital discharge. • Collect SOC hematology/chemistry results from EHR on Day 1 (pre-dose) (may be omitted for Day 1 if Screening visit conducted on same date as Study Day 1) then daily through Day 7 or until the clinician decides daily testing is no longer necessary. Ensure that Day 1 samples are obtained prior to first dose of study drug, if applicable. • Days 1 (pre-dose), 3, 5, 7: – Collect NEWS2 Assessments from EHR. – Collect results for inflammatory markers from EHR for those analyzed locally; collect, process and ship samples for DHO/brequinar PK and cytokine panel to be analyzed at the central laboratory per the Laboratory Manual. – Collect, process, and ship nasopharyngeal viral load samples. – Record hospitalization status (hospitalized, hospitalized in ICU, discharged); subject must be hospitalized Day 1 to meet inclusion criteria, do not record again.

	• Dispense study medication (Days 1 through 5 if in brequinar group). Keep the brequinar study drug administration interval to 24h as much as possible. Record date and time of study drug administration. • Drug accountability Day 7 ± 2 days. **Final Visit Day 15** (8 AM ± 2 days) • Review Progress Notes and medication records to collect information for any new adverse events or changes in ongoing adverse events or new or changed concomitant medications since Day 7 (collect from EHR if subject still hospitalized, otherwise by phone or other digital media). • Collect SOC hematology/chemistry results from EHR if subject still hospitalized. • Collect results for inflammatory markers from EHR for those analyzed locally; collect and process samples for DHO and cytokine panel to be analyzed at the central laboratory on. • Collect and process nasopharyngeal viral load samples. • Record hospitalization status (hospitalized, hospitalized in ICU, discharged). • Collect NEWS2 Assessments from EHR. • If the subject is being discharged prior to Day 15, follow procedures below. **Day 29 (8 AM ± 3 Days)** • Determine survival status from EHR if available or by telephone/digital media per institutional guidelines. <u>Hospital Discharge Before Day 15</u> Subjects discharged from the hospital prior to the Day 15 visit are to return to a research facility when feasible for the remaining study visits. All scheduled study assessments are to be completed at these visits when conducted at a research facility. For subjects in the brequinar treatment group discharged from the hospital prior to Day 5, the subject is to take home the remaining doses of brequinar for daily self-administration. All subjects (brequinar and SOC) should have the scheduled assessments, e.g. lab samples and the nasopharyngeal swab, on the day of discharge and enter these results on the appropriate EDC page. Following discharge, subjects are to return to the research or out-patient lab collection facility for the remaining study visits, if feasible. Out-patient lab results are to be entered into the EDC and reviewed by a member of the study team. It is important that every effort be made to have subjects return at least on Days 7 and 15, if feasible. Subjects in the brequinar group are to record brequinar dosing on the medication diary provided by the study team. The study team will arrange for the subject to return any unused study medication to the research facility.

	For all subjects, if discharge occurs on Days 10, 11, or 12, ensure a hematology/chemistry sample has been obtained on the day of discharge and record these results on the appropriate EDC page. Following discharge, the subject is to return to the research or out-patient lab collection facility for the Day 15 visit if feasible. Out-patient lab results are to be entered into the EDC and reviewed by a member of the study team. If discharge occurs on Days 13, 14 or 15, complete the Day 15 Final Visit activities prior to discharge. No further visits are required unless follow up is needed for a study drug-related AE or an SAE; the Day 29 mortality assessment is still to take place. If the subject is unable or not permitted to return for planned study visits, the visit activities will be conducted by contacting the subject (phone or other digital media) except for the lab draw. The hematology/chemistry sample will be obtained via outpatient laboratory, if feasible and the results entered into the EDC and reviewed by the study team. Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF. A subject is considered completed the study if they have assessments through Day 15, whether conducted in the hospital or contacted via phone or other digital media.
Safety/ Tolerability	**Safety/Tolerability** Adverse events will be collected from the time of informed consent through Day 15. After Day 15, collect/record only Serious Adverse Events (SAEs) or those judged by the Investigator or designated person to be related to study drug, including but not limited to potential hematologic toxicities. Post-randomization adverse events will be those with an onset after the date and time of randomization. Subjects who develop Grade 3 or 4 toxicities are to be re-evaluated every 2 days, as feasible, until the toxicity returns to Grade $\leq$ 2 severity.
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, safety laboratory data, and NEWS2 Assessments. Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of post randomization adverse events, defined as AEs 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, NEWS2 Criteria, and other clinical measures will be summarized using appropriate descriptive statistics.

STUDY PERSONNEL

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3 INTRODUCTION

3.1 Background

3.2 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]).

3.2.1 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]).

3.3 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.

3.4 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.

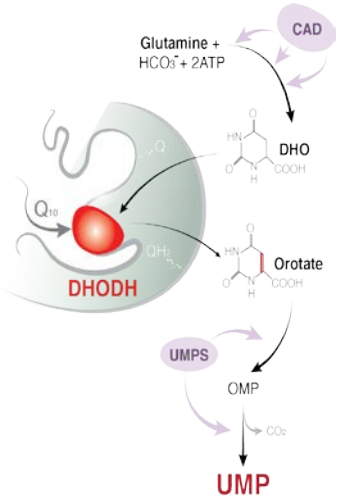

Figure 3-1. DHODH is a mitochondrial enzyme that catalyzes the 4th step of pyrimidine synthesis; it is completely essential for the generation of UMP.

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]).

3.5 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]).

3.6 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 CRISIS trial will study standard of care (SOC) and SOC with 5 days of DHODH inhibition. 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.

3.6.1 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 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 reassuring the safety of this regimen (see Brequinar IB [5]).

3.6.2 Risk/Benefit of Brequinar

As presented in the Brequinar IB [5], an extensive database exists with more than 800 cancer patients 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. Brequinar has also been utilized at lower doses than used in the cancer studies in 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. While no DHODHi has been tested to date in the clinic for infection with SARS-CoV-2 and no brequinar safety information is available in treatment of this disease, DHODHi therapy in the context of trials for patients with cancer has the expected safety side-effects of mucositis and bone marrow suppression. 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 mucositis and only 1 (2.6%) episode of mild thrombocytopenia. The 100 mg per day dose proposed for administration in this study should be safe and well tolerated.

The possible 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. As discussed above, inhibition of DHODH is expected to reduce the ability of the virus to replicate and it is for this reason that study CCB-CRISIS-01 will administer brequinar to patients with COVID-19.

3.7 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration of 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.

COVID-19 patients are at higher risk of complications and poor outcomes when their infection is combined with comorbidities including hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease (COPD) or asthma, cardiovascular disease (coronary artery disease or congestive heart failure), liver cirrhosis, age > 65, and BMI > 30 [15]. It is likely that participants in this protocol who are sick enough to be hospitalized will have at least one of these comorbidities.

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).

3.8 Possible Interactions with Concomitant Medical Treatments

While not previously tested in patients with viral infections, brequinar has been administered to subjects taking a variety of concomitant medications that are typical in severely ill cancer patients. 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. Brequinar has also been used concomitantly with antibiotics, antifungals and other critical care medications.

There is no experience with brequinar for treatment of SARS-CoV-2 and other severe viral infections and no formal interaction studies have been conducted.

3.8.1 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).

3.9 Steps to be Taken to Control or Mitigate Risks

All subjects will be treated in the hospital setting by highly experienced infectious disease or other critical care specialists and other qualified staff familiar with the treatment of severe viral infections and their complications. Subjects will be followed for study purposes through at least Day 15 even if improved enough to be discharged from the hospital.

Subjects in the Brequinar Treatment Group

If the subject is in the brequinar treatment group and is being discharged prior to completing the study, ensure a hematology/chemistry sample is obtained prior to discharge on the day of discharge. The subject is to return to the research or out-patient facility for the Days 7 and 15 visits if able and permitted. If unable or not permitted to return to the research facility due to COVID-19 restrictions, the remaining visit activities except for the lab draw will be conducted by phone

or other digital media. The lab draw will be performed by an outpatient laboratory at a designated facility. Lab draws for any outpatient visits for the Day 7 and 15 visits are limited to safety labs (hematology and chemistry). Additional outpatient laboratory or study visits are to be conducted as needed for follow up of adverse events including hematologic toxicities.

4 TRIAL OBJECTIVES

4.1 Primary Objective

- To determine the safety and tolerability of standard of care (SOC) and SOC plus brequinar in hospitalized COVID-19 subjects.

4.2 Secondary Objectives

The secondary objectives of this study are:

- To determine the changes in clinical status measures listed through Day 15:
  - Hospitalization status
  - Duration of hospitalization
  - National Early Warning System 2 Score (NEWS2) Score
- To determine survival status through Day 29

4.3 EXPLORATORY OBJECTIVES

- To determine the change in SARS-CoV-2 nasopharyngeal viral load through Day 15
- To determine the change in inflammatory markers through Day 15
- To determine the change in dihydroorotate dehydrogenase (DHO) through Day 15
- To determine the change in brequinar concentration levels through Day 7

5 TRIAL DESIGN

This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive standard of care per institutional guidelines for treatment of patients with SARS-CoV-2 infection. In addition to standard of care, the brequinar group will receive brequinar 100 mg once daily for 5 days.

The Massachusetts General Hospital (MGH) COVID-19 Treatment Guidance is provided in Appendix D Section 15.4. This guidance provides an example of standard of care instructions for treatment of COVID-19. The guidance is provided as informational only, it is not required that this guidance be used for treatment as standards of care may differ between institutions.

Subjects will have a Screening Visit followed as soon as possible with Study Day 1 (Day 1 may take place on the same day if entry criteria data are available). Study procedures are presented in detail in Section 8. Subjects will be followed through Day 15, with mortality assessed via a phone call/other digital media acceptable to institution on Day 29.

If the subject is being discharged prior to Day 7, see Section 8.5.

It is understood that some assessments may not be conducted if the subject is unable to return to the clinic after discharge due to restricted travel. If an assessment is missed due to after hospital discharge, e.g., samples or blood draws, this will not be counted as a protocol deviation. Any of the study visits may be conducted via telephone if the subject has been discharged from the hospital and is not permitted to or is unable to return to the hospital/clinic for these visits.

Information is to be collected using the electronic health record (EHR) whenever possible. It is not required to perform study-specific laboratory assessments, NEWS 2 assessments, etc. separately for study purposes.

6 TRIAL ENDPOINTS

6.1 Primary Endpoint

- Safety/tolerability measured by rates of post randomization adverse events and hematology/chemistry safety labs.

6.2 Secondary Endpoints

- Rates of/changes to the below clinical status measures through Day 15.
  - Hospitalization status
  - Duration of hospitalization in days
  - NEWS2 Assessments Days 1, 3, 5, 7, and Day 15 for hospitalized subjects.
- Mortality through Day 29

6.3 EXPLORATORY Endpoints

- SARS-CoV-2 nasopharyngeal viral load: Day 1 (pre-dose), Days 3, 5, 7, and 15
- Inflammatory markers (to be specified in the Laboratory Manual, may include but are not limited to erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), D-dimer, serum ferritin, and fibrinogen, procalcitonin, IL-6, IL-5, IL-2, IFN-ɣ, final list to be determined) on Day 1 pre-dose, D3, D5, D7, D15 or at frequency per institutional standard of care. The markers are to be tested locally when possible; requested tests as listed in the Laboratory Manual that are not analyzed locally are to be shipped to the central laboratory for analysis.
- DHO concentration levels through Day 15.
- Brequinar concentration levels through Day 7

7 TRIAL POPULATION

7.1 Number of Subjects

Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 24 subjects have completed the study. Subjects will be randomized to either standard of care or standard of care plus brequinar or in a 1:2: ratio (approximately 8 subjects assigned to standard of care alone and approximately 16 subjects on standard of care plus brequinar).

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. If discharged from the hospital prior to Study Day 15 or if follow up is needed for study drug-related adverse event, willing to go to an outpatient facility if feasible or be in contact with the study team (phone call or other digital media) for remaining study assessments.
4. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other Food and Drug Administration (FDA)-cleared commercial or public health assay.
5. Hospitalized (in patient with expected duration ≥ 24 hours)
6. 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.
7. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of brequinar.
8. ≤ 10 days since first COVID-19 symptom as determined by treating clinician.
9. COVID-19 symptoms of severity mild (fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea), moderate (any symptom of mild illness or shortness of breath with exertion), or severe (any symptom of moderate illness or shortness of breath at rest, or respiratory distress). [22].
10. COVID-19 signs of severity mild (no clinical signs), moderate (respiratory rate ≥ 20 breaths per minute, saturation of oxygen (SpO2) > 93% on room air at sea level, heart rate ≥ 90 beats per minute) or severe (respiratory rate ≥ 30 per minute, heart rate ≥ 125 per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300) [22].

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. Active malignancy other than squamous cell carcinoma; anticancer treatment such as chemotherapy or radiation therapy within the past month.
3. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test.
4. Treatment with another DHODH inhibitor (e.g., leflunomide or teriflunomide), tacrolimus, sirolimus.
5. Platelets ≤150,000 cell/mm^3.
6. Hemoglobin < 12 gm/dL
7. Absolute neutrophil count < 1500 cells/mm^3
8. Renal dysfunction, i.e., creatinine clearance < 30 mL/min
9. AST and/or ALT > 1.5 ULN, or total bilirubin > ULN
10. History of bleeding disorders or recent surgery in the six weeks preceding enrollment
11. Concomitant use of agents known to cause bone marrow suppression leading to thrombocytopenia
12. History of gastrointestinal ulcer, or history of gastrointestinal bleeding.
13. History of hepatitis B and/or C infection, active liver disease and/or cirrhosis.
14. 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).
15. Baseline COVID-19 severity characterized as “Critical” based on the FDA Guidance “COVID-19: Developing Drugs and Biological Products for the Treatment or Prevention (https://www.fda.gov/media/137926/download). Evidence of critical illness defined by at least one of the following:
    a. Respiratory failure based on resource utilization requiring at least one of the following:
        i. Endotracheal intubation and mechanical ventilation, oxygen delivered by high-flow nasal cannula (heated, humidified oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies may not be able to be administered in setting of resource limitation)
    b. Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)

16. Multi-organ dysfunction/failure. See [22].

7.4 Inclusion of Women and Minorities

Adult men and women of all races and ethnic groups are eligible for this trial.

8 STUDY TREATMENTS

8.1 Description of Study Medications

8.1.1 Brequinar

Brequinar will be supplied as 100 mg capsules. Dosing will be a single 5-day course of brequinar 100 mg once daily for 5 doses. The initial brequinar dose (Day 1) should be administered as soon as possible based on study drug availability from the investigational pharmacy. At least the first dose of study medication is to be taken in the hospital. Subjects in the brequinar group discharged before Day 5 will be dispensed brequinar to take at home daily until all 5 doses have been taken.

8.2 Treatment Administration

This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive standard of care (SOC) per institutional guidelines for SARS-CoV-2 infection. Subjects will be randomly assigned in a 1:2 ratio to standard of care alone or standard of care plus brequinar. The brequinar dosing interval should be 24h ± 6h. If discharged prior to Day 5, the subject may take any remaining doses once a day at home. In this case, the subject is to record dosing using a medication diary provided by the study team. The diary information will be provided to the study team either verbally or electronically or during an in-person visit.

8.2.1 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE).

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 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 (Study 785-001 [16], 785-003 [17], and 785-005 [18]) with five consecutive days of intravenous (IV) brequinar dosing and 168 subjects, there were no toxic deaths. For subjects from these three studies who were treated with a dose of 100 mg or below (as will be dosed in CCB-CRISIS-01), 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 [19], 785-031 [20] , and 785-034 [21]), 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 15 (or longer if needed to follow up study drug-related adverse events). Mortality is assessed via a phone call or other digital media at Day 29.

After treatment, participants will be monitored through at least Study Day 15 (or longer if needed to follow study drug-related AEs/SAEs). 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 symptomatic 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 symptomatic 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

Following assessment by the Data Safety Monitoring Board (DSMB, see Section 10.9), the study is to be stopped as shown below:

- If ≥ 4 subjects on the brequinar treatment arm develop the same Grade 3 or 4 adverse event or symptomatic laboratory abnormality
- If ≥ 8 subjects on the brequinar treatment arm develop any Grade 3 or 4 adverse event or symptomatic laboratory abnormality.

8.5 Hospital Discharge Prior to Study Day 15

Subjects discharged from the hospital prior to the Day 15 visit are to return to a research facility when feasible for the remaining study visits. All scheduled study assessments are to be completed at these visits when conducted at a research facility.

For subjects in the brequinar treatment group discharged from the hospital prior to Day 5, the subject is to take home the remaining doses of brequinar for daily self-administration. All subjects (brequinar and SOC) should have the scheduled assessments, e.g. lab samples and the nasopharyngeal swab, on the day of discharge and enter these results on the appropriate EDC page. Following discharge, subjects are to return to the research or out-patient lab collection facility for the remaining study visits, if feasible. Out-patient lab results are to be entered into the EDC and reviewed by a member of the study team. It is important that every effort be made to have subjects return at least on Days 7 and 15, if feasible. Subjects in the brequinar group are to record brequinar dosing on the medication diary provided by the study team. The study team will arrange for the subject to return any unused study medication to the research facility.

For all subjects, if discharge occurs on Days 10, 11, or 12, ensure a hematology/chemistry sample has been obtained on the day of discharge and record these results on the appropriate EDC page. Following discharge, the subject is to return to the research or out-patient lab collection facility for the Day 15 visit, if feasible. Out-patient lab results are to be entered into the EDC and reviewed by a member of the study team.

If discharge occurs on Days 13, 14 or 15, complete the Day 15 Final Visit activities prior to discharge. No further visits are required unless follow up is needed for a study drug-related AE or an SAE; the Day 29 mortality assessment is still to take place.

If the subject is unable or not permitted to return for planned study visits, the visit activities will be conducted by contacting the subject (phone or other digital media) except for the lab draw. The lab draw will be completed at a research facility or an outpatient laboratory, if feasible, and the results entered into the EDC and reviewed by the study team.

Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF. A subject is considered completed the study if they have assessments through Day 15, whether conducted in the hospital or contacted via phone or other digital media.

8.6 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 8.9.

8.7 Treatment Compliance

Compliance will be assessed by reviewing the subject's EHR, the study medication diary when applicable, and other study records as appropriate.

8.8 Storage, Stability, Labeling and Packaging

8.8.1 Storage and Stability

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

8.8.2 Labeling and Packaging

Each brequinar bottle/dispensing container for subject use will be labeled with at least the following information:

For Clinical Trial Use Only

Study Number: CCB-CRISIS-01

Contents: Brequinar 100 mg capsules

For oral use only. Take with approximately 8 ounces water.

Subject Number: XX-XXXX

Treatment Duration: As directed

Clinical Batch Number: XXXXXXX

Expiration Date: TBD

Storage: Store at controlled room temperature

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

Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

8.8.3 Blinding and Randomization

The trial will be conducted in an open-label manner with random assignment to standard of care or standard of care plus brequinar. The brequinar capsules will be provided to each participating institution in bulk to be dispensed by the institution's pharmacist for each subject. Randomization assignments will be provided by the sponsor.

8.8.4 Unblinding/Expectedness

It is not necessary to break the blind for this open label study as the treatment will be known for each subject.

Expectedness will be determined by establishing whether the 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.

8.8.5 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, used and discarded. It must be clear from the records whether the subject received study medication or was assigned to standard of care. 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.

Subjects in the brequinar group who are discharged prior to Day 5 will be given a study medication diary for recording at home treatment administration. The diary information will be collected by

the study team either verbally or electronically or in person during a visit to the research facility. Unused study drug at the patient's home is to be returned to the research facility.

At the end of the study, any unused study drug in the pharmacy will be returned to the Sponsor for destruction or may be destroyed locally; disposition of study drug will be documented. The study team will make arrangements for the subject to return any unused study medication to the research facility.

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.

8.9 Prohibited Medications

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

8.10 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 telephone or other digital media. Study information is to be collected from the EHR as much as possible such as NEWS2 Assessments, height, weight, hematology/chemistry, from Progress Notes for AEs, and from medication records for new or changed concomitant medications. Visits to an outpatient laboratory post hospital discharge may be required if subjects are not able or permitted to return to the research facility for follow up study visits.

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). Remdesivir may be used in this clinical trial as a component of standard of care of patients hospitalized with severe disease in settings where remdesivir is available via the Emergency Use Authorization (EUA) or other FDA approval.

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), 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.

Signed written informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to signing the informed consent but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. An original signed informed consent form will be subject to review by the Sponsor; a copy will be given to the subject and a copy will be filed with the subject's medical notes.

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.

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

NEWS2 Assessments, laboratory assessments, SARS-CoV-2 testing, and other observations will be conducted by experienced personnel throughout the study based on the Schedule of Events. The majority of study information is to be collected from the EHR. Phone calls or other digital media and outpatient visits for hematology/chemistry samples may be required to complete some study assessments if the subject is discharged prior to Study Day 15.

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), bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium), lactate dehydrogenase (LDH).

Inflammatory markers including D-dimer, ferritin, CRP, ESR, troponin, fibrinogen, and procalcitonin may be collected locally if available by the Institution. Additional inflammatory markers will be collected and analyzed by a central laboratory, as specified in the Laboratory Manual. A sample is to be collected for DHO and brequinar pharmacokinetics at the timepoints specified in the Laboratory Manual.

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

If urinalysis is clinically indicated, collect results from the EHR.

Nasopharyngeal swabs for SARS-CoV-2 viral load, inflammatory markers, and DHO samples will be collected Days 1, 3, 5, 7, and 15 (standardized collection instructions available in the supplied Laboratory Manual; please use the same nostril each time). Samples may be banked for future retrospective analyses.

NEWS2 Criteria are available in Appendix C Section 15.3.

Hospitalization status is to be recorded as hospitalized not in ICU, hospitalized in ICU, or discharged.

9.5 Study Conduct

Screening Visit (Since hospital admission)

These procedures must be completed since hospital admission and prior to starting dosing. Obtain the subject's written informed consent (be sure to note time of consent), then collect baseline information from the EHR. Do not perform study specific procedures for data available from the EHR. For Screening/Day 1 use the EHR results closest to the visit to confirm subject eligibility.

- Demographics (date of birth, gender, race, ethnicity, height and weight).
- Recent (within one year unless ongoing), relevant medical/surgical history and concomitant medications.
- Date of first symptom.
- Record any new or changed adverse events and new or changed concomitant medications since signing the ICF.
- Record any clinically significant abnormal physical examination findings as recorded in EHR.
- Hematology/chemistry from EHR.

- Ensure negative pregnancy test result is present in the EHR for women of childbearing potential (WOCBP).
- Polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay for SARS-CoV-2 infection (may utilize test results from external laboratory to meet entry criteria provided such results are accurately documented and can be confirmed).
- Confirm subject meets all inclusion and no exclusion criteria.

Treatment

The treatment period is up to 5 days: standard of care alone (SOC) or SOC + brequinar 100 mg daily for 5 days. Data points such as NEWS2 Assessments are to be collected from the EHR when possible, a separate visit by study staff is not to be conducted. The first dose of brequinar is to be given as soon as possible depending on availability of investigational pharmacy staff. If the subject is discharged from the hospital prior to Day 15, see Section 8.5 for how and when to conduct study assessments.

It is understood that some assessments may not be conducted if the subject is unable to return to the clinic after discharge due to restricted travel or if the study visit cannot be conducted remotely; this will not be counted as a protocol deviation. Collect information from the EHR, medication records and Progress Notes whenever possible

Days 1 - 7 (8 AM ± 8 hours)

- If Day 1 is a different date from Screening, confirm subject continues to meet all inclusion and no exclusion criteria.
- Randomize the subject (record date and time of randomization).
- Review Progress Notes and medication records to collect any new or changes to ongoing adverse events or new or changed concomitant medications since previous visit (may be omitted on Day 1 if Screening visit was conducted on same day as Study Day 1). Repeat daily until discharge.
- Collect SOC hematology/chemistry results from the EHR beginning on Day 1 (pre-dose) (may be omitted for Day 1 if Screening visit conducted on same date as Study Day 1) then daily through Day 7 or until the clinician decides daily testing is no longer necessary. Ensure that Day 1 samples are obtained prior to first dose of study drug, if applicable.
- Days 1 (pre-dose), 3, 5, 7:
  - Collect NEWS2 Assessments from the EHR.
  - Collect results for inflammatory markers from EHR for those analyzed locally; collect, process and ship samples for DHO/brequinar PK and cytokine panel to be analyzed at the central laboratory per the Laboratory Manual.
  - Collect and process SARS-CoV-2 nasopharyngeal viral load samples.
  - Record hospitalization status (hospitalized, hospitalized in ICU, discharged) (Day 1 already recorded as part of Inclusion criteria, do not record again).
- Dispense study medication (Days 1 through 5 if in brequinar group) and record date and time of brequinar administration. Keep the drug administration interval as close as possible

to 24 hours. Ensure Day 1 labs are drawn prior to first brequinar dose on Day 1. If a subject taking brequinar is discharged prior to Day 5, give the subject adequate study drug to take home along with a diary to record daily treatment administration through Day 5.

- Drug accountability Day 7 ± 2 days.

Final Visit Day 15 (8 AM ± 2 days)

- Review Progress Notes and the medication record to collect information for any adverse events or new concomitant medications since Day 7 (from EHR if subject still hospitalized, otherwise by phone or other digital media).
- Collect results for SOC hematology/chemistry from the EHR if subject still hospitalized.
- Collect inflammatory markers from EHR for those analyzed locally; collect samples for DHO and cytokine panel to be analyzed at the central laboratory if subject still hospitalized.
- Collect NEWS2 Assessments from the EHR.
- Collect nasopharyngeal viral load sample.
- Collect hospital status (hospitalized, hospitalized in ICU, discharged).

Day 29 (8 AM ± 3 days)

- Determine survival status from EHR if available or contact the subject by phone call/digital media as acceptable to the institution.

If the subject is being discharged before Day 15, follow the procedures outlined in Section 8.5.

9.5.1 Unscheduled Visits

Unscheduled visits and tests to assess AEs/SAEs are permitted as needed providing the AE related to study drug or SAE onset occurs within two (2) weeks after the final study dose.

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. Provided that activities are carried out within the identified windows it will not be necessary to file a protocol deviation. It is understood that some scheduled study assessments may not be able to be conducted if the subject is unable to return to the clinic after discharge due to COVID-19 restricted travel; it is also understood that crowded hospital conditions/lack of personnel may make it impossible to carry out all requested study procedures; this will not be counted as a protocol deviation. The Day 7 and 15 visits are to be conducted via telephone if the subject has been discharged from the hospital with lab draws for subjects in the brequinar treatment group as described in Section 8.5.

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 be withdrawn from the study 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 evaluations for subjects who withdraw from the study 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).

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 15. After Day 15, collect/record only Serious Adverse Events (SAEs) or those judged 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.

Any serious adverse events (SAEs) experienced after 30 days post the last dose of study drug should only be reported to the sponsor if the investigator suspects a causal relationship to the 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, or require therapy.

Death due to disease progression should not be reported as an SAE. Report death from disease progression on the appropriate electronic data capture form.

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 progression of the disease under study.

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 descriptions and grading scales found in the revised National Cancer Institute (NCI) Common Terminology *Criteria for Adverse Events (CTCAE) version 4.03* will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html)*.

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 descriptions and grading scales found in the revised NCI CTCAE version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria. The CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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:

- 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, or
- is a congenital anomaly / birth defect;
- all other events that are 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 the studied indication, 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;
- Note that 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 is not an SAE.

Death due to disease progression is considered to be an Expected event in patients with severe SARS-CoV-2 infection and does not require reporting on an expedited basis.

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 the Sponsor contact until the event has subsided or, in case of permanent impairment, it stabilizes, and the overall clinical outcome has been ascertained.

SAE REPORTING EMAIL: Safety-CCB-CRISIS-01@prosoftclinical.com

Medical Monitor:

Sharon Levy, MD	Telephone:	O: (484) 320-2062

Sponsor Representative:

Barbara Powers, MSN, Ph.D.	Telephone: Email:	M: 484-686-0545 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 Medical Monitor 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 is to 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 the Medical Monitor/Sponsor. Follow-up information is to be subsequently communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs are to 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 knowledge by the Medical Monitor/Sponsor.

The Medical Monitor/Sponsor or designee must 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 the Sponsor Contact 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 pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should also be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as 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-up with 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 initially be hospitalized as in-patients and will be under the care of highly qualified infectious disease, critical care, and associated medical personnel. As is standard of care for moderately to severely ill in-patients, daily samples will be obtained for hematology assessments including complete blood count with full differential (WBC, RBC, hemoglobin, hematocrit, platelet count, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils). Any clinically significant out-of-range laboratory values will be assessed by hospital staff in a timely manner and treatment needs addressed as appropriate. 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 Clear Creek Medical Monitor will assess the available hematology data on a weekly 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, the Sponsor, and the Medical Monitor. In addition, the Data Safety Monitoring Board 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.

Subjects who are discharged from the hospital before Day 7 will have follow up contacts with study staff (phone calls or other digital media) on Days 7, 15 and 29. Early discharge subjects in the brequinar treatment group will also have samples for safety labs (hematology and chemistry) obtained either at the research facility or at an outpatient laboratory on Study Days 7 ± 2 and 15 ± 2. The safety laboratory results are to be initially assessed in real time by the Principal Investigator or designated person and the Medical Monitor. 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-hospital assessments and phone call visits will specifically ask about possible hematologic toxicity including any evidence of the list below. Early discharge 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 Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be established to provide independent oversight to this trial. The primary responsibility of the DSMB 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 DSMB will be detailed in a separate DSMB charter. The DSMB 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 DSMB Chair will advise the Sponsor that the study be stopped, the design changed, or that the study may continue per protocol.

10.9.1 DSMB Safety Review Schedule

The DSMB is to review adverse events and safety laboratory assessments after the first six subjects complete Day 5 of treatment, and again after the first 12 subjects complete Day 5 of treatment.

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 analyses will be based on the ITT population, which is defined as all randomized subjects.

11.2 Safety Analyses

Safety and tolerability will be assessed in terms of AEs, SAEs, NEWS2 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 NEWS2 Assessments will be summarized using appropriate descriptive statistics.

11.3 Efficacy Analyses

Efficacy will be assessed in terms of mortality, hospitalization status and duration, NEWS2 score, viral load (plasma and nasopharyngeal), and inflammatory markers.

11.4 DHO and Brequinar Concentration Levels

DHO and brequinar concentrations levels will be summarized using descriptive statistics.

11.5 Sample Size Considerations

Formal sample size calculations are not applicable for this phase 1a, open label study. Up to 24 subjects are planned to be entered in this trial. Additional subjects may be enrolled following data review.

11.6 Randomization

A randomization scheme will be provided by the Sponsor to ensure subjects are randomly assigned to SOC or SOC + brequinar in a 1:2 ratio.

11.7 Pooling of Study Centers

Not applicable to this small, early phase study.

11.8 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.

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) 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.

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16. Study DUP 785-001 Clinical Study Report (on file with Clear Creek)
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19. Study DUP 785-022 Clinical Study Report (on file with Clear Creek)
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21. Study DUP 785-034 Clinical Study Report (on file with Clear Creek)
22. 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-01 Schedule of Events

CCB-CRISIS-01 Schedule of Events **Procedures**	**Screen**	**D1**	**D2 - D7 (± 8 hours)**	**Final Visit D15 (± 2 days)**	**F/U Phone Call 2 weeks/ Survival (± 3 days)**
Informed Consent	X				
AE/Concomitant Medications (daily until discharge)	X	X	D1-7	X	
Medical history / History of current illness	X				
Demographics, collect Height and weight	X				
Check for Physical Exam abnormalities	X				
Pregnancy Test (urine or serum)	X				
Hematology/Chemistry	X	X (pre-dose)	D1-7	X	
Inflammatory Markers*		X (pre-dose)	D3, D5, D7	X	
DHO/brequinar PK Sample Collection & Processing		X (pre-dose)	D3, D5, D7	X (DHO only)	
Swab collection for nasopharyngeal viral load		X (pre-dose)	D3, D5, D7	X	
Clinical SARS-CoV-2 testing RT-PCR	X				
Hospital Status			D3, D5, D7	X	
NEWS2 Assessments		X	D3, D5, D7	X	
Dispense Study Medication if assigned to brequinar**		X	D2 – 5		
Drug Accountability			D7		
Survival Assessment Day 29					X

Collect information from available electronic health record (EHR), Progress Notes, and medication records; a special visit by research staff is not to be performed. Results for Hematology, Chemistry and available inflammatory markers analyzed locally are to be obtained from the EHR; do not draw another set of labs. Missed samples due to hospital staff too busy or for technical reasons unable to obtain samples will not be counted as protocol deviations. Record urinalysis results if urinalysis is clinically indicated and results are available in the EHR. Note that if the subject is discharged before Day 15, follow instructions provided in Section 8.5.

Note that any visits other than Screening/Day 1 may be conducted via telephone or digital media. Missed samples/assessments when phone visits occur will not be counted as protocol deviations.

*Inflammatory markers are to be collected from the EHR when available; otherwise process and ship samples to the central laboratory per the Laboratory Manual. DHO and brequinar samples will also be sent to the central laboratory.

**If a subject in the brequinar group is discharged prior to Day 5 (has not completed taking brequinar all 5 days) the subject may be dispensed study medication to take at home on a daily basis. In this instance the subject is also to be provided with the study medication diary for drug accountability purposes.

15.2 Appendix B: Investigator's Statement and Agreement

STUDY NUMBER: CCB-CRISIS-01

STUDY TITLE: The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19).

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:** _____

Site Address:

_____

_____

15.3 Appendix C: National Early Warning Score (NEWS2)

Chart 1: The NEWS scoring system

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Use SpO_2 Scale 2 if target range is 88 – 92%, e.g., in hypercapnic respiratory failure.

National Early Warning System Score (NEWS) 2 Royal College of Physicians 2017 [14].

15.4 Appendix D: Massachusetts General Hospital COVID-19 Treatment Guidance.

Recommended daily labs: • CBC with diff • CMP • CPK (creatine kinase)	If Clinically Indicated: • Blood cultures • For acute kidney injury- urinalysis and spot urine protein creatinine • Procalcitonin • IL-6
Recommended repeated labs q 2-3 days: • D-dimer • Ferritin/CRP/ESR • LDH • Troponin • Baseline ECG	Radiology: • Chest X-ray at admission
Viral Serologies: • HBV serologies (sAb, cAb, sAg) • HCV antibody • HIV ½ Ab/Ag	

Risk Factors for COVID-19 Progression:

Epidemiological - Category 1	
Age > 65	Vital Signs – Category 2
Pre-existing pulmonary disease	Respiratory Rate > 24 breaths per minute
Chronic kidney disease	Heart rate > 125 beats per minute
Diabetes with A1c > 7.6%	Sp02 ≤ 93%
History of hypertension	
History of cardiovascular disease	Labs – Category 3
Obesity (BMI > 30)	D-dimer > 1000 ng/mL
Use of biologics	CRP > 100
History of transplant or other immunosuppression	LDH > 245 U/L
HIV, CD4 cell count < 200 or unknown CD4 count	Elevated troponin
	Admission absolute lymphocyte count < 0.8
	Ferritin > 500 µg/L

STUDY PROTOCOL

The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)

Study No: CCB-CRISIS-01

Version Date: 05 August 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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LIST OF FIGURES

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
DSMB	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-01 SYNOPSIS	
IND	149291
Title	The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)
Protocol	CCB-CRISIS-01
Rationale	Brequinar is a potent DHODH inhibitor that has been studied in more than 1,000 cancer, psoriasis, and organ transplant patients. 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. 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 primary dose-limiting adverse effects have included thrombocytopenia and mucositis. The CRISIS trial will study standard of care (SOC) and SOC with 5 days of DHODH inhibition. 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. 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. Brequinar has not been previously tested as an anti-viral.
Investigational Product and Dosage	Subjects will be randomized in a 1:2 ratio to either standard of care (SOC) alone, or SOC + brequinar. Brequinar is available as 100 mg oral capsules. Five once daily doses of brequinar 100 mg are to be administered on Study Days 1 – 5 for those assigned to the SOC + brequinar group.

	Treatment assignment will be randomized, open label.
Primary Objective	● To determine the safety and tolerability of SOC and SOC plus brequinar in hospitalized COVID-19 subjects.
Secondary Objectives	● To determine the rates of/changes in clinical status measures listed through Day 15: – Hospitalization status – Duration of hospitalization – NEWS2 Score ● Mortality through Day 29
Exploratory Objectives	• To determine the change in SARS-CoV-2 nasopharyngeal viral load through Day 15 ● To determine the change in inflammatory markers through Day 15 ● To determine the change in DHO levels through Day 15 ● To determine the change in brequinar concentration levels through Day 7
Design	This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive SOC per institutional guidelines for treatment of patients with COVID-19 infection. In addition to SOC, the brequinar group will receive brequinar 100 mg once daily for 5 days. Subjects will have a Screening Visit followed as soon as possible with Study Day 1 (Day 1 may take place on the same day if entry criteria data are available). Study procedures are presented in detail in the procedures section, see below. Subjects will be followed through Day 15. Mortality will be assessed at Day 29. See below for instructions regarding hospital discharge prior to Day 15. Hematology and chemistry results and study information such as NEWS2 criteria are to be collected using the available EHR data as much as possible to avoid extra procedures for the study.
Sample Size:	Approximately 24 subjects will be randomized to either standard of care or standard of care plus brequinar in a 1:2 ratio (approximately 8 assigned to standard of care and 16 subjects on brequinar).
Number of Sites:	1 - 8
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. If discharged from the hospital prior to Study Day 15 or if follow up is needed for study drug-related adverse event, willing to go to an outpatient facility if feasible or be in contact with the study team (phone call or other digital media) for remaining study assessments. 4. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay. 5. Hospitalized (in patient with expected duration ≥ 24 hours) 6. 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. 7. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of brequinar. 8. ≤ 10 days since first COVID-19 symptom as determined by treating clinician. 9. Able to swallow capsules. 10. 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, dysgeusia, or other symptom commonly associated with COVID-19.
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. Active malignancy other than squamous cell carcinoma; anticancer treatment such as chemotherapy or radiation therapy within the past month. 3. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test. 4. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide), tacrolimus, sirolimus.

	5. Platelets ≤150,000 cell/mm^3. 6. Hemoglobin < 10 gm/dL for menstruating women and < 12 gm/dL for all other subjects 7. Absolute neutrophil count < 1500 cells/mm^3 8. Renal dysfunction, i.e., creatinine clearance < 30 mL/min 9. AST and/or ALT > 1.5 ULN, or total bilirubin > ULN 10. History of bleeding disorders or recent surgery in the six weeks preceding enrollment 11. Concomitant use of agents known to cause bone marrow suppression leading to thrombocytopenia 12. History of gastrointestinal ulcer, or history of gastrointestinal bleeding. 13. History of hepatitis B and/or C infection, active liver disease and/or cirrhosis. 14. 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). 15. Life expectancy of < 5 days in the judgment of the treating clinician. 16. Evidence of critical illness defined by at least one of the following: a. Respiratory failure requiring at least one of the following: i. Endotracheal intubation and mechanical ventilation, noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies may not be able to be administered in setting of resource limitation) ii. Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors) b. Multi-organ dysfunction/failure.
Treatment	All subjects will receive standard of care (SOC) per institutional guidelines. Subjects will be randomly assigned to SOC alone or SOC plus brequinar 100 mg daily x 5 days.
Stopping Criteria	Individual Criteria: • Participants who develop a Grade 3 symptomatic 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 symptomatic 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. Study-Level Stopping Criteria: The study is to be stopped as shown below: • If ≥ 4 subjects on the brequinar treatment arm develop the same Grade 3 or 4 adverse event or symptomatic laboratory abnormality • If ≥ 8 subjects on the brequinar treatment arm develop any Grade 3 or 4 adverse event or symptomatic laboratory abnormality.
DSMB	A Data Safety Monitoring Board (DSMB) will meet periodically to review the safety and scientific conduct of the study. At a minimum, the DSMB is to review adverse events and safety laboratory assessments after the first six subjects complete Day 5 of treatment, and again after the first 12 subjects complete Day 5 of treatment.
Procedures	**Screening Visit (Since hospital admission)** Results of these procedures must be available in the EHR and completed since hospital admission. Obtain the subject's written informed consent (be sure to note time of consent), then collect baseline information. Collect information from EHR. Do not perform study-specific procedures for data available from EHR. • Demographics (height, weight, date of birth, gender, race, ethnicity). • Recent (within one year unless ongoing), relevant medical/surgical history and concomitant medications. • Date of first symptom. • Record any clinically significant abnormal physical examination findings. • Ensure EHR has negative pregnancy test result for women of childbearing potential (WOCBP). • Record any adverse events that occurred since signing the ICF. • Record any new or changed concomitant medications since signing the ICF. Concomitant medications information is to include the medication, dosage, and duration of administration. • Hematology/chemistry from EHR for Inclusion/Exclusion criteria check. • Polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay for SARS-CoV-2 infection (may utilize test results from

	external laboratory to meet entry criteria provided such results are accurately documented and can be confirmed). • Confirm subject meets all inclusion and no exclusion criteria. **Treatment** The treatment period is up to 5 days: standard of care alone (SOC) or SOC + brequinar 100 mg daily x 5 days. Data points such as NEWS2 Assessments and safety labs are to be collected from the EHR, a separate visit by study staff is not to be performed. Give the first dose of brequinar as soon as possible after randomization. See below regarding hospital discharge prior to Day 15. **Days 1 – 7 (8 AM ± 8 hours):** • If Day 1 is different date from Screening, confirm subject continues to meet all inclusion and no exclusion criteria. • Randomize subject and record the time and date of randomization. • Review Progress Notes and medication records to collect any new or ongoing adverse events or new or changed concomitant medications since previous visit (may be omitted on Day 1 if Screening visit is conducted on same day as Study Day 1). Repeat daily through hospital discharge. • Collect SOC hematology/chemistry results from EHR on Day 1 (pre-dose) (may be omitted for Day 1 if Screening visit conducted on same date as Study Day 1) then daily through Day 7 or until the clinician decides daily testing is no longer necessary. Ensure that Day 1 samples are obtained prior to first dose of study drug, if applicable. • Days 1 (pre-dose), 3, 5, 7: – Collect NEWS2 Assessments from EHR. – Collect results for inflammatory markers from EHR for those analyzed locally; collect, process and ship samples for DHO/brequinar PK and cytokine panel to be analyzed at the central laboratory per the Laboratory Manual. – Collect, process, and ship nasopharyngeal viral load samples. – Record hospitalization status (hospitalized, hospitalized in ICU, discharged); subject must be hospitalized Day 1 to meet inclusion criteria, do not record again. • Dispense study medication (Days 1 through 5 if in brequinar group). Keep the brequinar study drug administration interval to 24h as much as possible. Record date and time of study drug administration. • Drug accountability Day 7 ± 2 days. **Final Visit Day 15** (8 AM ± 2 days) • Review Progress Notes and medication records to collect information for any new adverse events or changes in ongoing adverse events or new or

	changed concomitant medications since Day 7 (collect from EHR if subject still hospitalized, otherwise by phone or other digital media). • Collect SOC hematology/chemistry results from EHR if subject still hospitalized. • Collect results for inflammatory markers from EHR for those analyzed locally; collect and process samples for DHO and cytokine panel to be analyzed at the central laboratory on. • Collect and process nasopharyngeal viral load samples. • Record hospitalization status (hospitalized, hospitalized in ICU, discharged). • Collect NEWS2 Assessments from EHR. • If the subject is being discharged prior to Day 15, follow procedures below. **Day 29 (8 AM ± 3 Days)** • Determine survival status from EHR if available or by telephone/digital media per institutional guidelines. <u>Hospital Discharge Before Day 15</u> Subjects discharged from the hospital prior to the Day 15 visit are to return to a research facility when feasible for the remaining study visits. All scheduled study assessments are to be completed at these visits when conducted at a research facility. For subjects in the brequinar treatment group discharged from the hospital prior to Day 5, the subject is to take home the remaining doses of brequinar for daily self-administration. All subjects (brequinar and SOC) should have the scheduled assessments, e.g. lab samples and the nasopharyngeal swab, on the day of discharge and enter these results on the appropriate EDC page. Following discharge, subjects are to return to the research or out-patient lab collection facility for the remaining study visits, if feasible. Out-patient lab results are to be entered into the EDC and reviewed by a member of the study team. It is important that every effort be made to have subjects return at least on Days 7 and 15, if feasible. Subjects in the brequinar group are to record brequinar dosing on the medication diary provided by the study team. The study team will arrange for the subject to return any unused study medication to the research facility. For all subjects, if discharge occurs on Days 10, 11, or 12, ensure a hematology/chemistry sample has been obtained on the day of discharge and record these results on the appropriate EDC page. Following discharge, the subject is to return to the research or out-patient lab collection facility for the Day 15 visit if feasible. Out-patient lab results are to be entered into the EDC and reviewed by a member of the study team. If discharge occurs on Days 13, 14 or 15, complete the Day 15 Final Visit activities prior to discharge. No further visits are required unless follow up is needed for a

	study drug-related AE or an SAE; the Day 29 mortality assessment is still to take place. If the subject is unable or not permitted to return for planned study visits, the visit activities will be conducted by contacting the subject (phone or other digital media) except for the lab draw. The hematology/chemistry sample will be obtained via outpatient laboratory, if feasible and the results entered into the EDC and reviewed by the study team. Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF. A subject is considered completed the study if they have assessments through Day 15, whether conducted in the hospital or contacted via phone or other digital media.
Safety/ Tolerability	**Safety/Tolerability** Adverse events will be collected from the time of informed consent through Day 15. After Day 15, collect/record only Serious Adverse Events (SAEs) or those judged by the Investigator or designated person to be related to study drug, including but not limited to potential hematologic toxicities. Post-randomization adverse events will be those with an onset after the date and time of randomization. Subjects who develop Grade 3 or 4 toxicities are to be re-evaluated every 2 days, as feasible, until the toxicity returns to Grade $\leq$ 2 severity.
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, safety laboratory data, and NEWS2 Assessments. Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of post randomization adverse events, defined as AEs 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, NEWS2 Criteria, and other clinical measures will be summarized using appropriate descriptive statistics.

STUDY PERSONNEL

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3 INTRODUCTION

3.1 Background

3.2 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]).

3.2.1 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]).

3.3 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.

3.4 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.

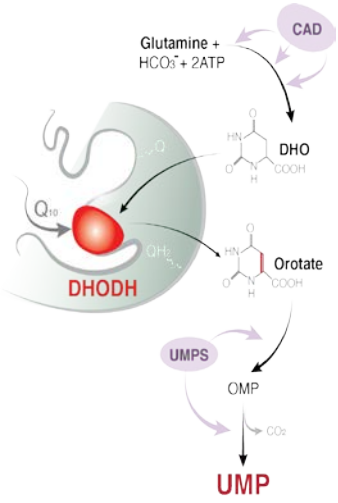

Figure 3-1. DHODH is a mitochondrial enzyme that catalyzes the 4th step of pyrimidine synthesis; it is completely essential for the generation of UMP.

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]).

3.5 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]).

3.6 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 CRISIS trial will study standard of care (SOC) and SOC with 5 days of DHODH inhibition. 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.

3.6.1 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 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 reassuring the safety of this regimen (see Brequinar IB [5]).

3.6.2 Risk/Benefit of Brequinar

As presented in the Brequinar IB [5], an extensive database exists with more than 800 cancer patients 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. Brequinar has also been utilized at lower doses than used in the cancer studies in 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. While no DHODHi has been tested to date in the clinic for infection with SARS-CoV-2 and no brequinar safety information is available in treatment of this disease, DHODHi therapy in the context of trials for patients with cancer has the expected safety side-effects of mucositis and bone marrow suppression. 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 mucositis and only 1 (2.6%) episode of mild thrombocytopenia. The 100 mg per day dose proposed for administration in this study should be safe and well tolerated.

The possible 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. As discussed above, inhibition of DHODH is expected to reduce the ability of the virus to replicate and it is for this reason that study CCB-CRISIS-01 will administer brequinar to patients with COVID-19.

3.7 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration of 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.

COVID-19 patients are at higher risk of complications and poor outcomes when their infection is combined with comorbidities including hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease (COPD) or asthma, cardiovascular disease (coronary artery disease or congestive heart failure), liver cirrhosis, age > 65, and BMI > 30 [15]. It is likely that participants in this protocol who are sick enough to be hospitalized will have at least one of these comorbidities.

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).

3.8 Possible Interactions with Concomitant Medical Treatments

While not previously tested in patients with viral infections, brequinar has been administered to subjects taking a variety of concomitant medications that are typical in severely ill cancer patients. 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. Brequinar has also been used concomitantly with antibiotics, antifungals and other critical care medications.

There is no experience with brequinar for treatment of SARS-CoV-2 and other severe viral infections and no formal interaction studies have been conducted.

3.8.1 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).

3.9 Steps to be Taken to Control or Mitigate Risks

All subjects will be treated in the hospital setting by highly experienced infectious disease or other critical care specialists and other qualified staff familiar with the treatment of severe viral infections and their complications. Subjects will be followed for study purposes through at least Day 15 even if improved enough to be discharged from the hospital.

Subjects in the Brequinar Treatment Group

If the subject is in the brequinar treatment group and is being discharged prior to completing the study, ensure a hematology/chemistry sample is obtained prior to discharge on the day of discharge. The subject is to return to the research or out-patient facility for the Days 7 and 15 visits if able and permitted. If unable or not permitted to return to the research facility due to COVID-19 restrictions, the remaining visit activities except for the lab draw will be conducted by phone

or other digital media. The lab draw will be performed by an outpatient laboratory at a designated facility. Lab draws for any outpatient visits for the Day 7 and 15 visits are limited to safety labs (hematology and chemistry). Additional outpatient laboratory or study visits are to be conducted as needed for follow up of adverse events including hematologic toxicities.

4 TRIAL OBJECTIVES

4.1 Primary Objective

- To determine the safety and tolerability of standard of care (SOC) and SOC plus brequinar in hospitalized COVID-19 subjects.

4.2 Secondary Objectives

The secondary objectives of this study are:

- To determine the changes in clinical status measures listed through Day 15:
  - Hospitalization status
  - Duration of hospitalization
  - National Early Warning System 2 Score (NEWS2) Score
- To determine survival status through Day 29

4.3 EXPLORATORY OBJECTIVES

- To determine the change in SARS-CoV-2 nasopharyngeal viral load through Day 15
- To determine the change in inflammatory markers through Day 15
- To determine the change in dihydroorotate dehydrogenase (DHO) through Day 15
- To determine the change in brequinar concentration levels through Day 7

5 TRIAL DESIGN

This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive standard of care per institutional guidelines for treatment of patients with SARS-CoV-2 infection. In addition to standard of care, the brequinar group will receive brequinar 100 mg once daily for 5 days.

The Massachusetts General Hospital (MGH) COVID-19 Treatment Guidance is provided in Appendix D Section 15.4. This guidance provides an example of standard of care instructions for treatment of COVID-19. The guidance is provided as informational only, it is not required that this guidance be used for treatment as standards of care may differ between institutions.

Subjects will have a Screening Visit followed as soon as possible with Study Day 1 (Day 1 may take place on the same day if entry criteria data are available). Study procedures are presented in detail in Section 8. Subjects will be followed through Day 15, with mortality assessed via a phone call/other digital media acceptable to institution on Day 29.

If the subject is being discharged prior to Day 7, see Section 8.5.

It is understood that some assessments may not be conducted if the subject is unable to return to the clinic after discharge due to restricted travel. If an assessment is missed due to after hospital discharge, e.g., samples or blood draws, this will not be counted as a protocol deviation. Any of the study visits may be conducted via telephone if the subject has been discharged from the hospital and is not permitted to or is unable to return to the hospital/clinic for these visits.

Information is to be collected using the electronic health record (EHR) whenever possible. It is not required to perform study-specific laboratory assessments, NEWS 2 assessments, etc. separately for study purposes.

6 TRIAL ENDPOINTS

6.1 Primary Endpoint

- Safety/tolerability measured by rates of post randomization adverse events and hematology/chemistry safety labs.

6.2 Secondary Endpoints

- Rates of/changes to the below clinical status measures through Day 15.
  - Hospitalization status
  - Duration of hospitalization in days
  - NEWS2 Assessments Days 1, 3, 5, 7, and Day 15 for hospitalized subjects.
- Mortality through Day 29

6.3 EXPLORATORY Endpoints

- SARS-CoV-2 nasopharyngeal viral load: Day 1 (pre-dose), Days 3, 5, 7, and 15
- Inflammatory markers (to be specified in the Laboratory Manual, may include but are not limited to erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), D-dimer, serum ferritin, and fibrinogen, procalcitonin, IL-6, IL-5, IL-2, IFN-ɣ, final list to be determined) on Day 1 pre-dose, D3, D5, D7, D15 or at frequency per institutional standard of care. The markers are to be tested locally when possible; requested tests as listed in the Laboratory Manual that are not analyzed locally are to be shipped to the central laboratory for analysis.
- DHO concentration levels through Day 15.
- Brequinar concentration levels through Day 7

7 TRIAL POPULATION

7.1 Number of Subjects

Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 24 subjects have completed the study. Subjects will be randomized to either standard of care or standard of care plus brequinar or in a 1:2: ratio (approximately 8 subjects assigned to standard of care alone and approximately 16 subjects on standard of care plus brequinar).

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. If discharged from the hospital prior to Study Day 15 or if follow up is needed for study drug-related adverse event, willing to go to an outpatient facility if feasible or be in contact with the study team (phone call or other digital media) for remaining study assessments.
4. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other Food and Drug Administration (FDA)-cleared commercial or public health assay.
5. Hospitalized (in patient with expected duration ≥ 24 hours)
6. 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.
7. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of brequinar.
8. ≤ 10 days since first COVID-19 symptom as determined by treating clinician.
9. Able to swallow capsules.
10. 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, dysgeusia, or other symptom commonly associated with COVID-19. [22].

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. Active malignancy other than squamous cell carcinoma; anticancer treatment such as chemotherapy or radiation therapy within the past month.

3. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test.
4. Treatment with another DHODH inhibitor (e.g., leflunomide or teriflunomide), tacrolimus, sirolimus.
5. Platelets ≤150,000 cell/mm^3.
6. Hemoglobin < 10 gm/dL for menstruating women and < 12 gm/dL for all other subjects
7. Absolute neutrophil count < 1500 cells/mm^3
8. Renal dysfunction, i.e., creatinine clearance < 30 mL/min
9. AST and/or ALT > 1.5 ULN, or total bilirubin > ULN
10. History of bleeding disorders or recent surgery in the six weeks preceding enrollment
11. Concomitant use of agents known to cause bone marrow suppression leading to thrombocytopenia
12. History of gastrointestinal ulcer, or history of gastrointestinal bleeding.
13. History of hepatitis B and/or C infection, active liver disease and/or cirrhosis.
14. 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).
15. Life expectancy of < 5 days in the judgment of the treating clinician.
16. Evidence of critical illness defined by at least one of the following:
    a. Respiratory failure requiring at least one of the following:
        i. Endotracheal intubation and mechanical ventilation, noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies may not be able to be administered in setting of resource limitation)
        ii. Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)
    b. Multi-organ dysfunction/failure. See [22].

7.4 Inclusion of Women and Minorities

Adult men and women of all races and ethnic groups are eligible for this trial.

8 STUDY TREATMENTS

8.1 Description of Study Medications

8.1.1 Brequinar

Brequinar will be supplied as 100 mg capsules. Dosing will be a single 5-day course of brequinar 100 mg once daily for 5 doses. The initial brequinar dose (Day 1) should be administered as soon as possible based on study drug availability from the investigational pharmacy. At least the first dose of study medication is to be taken in the hospital. Subjects in the brequinar group discharged before Day 5 will be dispensed brequinar to take at home daily until all 5 doses have been taken.

8.2 Treatment Administration

This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive standard of care (SOC) per institutional guidelines for SARS-CoV-2 infection. Subjects will be randomly assigned in a 1:2 ratio to standard of care alone or standard of care plus brequinar. The brequinar dosing interval should be 24h ± 6h. If discharged prior to Day 5, the subject may take any remaining doses once a day at home. In this case, the subject is to record dosing using a medication diary provided by the study team. The diary information will be provided to the study team either verbally or electronically or during an in-person visit.

8.2.1 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE).

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 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 (Study 785-001 [16], 785-003 [17], and 785-005 [18]) with five consecutive days of intravenous (IV) brequinar dosing and 168 subjects, there were no toxic deaths. For subjects from these three studies who were treated with a dose of 100 mg or below (as will be dosed in CCB-CRISIS-01), 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 [19], 785-031 [20] , and 785-034 [21]), 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 15 (or longer if needed to follow up study drug-related adverse events). Mortality is assessed via a phone call or other digital media at Day 29.

After treatment, participants will be monitored through at least Study Day 15 (or longer if needed to follow study drug-related AEs/SAEs). 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 symptomatic 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 symptomatic 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

Following assessment by the Data Safety Monitoring Board (DSMB, see Section 10.9), the study is to be stopped as shown below:

- If ≥ 4 subjects on the brequinar treatment arm develop the same Grade 3 or 4 adverse event or symptomatic laboratory abnormality
- If ≥ 8 subjects on the brequinar treatment arm develop any Grade 3 or 4 adverse event or symptomatic laboratory abnormality.

8.5 Hospital Discharge Prior to Study Day 15

Subjects discharged from the hospital prior to the Day 15 visit are to return to a research facility when feasible for the remaining study visits. All scheduled study assessments are to be completed at these visits when conducted at a research facility.

For subjects in the brequinar treatment group discharged from the hospital prior to Day 5, the subject is to take home the remaining doses of brequinar for daily self-administration. All subjects (brequinar and SOC) should have the scheduled assessments, e.g. lab samples and the nasopharyngeal swab, on the day of discharge and enter these results on the appropriate EDC page. Following discharge, subjects are to return to the research or out-patient lab collection facility for the remaining study visits, if feasible. Out-patient lab results are to be entered into the EDC and reviewed by a member of the study team. It is important that every effort be made to have subjects return at least on Days 7 and 15, if feasible. Subjects in the brequinar group are to record brequinar dosing on the medication diary provided by the study team. The study team will arrange for the subject to return any unused study medication to the research facility.

For all subjects, if discharge occurs on Days 10, 11, or 12, ensure a hematology/chemistry sample has been obtained on the day of discharge and record these results on the appropriate EDC page. Following discharge, the subject is to return to the research or out-patient lab collection facility for the Day 15 visit, if feasible. Out-patient lab results are to be entered into the EDC and reviewed by a member of the study team.

If discharge occurs on Days 13, 14 or 15, complete the Day 15 Final Visit activities prior to discharge. No further visits are required unless follow up is needed for a study drug-related AE or an SAE; the Day 29 mortality assessment is still to take place.

If the subject is unable or not permitted to return for planned study visits, the visit activities will be conducted by contacting the subject (phone or other digital media) except for the lab draw. The lab draw will be completed at a research facility or an outpatient laboratory, if feasible, and the results entered into the EDC and reviewed by the study team.

Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF. A subject is considered completed the study if they have assessments through Day 15, whether conducted in the hospital or contacted via phone or other digital media.

8.6 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 8.9.

8.7 Treatment Compliance

Compliance will be assessed by reviewing the subject's EHR, the study medication diary when applicable, and other study records as appropriate.

8.8 Storage, Stability, Labeling and Packaging

8.8.1 Storage and Stability

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

8.8.2 Labeling and Packaging

Each brequinar bottle/dispensing container for subject use will be labeled with at least the following information:

For Clinical Trial Use Only

Study Number: CCB-CRISIS-01

Contents: Brequinar 100 mg capsules

For oral use only. Take with approximately 8 ounces water.

Subject Number: XX-XXXX

Treatment Duration: As directed

Clinical Batch Number: XXXXXXX

Expiration Date: TBD

Storage: Store at controlled room temperature

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

Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

8.8.3 Blinding and Randomization

The trial will be conducted in an open-label manner with random assignment to standard of care or standard of care plus brequinar. The brequinar capsules will be provided to each participating institution in bulk to be dispensed by the institution's pharmacist for each subject. Randomization assignments will be provided by the sponsor.

8.8.4 Unblinding/Expectedness

It is not necessary to break the blind for this open label study as the treatment will be known for each subject.

Expectedness will be determined by establishing whether the 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.

8.8.5 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, used and discarded. It must be clear from the records whether the subject received study medication or was assigned to standard of care. 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.

Subjects in the brequinar group who are discharged prior to Day 5 will be given a study medication diary for recording at home treatment administration. The diary information will be collected by

the study team either verbally or electronically or in person during a visit to the research facility. Unused study drug at the patient's home is to be returned to the research facility.

At the end of the study, any unused study drug in the pharmacy will be returned to the Sponsor for destruction or may be destroyed locally; disposition of study drug will be documented. The study team will make arrangements for the subject to return any unused study medication to the research facility.

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.

8.9 Prohibited Medications

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

8.10 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 telephone or other digital media. Study information is to be collected from the EHR as much as possible such as NEWS2 Assessments, height, weight, hematology/chemistry, from Progress Notes for AEs, and from medication records for new or changed concomitant medications. Visits to an outpatient laboratory post hospital discharge may be required if subjects are not able or permitted to return to the research facility for follow up study visits.

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). Remdesivir may be used in this clinical trial as a component of standard of care of patients hospitalized with severe disease in settings where remdesivir is available via the Emergency Use Authorization (EUA) or other FDA approval.

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), 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.

Signed written informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to signing the informed consent but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. An original signed informed consent form will be subject to review by the Sponsor; a copy will be given to the subject and a copy will be filed with the subject's medical notes.

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.

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

NEWS2 Assessments, laboratory assessments, SARS-CoV-2 testing, and other observations will be conducted by experienced personnel throughout the study based on the Schedule of Events. The majority of study information is to be collected from the EHR. Phone calls or other digital media and outpatient visits for hematology/chemistry samples may be required to complete some study assessments if the subject is discharged prior to Study Day 15.

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), bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium), lactate dehydrogenase (LDH).

Inflammatory markers including D-dimer, ferritin, CRP, ESR, troponin, fibrinogen, and procalcitonin may be collected locally if available by the Institution. Additional inflammatory markers will be collected and analyzed by a central laboratory, as specified in the Laboratory Manual. A sample is to be collected for DHO and brequinar pharmacokinetics at the timepoints specified in the Laboratory Manual.

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

If urinalysis is clinically indicated, collect results from the EHR.

Nasopharyngeal swabs for SARS-CoV-2 viral load, inflammatory markers, and DHO samples will be collected Days 1, 3, 5, 7, and 15 (standardized collection instructions available in the supplied Laboratory Manual; please use the same nostril each time). Samples may be banked for future retrospective analyses.

NEWS2 Criteria are available in Appendix C Section 15.3.

Hospitalization status is to be recorded as hospitalized not in ICU, hospitalized in ICU, or discharged.

9.5 Study Conduct

Screening Visit (Since hospital admission)

These procedures must be completed since hospital admission and prior to starting dosing. Obtain the subject's written informed consent (be sure to note time of consent), then collect baseline information from the EHR. Do not perform study specific procedures for data available from the EHR. For Screening/Day 1 use the EHR results closest to the visit to confirm subject eligibility.

- Demographics (date of birth, gender, race, ethnicity, height and weight).
- Recent (within one year unless ongoing), relevant medical/surgical history and concomitant medications.
- Date of first symptom.
- Record any new or changed adverse events and new or changed concomitant medications since signing the ICF.
- Record any clinically significant abnormal physical examination findings as recorded in EHR.
- Hematology/chemistry from EHR.

- Ensure negative pregnancy test result is present in the EHR for women of childbearing potential (WOCBP).
- Polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay for SARS-CoV-2 infection (may utilize test results from external laboratory to meet entry criteria provided such results are accurately documented and can be confirmed).
- Confirm subject meets all inclusion and no exclusion criteria.

Treatment

The treatment period is up to 5 days: standard of care alone (SOC) or SOC + brequinar 100 mg daily for 5 days. Data points such as NEWS2 Assessments are to be collected from the EHR when possible, a separate visit by study staff is not to be conducted. The first dose of brequinar is to be given as soon as possible depending on availability of investigational pharmacy staff. If the subject is discharged from the hospital prior to Day 15, see Section 8.5 for how and when to conduct study assessments.

It is understood that some assessments may not be conducted if the subject is unable to return to the clinic after discharge due to restricted travel or if the study visit cannot be conducted remotely; this will not be counted as a protocol deviation. Collect information from the EHR, medication records and Progress Notes whenever possible

Days 1 - 7 (8 AM ± 8 hours)

- If Day 1 is a different date from Screening, confirm subject continues to meet all inclusion and no exclusion criteria.
- Randomize the subject (record date and time of randomization).
- Review Progress Notes and medication records to collect any new or changes to ongoing adverse events or new or changed concomitant medications since previous visit (may be omitted on Day 1 if Screening visit was conducted on same day as Study Day 1). Repeat daily until discharge.
- Collect SOC hematology/chemistry results from the EHR beginning on Day 1 (pre-dose) (may be omitted for Day 1 if Screening visit conducted on same date as Study Day 1) then daily through Day 7 or until the clinician decides daily testing is no longer necessary. Ensure that Day 1 samples are obtained prior to first dose of study drug, if applicable.
- Days 1 (pre-dose), 3, 5, 7:
  - Collect NEWS2 Assessments from the EHR.
  - Collect results for inflammatory markers from EHR for those analyzed locally; collect, process and ship samples for DHO/brequinar PK and cytokine panel to be analyzed at the central laboratory per the Laboratory Manual.
  - Collect and process SARS-CoV-2 nasopharyngeal viral load samples.
  - Record hospitalization status (hospitalized, hospitalized in ICU, discharged) (Day 1 already recorded as part of Inclusion criteria, do not record again).
- Dispense study medication (Days 1 through 5 if in brequinar group) and record date and time of brequinar administration. Keep the drug administration interval as close as possible

to 24 hours. Ensure Day 1 labs are drawn prior to first brequinar dose on Day 1. If a subject taking brequinar is discharged prior to Day 5, give the subject adequate study drug to take home along with a diary to record daily treatment administration through Day 5.

- Drug accountability Day 7 ± 2 days.

Final Visit Day 15 (8 AM ± 2 days)

- Review Progress Notes and the medication record to collect information for any adverse events or new concomitant medications since Day 7 (from EHR if subject still hospitalized, otherwise by phone or other digital media).
- Collect results for SOC hematology/chemistry from the EHR if subject still hospitalized.
- Collect inflammatory markers from EHR for those analyzed locally; collect samples for DHO and cytokine panel to be analyzed at the central laboratory if subject still hospitalized.
- Collect NEWS2 Assessments from the EHR.
- Collect nasopharyngeal viral load sample.
- Collect hospital status (hospitalized, hospitalized in ICU, discharged).

Day 29 (8 AM ± 3 days)

- Determine survival status from EHR if available or contact the subject by phone call/digital media as acceptable to the institution.

If the subject is being discharged before Day 15, follow the procedures outlined in Section 8.5.

9.5.1 Unscheduled Visits

Unscheduled visits and tests to assess AEs/SAEs are permitted as needed providing the AE related to study drug or SAE onset occurs within two (2) weeks after the final study dose.

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. Provided that activities are carried out within the identified windows it will not be necessary to file a protocol deviation. It is understood that some scheduled study assessments may not be able to be conducted if the subject is unable to return to the clinic after discharge due to COVID-19 restricted travel; it is also understood that crowded hospital conditions/lack of personnel may make it impossible to carry out all requested study procedures; this will not be counted as a protocol deviation. The Day 7 and 15 visits are to be conducted via telephone if the subject has been discharged from the hospital with lab draws for subjects in the brequinar treatment group as described in Section 8.5.

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 be withdrawn from the study 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 evaluations for subjects who withdraw from the study 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).

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 15. After Day 15, collect/record only Serious Adverse Events (SAEs) or those judged 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.

Any serious adverse events (SAEs) experienced after 30 days post the last dose of study drug should only be reported to the sponsor if the investigator suspects a causal relationship to the 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, or require therapy.

Death due to disease progression should not be reported as an SAE. Report death from disease progression on the appropriate electronic data capture form.

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 progression of the disease under study.

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 descriptions and grading scales found in the revised National Cancer Institute (NCI) Common Terminology *Criteria for Adverse Events (CTCAE) version 4.03* will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html)*.

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 descriptions and grading scales found in the revised NCI CTCAE version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria. The CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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:

- 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, or
- is a congenital anomaly / birth defect;
- all other events that are 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 the studied indication, 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;
- Note that 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 is not an SAE.

Death due to disease progression is considered to be an Expected event in patients with severe SARS-CoV-2 infection and does not require reporting on an expedited basis.

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 the Sponsor contact until the event has subsided or, in case of permanent impairment, it stabilizes, and the overall clinical outcome has been ascertained.

SAE REPORTING EMAIL: Safety-CCB-CRISIS-01@prosoftclinical.com

Medical Monitor:

Sharon Levy, MD	Telephone:	O: (484) 320-2062

Sponsor Representative:

Barbara Powers, MSN, Ph.D.	Telephone: Email:	M: 484-686-0545 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 Medical Monitor 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 is to 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 the Medical Monitor/Sponsor. Follow-up information is to be subsequently communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs are to 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 knowledge by the Medical Monitor/Sponsor.

The Medical Monitor/Sponsor or designee must 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 the Sponsor Contact 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 pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should also be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as 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-up with 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 initially be hospitalized as in-patients and will be under the care of highly qualified infectious disease, critical care, and associated medical personnel. As is standard of care for moderately to severely ill in-patients, daily samples will be obtained for hematology assessments including complete blood count with full differential (WBC, RBC, hemoglobin, hematocrit, platelet count, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils). Any clinically significant out-of-range laboratory values will be assessed by hospital staff in a timely manner and treatment needs addressed as appropriate. 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 Clear Creek Medical Monitor will assess the available hematology data on a weekly 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, the Sponsor, and the Medical Monitor. In addition, the Data Safety Monitoring Board 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.

Subjects who are discharged from the hospital before Day 7 will have follow up contacts with study staff (phone calls or other digital media) on Days 7, 15 and 29. Early discharge subjects in the brequinar treatment group will also have samples for safety labs (hematology and chemistry) obtained either at the research facility or at an outpatient laboratory on Study Days 7 ± 2 and 15 ± 2. The safety laboratory results are to be initially assessed in real time by the Principal Investigator or designated person and the Medical Monitor. 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-hospital assessments and phone call visits will specifically ask about possible hematologic toxicity including any evidence of the list below. Early discharge 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 Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be established to provide independent oversight to this trial. The primary responsibility of the DSMB 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 DSMB will be detailed in a separate DSMB charter. The DSMB 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 DSMB Chair will advise the Sponsor that the study be stopped, the design changed, or that the study may continue per protocol.

10.9.1 DSMB Safety Review Schedule

The DSMB is to review adverse events and safety laboratory assessments after the first six subjects complete Day 5 of treatment, and again after the first 12 subjects complete Day 5 of treatment.

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 analyses will be based on the ITT population, which is defined as all randomized subjects.

11.2 Safety Analyses

Safety and tolerability will be assessed in terms of AEs, SAEs, NEWS2 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 NEWS2 Assessments will be summarized using appropriate descriptive statistics.

11.3 Efficacy Analyses

Efficacy will be assessed in terms of mortality, hospitalization status and duration, NEWS2 score, viral load (plasma and nasopharyngeal), and inflammatory markers.

11.4 DHO and Brequinar Concentration Levels

DHO and brequinar concentrations levels will be summarized using descriptive statistics.

11.5 Sample Size Considerations

Formal sample size calculations are not applicable for this phase 1a, open label study. Up to 24 subjects are planned to be entered in this trial. Additional subjects may be enrolled following data review.

11.6 Randomization

A randomization scheme will be provided by the Sponsor to ensure subjects are randomly assigned to SOC or SOC + brequinar in a 1:2 ratio.

11.7 Pooling of Study Centers

Not applicable to this small, early phase study.

11.8 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.

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) 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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16. Study DUP 785-001 Clinical Study Report (on file with Clear Creek)
17. Study DUP 785-003 Clinical Study Report (on file with Clear Creek)

18. Study DUP 785-005 Clinical Study Report (on file with Clear Creek)
19. Study DUP 785-022 Clinical Study Report (on file with Clear Creek)
20. Study DUP 785-031 Clinical Study Report (on file with Clear Creek)
21. Study DUP 785-034 Clinical Study Report (on file with Clear Creek)
22. 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-01 Schedule of Events

CCB-CRISIS-01 Schedule of Events **Procedures**	**Screen**	**D1**	**D2 - D7 (± 8 hours)**	**Final Visit D15 (± 2 days)**	**F/U Phone Call 2 weeks/ Survival (± 3 days)**
Informed Consent	X				
AE/Concomitant Medications (daily until discharge)	X	X	D1-7	X	
Medical history / History of current illness	X				
Demographics, collect Height and weight	X				
Check for Physical Exam abnormalities	X				
Pregnancy Test (urine or serum)	X				
Hematology/Chemistry	X	X (pre-dose)	D1-7	X	
Inflammatory Markers*		X (pre-dose)	D3, D5, D7	X	
DHO/brequinar PK Sample Collection & Processing		X (pre-dose)	D3, D5, D7	X (DHO only)	
Swab collection for nasopharyngeal viral load		X (pre-dose)	D3, D5, D7	X	
Clinical SARS-CoV-2 testing RT-PCR	X				
Hospital Status			D3, D5, D7	X	
NEWS2 Assessments		X	D3, D5, D7	X	
Dispense Study Medication if assigned to brequinar**		X	D2 – 5		
Drug Accountability			D7		
Survival Assessment Day 29					X

Collect information from available electronic health record (EHR), Progress Notes, and medication records; a special visit by research staff is not to be performed. Results for Hematology, Chemistry and available inflammatory markers analyzed locally are to be obtained from the EHR; do not draw another set of labs. Missed samples due to hospital staff too busy or for technical reasons unable to obtain samples will not be counted as protocol deviations. Record urinalysis results if urinalysis is clinically indicated and results are available in the EHR. Note that if the subject is discharged before Day 15, follow instructions provided in Section 8.5.

Note that any visits other than Screening/Day 1 may be conducted via telephone or digital media. Missed samples/assessments when phone visits occur will not be counted as protocol deviations.

*Inflammatory markers are to be collected from the EHR when available; otherwise process and ship samples to the central laboratory per the Laboratory Manual. DHO and brequinar samples will also be sent to the central laboratory.

**If a subject in the brequinar group is discharged prior to Day 5 (has not completed taking brequinar all 5 days) the subject may be dispensed study medication to take at home on a daily basis. In this instance the subject is also to be provided with the study medication diary for drug accountability purposes.

15.2 Appendix B: Investigator's Statement and Agreement

STUDY NUMBER: CCB-CRISIS-01

STUDY TITLE: The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19).

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:** _____

Site Address:

_____

_____

15.3 Appendix C: National Early Warning Score (NEWS2)

Chart 1: The NEWS scoring system

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Use SpO_2 Scale 2 if target range is 88 – 92%, e.g., in hypercapnic respiratory failure.

National Early Warning System Score (NEWS) 2 Royal College of Physicians 2017 [14].

15.4 Appendix D: Massachusetts General Hospital COVID-19 Treatment Guidance.

Recommended daily labs: • CBC with diff • CMP • CPK (creatine kinase)	If Clinically Indicated: • Blood cultures • For acute kidney injury- urinalysis and spot urine protein creatinine • Procalcitonin • IL-6
Recommended repeated labs q 2-3 days: • D-dimer • Ferritin/CRP/ESR • LDH • Troponin • Baseline ECG	Radiology: • Chest X-ray at admission
Viral Serologies: • HBV serologies (sAb, cAb, sAg) • HCV antibody • HIV ½ Ab/Ag	

Risk Factors for COVID-19 Progression:

Epidemiological - Category 1	
Age > 65	Vital Signs – Category 2
Pre-existing pulmonary disease	Respiratory Rate > 24 breaths per minute
Chronic kidney disease	Heart rate > 125 beats per minute
Diabetes with A1c > 7.6%	Sp02 ≤ 93%
History of hypertension	
History of cardiovascular disease	Labs – Category 3
Obesity (BMI > 30)	D-dimer > 1000 ng/mL
Use of biologics	CRP > 100
History of transplant or other immunosuppression	LDH > 245 U/L
HIV, CD4 cell count < 200 or unknown CD4 count	Elevated troponin
	Admission absolute lymphocyte count < 0.8
	Ferritin > 500 µg/L

STUDY PROTOCOL

The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)

Study No: CCB-CRISIS-01

Version Date: 10 SEPTEMBER 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
DSMB	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-01 SYNOPSIS	
IND	149291
Title	The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)
Protocol	CCB-CRISIS-01
Rationale	Brequinar is a potent DHODH inhibitor that has been studied in more than 1,000 cancer, psoriasis, and organ transplant patients. 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. 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 primary dose-limiting adverse effects have included thrombocytopenia and mucositis. The CRISIS trial will study standard of care (SOC) and SOC with 5 days of DHODH inhibition. 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. 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. Brequinar has not been previously tested as an anti-viral.
Investigational Product and Dosage	Subjects will be randomized in a 1:2 ratio to either standard of care (SOC) alone, or SOC + brequinar. Brequinar is available as 100 mg oral capsules. Five once daily doses of brequinar 100 mg are to be administered on Study Days 1 – 5 for those assigned to the SOC + brequinar group.

	Treatment assignment will be randomized, open label.
Primary Objective	● To determine the safety and tolerability of SOC and SOC plus brequinar in hospitalized COVID-19 subjects.
Secondary Objectives	● To determine the rates of/changes in clinical status measures listed through Day 15: – Hospitalization status – Duration of hospitalization – NEWS2 Score ● Mortality through Day 29
Exploratory Objectives	• To determine the change in SARS-CoV-2 nasopharyngeal viral load through Day 15 ● To determine the change in inflammatory markers through Day 15 ● To determine the change in DHO levels through Day 15 ● To determine the change in brequinar concentration levels through Day 7
Design	This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive SOC per institutional guidelines for treatment of patients with COVID-19 infection. In addition to SOC, the brequinar group will receive brequinar 100 mg once daily for 5 days. Subjects will have a Screening Visit followed as soon as possible with Study Day 1 (Day 1 may take place on the same day if entry criteria data are available). Study procedures are presented in detail in the procedures section, see below. Subjects will be followed through Day 15. Mortality will be assessed at Day 29. See below for instructions regarding hospital discharge prior to Day 15. Hematology and chemistry results and study information such as NEWS2 criteria are to be collected using the available EHR data as much as possible to avoid extra procedures for the study.
Sample Size:	Approximately 24 subjects will be randomized to either standard of care or standard of care plus brequinar in a 1:2 ratio (approximately 8 assigned to standard of care and 16 subjects on brequinar).
Number of Sites:	1 - 8
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. If discharged from the hospital prior to Study Day 15 or if follow up is needed for study drug-related adverse event, willing to go to an outpatient facility if feasible or be in contact with the study team (phone call or other digital media) for remaining study assessments. 4. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay. 5. Hospitalized (in patient with expected duration ≥ 24 hours) 6. 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. 7. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of brequinar. 8. ≤ 10 days since first COVID-19 symptom as determined by treating clinician. 9. Able to swallow capsules. 10. 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, dysgeusia, or other symptom commonly associated with COVID-19.
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. Active malignancy other than squamous cell carcinoma; anticancer treatment such as chemotherapy or radiation therapy within the past month. 3. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test. 4. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide), tacrolimus, sirolimus.

	5. Platelets ≤150,000 cell/mm^3. 6. Hemoglobin < 10 gm/dL 7. Absolute neutrophil count < 1500 cells/mm^3 8. Renal dysfunction, i.e., creatinine clearance < 30 mL/min 9. AST and/or ALT > 1.5 ULN, or total bilirubin > ULN 10. History of bleeding disorders or recent surgery in the six weeks preceding enrollment 11. Concomitant use of agents known to cause bone marrow suppression leading to thrombocytopenia 12. History of gastrointestinal ulcer, or history of gastrointestinal bleeding. 13. History of hepatitis B and/or C infection, active liver disease and/or cirrhosis. 14. 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). 15. Life expectancy of < 5 days in the judgment of the treating clinician. 16. Evidence of critical illness defined by at least one of the following: a. Respiratory failure requiring at least one of the following: i. Endotracheal intubation and mechanical ventilation, noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies may not be able to be administered in setting of resource limitation) ii. Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors) b. Multi-organ dysfunction/failure.
Treatment	All subjects will receive standard of care (SOC) per institutional guidelines. Subjects will be randomly assigned to SOC alone or SOC plus brequinar 100 mg daily x 5 days.
Stopping Criteria	Individual Criteria: • Participants who develop a Grade 3 symptomatic 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 symptomatic 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. Study-Level Stopping Criteria: The study is to be stopped as shown below: • If ≥ 4 subjects on the brequinar treatment arm develop the same Grade 3 or 4 adverse event or symptomatic laboratory abnormality • If ≥ 8 subjects on the brequinar treatment arm develop any Grade 3 or 4 adverse event or symptomatic laboratory abnormality.
DSMB	A Data Safety Monitoring Board (DSMB) will meet periodically to review the safety and scientific conduct of the study. At a minimum, the DSMB is to review adverse events and safety laboratory assessments after the first six subjects complete Day 5 of treatment, and again after the first 12 subjects complete Day 5 of treatment.
Procedures	**Screening Visit (Since hospital admission)** Results of these procedures must be available in the EHR and completed since hospital admission. Obtain the subject's written informed consent (be sure to note time of consent), then collect baseline information. Collect information from EHR. Do not perform study-specific procedures for data available from EHR. • Demographics (height, weight, date of birth, gender, race, ethnicity). • Recent (within one year unless ongoing), relevant medical/surgical history and concomitant medications. • Date of first symptom. • Record any clinically significant abnormal physical examination findings. • Ensure EHR has negative pregnancy test result for women of childbearing potential (WOCBP). • Record any adverse events that occurred since signing the ICF. • Record any new or changed concomitant medications since signing the ICF. Concomitant medications information is to include the medication, dosage, and duration of administration. • Hematology/chemistry from EHR for Inclusion/Exclusion criteria check. • Polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay for SARS-CoV-2 infection (may utilize test results from

	external laboratory to meet entry criteria provided such results are accurately documented and can be confirmed). • Confirm subject meets all inclusion and no exclusion criteria. **Treatment** The treatment period is up to 5 days: standard of care alone (SOC) or SOC + brequinar 100 mg daily x 5 days. Data points such as NEWS2 Assessments and safety labs are to be collected from the EHR, a separate visit by study staff is not to be performed. Give the first dose of brequinar as soon as possible after randomization. See below regarding hospital discharge prior to Day 15. **Days 1 – 7 (8 AM ± 8 hours):** • If Day 1 is different date from Screening, confirm subject continues to meet all inclusion and no exclusion criteria. • Randomize subject and record the time and date of randomization. • Review Progress Notes and medication records to collect any new or ongoing adverse events or new or changed concomitant medications since previous visit (may be omitted on Day 1 if Screening visit is conducted on same day as Study Day 1). Repeat daily through hospital discharge. • Collect SOC hematology/chemistry results from EHR on Day 1 (pre-dose) (may be omitted for Day 1 if Screening visit conducted on same date as Study Day 1) then daily through Day 7 or until the clinician decides daily testing is no longer necessary. Ensure that Day 1 samples are obtained prior to first dose of study drug, if applicable. • Days 1 (pre-dose), 3, 5, 7: – Collect NEWS2 Assessments from EHR. – Collect results for inflammatory markers from EHR for those analyzed locally; collect, process and ship samples for DHO/brequinar PK and cytokine panel to be analyzed at the central laboratory per the Laboratory Manual. – Collect, process, and ship nasopharyngeal viral load samples. – Record hospitalization status (hospitalized, hospitalized in ICU, discharged); subject must be hospitalized Day 1 to meet inclusion criteria, do not record again. • Dispense study medication (Days 1 through 5 if in brequinar group). Keep the brequinar study drug administration interval to 24h as much as possible. Record date and time of study drug administration. • Drug accountability Day 7 ± 2 days. **Final Visit Day 15** (8 AM ± 2 days) • Review Progress Notes and medication records to collect information for any new adverse events or changes in ongoing adverse events or new or

	changed concomitant medications since Day 7 (collect from EHR if subject still hospitalized, otherwise by phone or other digital media). • Collect SOC hematology/chemistry results from EHR if subject still hospitalized. • Collect results for inflammatory markers from EHR for those analyzed locally; collect and process samples for DHO and cytokine panel to be analyzed at the central laboratory on. • Collect and process nasopharyngeal viral load samples. • Record hospitalization status (hospitalized, hospitalized in ICU, discharged). • Collect NEWS2 Assessments from EHR. • If the subject is being discharged prior to Day 15, follow procedures below. **Day 29 (8 AM ± 3 Days)** • Determine survival status from EHR if available or by telephone/digital media per institutional guidelines. <u>Hospital Discharge Before Day 15</u> Subjects discharged from the hospital prior to the Day 15 visit are to return to a research facility when feasible for the remaining study visits. All scheduled study assessments are to be completed at these visits when conducted at a research facility. For subjects in the brequinar treatment group discharged from the hospital prior to Day 5, the subject is to take home the remaining doses of brequinar for daily self-administration. All subjects (brequinar and SOC) should have the scheduled assessments, e.g. lab samples and the nasopharyngeal swab, on the day of discharge and enter these results on the appropriate EDC page. Following discharge, subjects are to return to the research or out-patient lab collection facility for the remaining study visits, if feasible. Out-patient lab results are to be entered into the EDC and reviewed by a member of the study team. It is important that every effort be made to have subjects return at least on Days 7 and 15, if feasible. Subjects in the brequinar group are to record brequinar dosing on the medication diary provided by the study team. The study team will arrange for the subject to return any unused study medication to the research facility. For all subjects, if discharge occurs on Days 10, 11, or 12, ensure a hematology/chemistry sample has been obtained on the day of discharge and record these results on the appropriate EDC page. Following discharge, the subject is to return to the research or out-patient lab collection facility for the Day 15 visit if feasible. Out-patient lab results are to be entered into the EDC and reviewed by a member of the study team. If discharge occurs on Days 13, 14 or 15, complete the Day 15 Final Visit activities prior to discharge. No further visits are required unless follow up is needed for a

	study drug-related AE or an SAE; the Day 29 mortality assessment is still to take place. If the subject is unable or not permitted to return for planned study visits, the visit activities will be conducted by contacting the subject (phone or other digital media) except for the lab draw. The hematology/chemistry sample will be obtained via outpatient laboratory, if feasible and the results entered into the EDC and reviewed by the study team. Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF. A subject is considered completed the study if they have assessments through Day 15, whether conducted in the hospital or contacted via phone or other digital media.
Safety/ Tolerability	**Safety/Tolerability** Adverse events will be collected from the time of informed consent through Day 15. After Day 15, collect/record only Serious Adverse Events (SAEs) or those judged by the Investigator or designated person to be related to study drug, including but not limited to potential hematologic toxicities. Post-randomization adverse events will be those with an onset after the date and time of randomization. Subjects who develop Grade 3 or 4 toxicities are to be re-evaluated every 2 days, as feasible, until the toxicity returns to Grade $\leq$ 2 severity.
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, safety laboratory data, and NEWS2 Assessments. Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of post randomization adverse events, defined as AEs 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, NEWS2 Criteria, and other clinical measures will be summarized using appropriate descriptive statistics.

STUDY PERSONNEL

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3 INTRODUCTION

3.1 Background

3.2 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]).

3.2.1 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]).

3.3 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.

3.4 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.

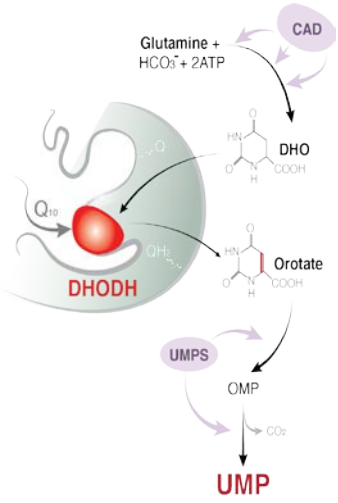

Figure 3-1. DHODH is a mitochondrial enzyme that catalyzes the 4th step of pyrimidine synthesis; it is completely essential for the generation of UMP.

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]).

3.5 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]).

3.6 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 CRISIS trial will study standard of care (SOC) and SOC with 5 days of DHODH inhibition. 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.

3.6.1 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 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 reassuring the safety of this regimen (see Brequinar IB [5]).

3.6.2 Risk/Benefit of Brequinar

As presented in the Brequinar IB [5], an extensive database exists with more than 800 cancer patients 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. Brequinar has also been utilized at lower doses than used in the cancer studies in 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. While no DHODHi has been tested to date in the clinic for infection with SARS-CoV-2 and no brequinar safety information is available in treatment of this disease, DHODHi therapy in the context of trials for patients with cancer has the expected safety side-effects of mucositis and bone marrow suppression. 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 mucositis and only 1 (2.6%) episode of mild thrombocytopenia. The 100 mg per day dose proposed for administration in this study should be safe and well tolerated.

The possible 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. As discussed above, inhibition of DHODH is expected to reduce the ability of the virus to replicate and it is for this reason that study CCB-CRISIS-01 will administer brequinar to patients with COVID-19.

3.7 Risks Associated with Participation in the Clinical Study

In studies utilizing the weekly schedule of administration of 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.

COVID-19 patients are at higher risk of complications and poor outcomes when their infection is combined with comorbidities including hypertension, diabetes, chronic kidney disease, chronic obstructive pulmonary disease (COPD) or asthma, cardiovascular disease (coronary artery disease or congestive heart failure), liver cirrhosis, age > 65, and BMI > 30 [15]. It is likely that participants in this protocol who are sick enough to be hospitalized will have at least one of these comorbidities.

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).

3.8 Possible Interactions with Concomitant Medical Treatments

While not previously tested in patients with viral infections, brequinar has been administered to subjects taking a variety of concomitant medications that are typical in severely ill cancer patients. 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. Brequinar has also been used concomitantly with antibiotics, antifungals and other critical care medications.

There is no experience with brequinar for treatment of SARS-CoV-2 and other severe viral infections and no formal interaction studies have been conducted.

3.8.1 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).

3.9 Steps to be Taken to Control or Mitigate Risks

All subjects will be treated in the hospital setting by highly experienced infectious disease or other critical care specialists and other qualified staff familiar with the treatment of severe viral infections and their complications. Subjects will be followed for study purposes through at least Day 15 even if improved enough to be discharged from the hospital.

Subjects in the Brequinar Treatment Group

If the subject is in the brequinar treatment group and is being discharged prior to completing the study, ensure a hematology/chemistry sample is obtained prior to discharge on the day of discharge. The subject is to return to the research or out-patient facility for the Days 7 and 15 visits if able and permitted. If unable or not permitted to return to the research facility due to COVID-19 restrictions, the remaining visit activities except for the lab draw will be conducted by phone

or other digital media. The lab draw will be performed by an outpatient laboratory at a designated facility. Lab draws for any outpatient visits for the Day 7 and 15 visits are limited to safety labs (hematology and chemistry). Additional outpatient laboratory or study visits are to be conducted as needed for follow up of adverse events including hematologic toxicities.

4 TRIAL OBJECTIVES

4.1 Primary Objective

- To determine the safety and tolerability of standard of care (SOC) and SOC plus brequinar in hospitalized COVID-19 subjects.

4.2 Secondary Objectives

The secondary objectives of this study are:

- To determine the changes in clinical status measures listed through Day 15:
  - Hospitalization status
  - Duration of hospitalization
  - National Early Warning System 2 Score (NEWS2) Score
- To determine survival status through Day 29

4.3 EXPLORATORY OBJECTIVES

- To determine the change in SARS-CoV-2 nasopharyngeal viral load through Day 15
- To determine the change in inflammatory markers through Day 15
- To determine the change in dihydroorotate dehydrogenase (DHO) through Day 15
- To determine the change in brequinar concentration levels through Day 7

5 TRIAL DESIGN

This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive standard of care per institutional guidelines for treatment of patients with SARS-CoV-2 infection. In addition to standard of care, the brequinar group will receive brequinar 100 mg once daily for 5 days.

The Massachusetts General Hospital (MGH) COVID-19 Treatment Guidance is provided in Appendix D Section 15.4. This guidance provides an example of standard of care instructions for treatment of COVID-19. The guidance is provided as informational only, it is not required that this guidance be used for treatment as standards of care may differ between institutions.

Subjects will have a Screening Visit followed as soon as possible with Study Day 1 (Day 1 may take place on the same day if entry criteria data are available). Study procedures are presented in detail in Section 8. Subjects will be followed through Day 15, with mortality assessed via a phone call/other digital media acceptable to institution on Day 29.

If the subject is being discharged prior to Day 7, see Section 8.5.

It is understood that some assessments may not be conducted if the subject is unable to return to the clinic after discharge due to restricted travel. If an assessment is missed due to after hospital discharge, e.g., samples or blood draws, this will not be counted as a protocol deviation. Any of the study visits may be conducted via telephone if the subject has been discharged from the hospital and is not permitted to or is unable to return to the hospital/clinic for these visits.

Information is to be collected using the electronic health record (EHR) whenever possible. It is not required to perform study-specific laboratory assessments, NEWS 2 assessments, etc. separately for study purposes.

6 TRIAL ENDPOINTS

6.1 Primary Endpoint

- Safety/tolerability measured by rates of post randomization adverse events and hematology/chemistry safety labs.

6.2 Secondary Endpoints

- Rates of/changes to the below clinical status measures through Day 15.
  - Hospitalization status
  - Duration of hospitalization in days
  - NEWS2 Assessments Days 1, 3, 5, 7, and Day 15 for hospitalized subjects.
- Mortality through Day 29

6.3 EXPLORATORY Endpoints

- SARS-CoV-2 nasopharyngeal viral load: Day 1 (pre-dose), Days 3, 5, 7, and 15
- Inflammatory markers (to be specified in the Laboratory Manual, may include but are not limited to erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), D-dimer, serum ferritin, and fibrinogen, procalcitonin, IL-6, IL-5, IL-2, IFN-ɣ, final list to be determined) on Day 1 pre-dose, D3, D5, D7, D15 or at frequency per institutional standard of care. The markers are to be tested locally when possible; requested tests as listed in the Laboratory Manual that are not analyzed locally are to be shipped to the central laboratory for analysis.
- DHO concentration levels through Day 15.
- Brequinar concentration levels through Day 7

7 TRIAL POPULATION

7.1 Number of Subjects

Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 24 subjects have completed the study. Subjects will be randomized to either standard of care or standard of care plus brequinar or in a 1:2: ratio (approximately 8 subjects assigned to standard of care alone and approximately 16 subjects on standard of care plus brequinar).

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. If discharged from the hospital prior to Study Day 15 or if follow up is needed for study drug-related adverse event, willing to go to an outpatient facility if feasible or be in contact with the study team (phone call or other digital media) for remaining study assessments.
4. Laboratory-confirmed SARS-CoV-2 infection as determined by real time polymerase chain reaction (RT-PCR) or other Food and Drug Administration (FDA)-cleared commercial or public health assay.
5. Hospitalized (in patient with expected duration ≥ 24 hours)
6. 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.
7. Male subjects must agree to refrain from sperm donation from initial study drug administration until 90 days after the last dose of brequinar.
8. ≤ 10 days since first COVID-19 symptom as determined by treating clinician.
9. Able to swallow capsules.
10. 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, dysgeusia, or other symptom commonly associated with COVID-19. [22].

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. Active malignancy other than squamous cell carcinoma; anticancer treatment such as chemotherapy or radiation therapy within the past month.

3. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test.
4. Treatment with another DHODH inhibitor (e.g., leflunomide or teriflunomide), tacrolimus, sirolimus.
5. Platelets ≤150,000 cell/mm^3.
6. Hemoglobin < 10 gm/dL
7. Absolute neutrophil count < 1500 cells/mm^3
8. Renal dysfunction, i.e., creatinine clearance < 30 mL/min
9. AST and/or ALT > 1.5 ULN, or total bilirubin > ULN
10. History of bleeding disorders or recent surgery in the six weeks preceding enrollment
11. Concomitant use of agents known to cause bone marrow suppression leading to thrombocytopenia
12. History of gastrointestinal ulcer, or history of gastrointestinal bleeding.
13. History of hepatitis B and/or C infection, active liver disease and/or cirrhosis.
14. 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).
15. Life expectancy of < 5 days in the judgment of the treating clinician.
16. Evidence of critical illness defined by at least one of the following:
    a. Respiratory failure requiring at least one of the following:
        i. Endotracheal intubation and mechanical ventilation, noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (i.e., clinical need for one of the preceding therapies, but preceding therapies may not be able to be administered in setting of resource limitation)
        ii. Shock (defined by systolic blood pressure < 90 mm Hg, or diastolic blood pressure < 60 mm Hg or requiring vasopressors)
    b. Multi-organ dysfunction/failure. See [22].

7.4 Inclusion of Women and Minorities

Adult men and women of all races and ethnic groups are eligible for this trial.

8 STUDY TREATMENTS

8.1 Description of Study Medications

8.1.1 Brequinar

Brequinar will be supplied as 100 mg capsules. Dosing will be a single 5-day course of brequinar 100 mg once daily for 5 doses. The initial brequinar dose (Day 1) should be administered as soon as possible based on study drug availability from the investigational pharmacy. At least the first dose of study medication is to be taken in the hospital. Subjects in the brequinar group discharged before Day 5 will be dispensed brequinar to take at home daily until all 5 doses have been taken.

8.2 Treatment Administration

This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive standard of care (SOC) per institutional guidelines for SARS-CoV-2 infection. Subjects will be randomly assigned in a 1:2 ratio to standard of care alone or standard of care plus brequinar. The brequinar dosing interval should be 24h ± 6h. If discharged prior to Day 5, the subject may take any remaining doses once a day at home. In this case, the subject is to record dosing using a medication diary provided by the study team. The diary information will be provided to the study team either verbally or electronically or during an in-person visit.

8.2.1 Safety/Tolerability

Safety/tolerability is assessed for each subject at each study visit using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE).

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 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 (Study 785-001 [16], 785-003 [17], and 785-005 [18]) with five consecutive days of intravenous (IV) brequinar dosing and 168 subjects, there were no toxic deaths. For subjects from these three studies who were treated with a dose of 100 mg or below (as will be dosed in CCB-CRISIS-01), 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 [19], 785-031 [20] , and 785-034 [21]), 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 15 (or longer if needed to follow up study drug-related adverse events). Mortality is assessed via a phone call or other digital media at Day 29.

After treatment, participants will be monitored through at least Study Day 15 (or longer if needed to follow study drug-related AEs/SAEs). 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 symptomatic 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 symptomatic 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

Following assessment by the Data Safety Monitoring Board (DSMB, see Section 10.9), the study is to be stopped as shown below:

- If ≥ 4 subjects on the brequinar treatment arm develop the same Grade 3 or 4 adverse event or symptomatic laboratory abnormality
- If ≥ 8 subjects on the brequinar treatment arm develop any Grade 3 or 4 adverse event or symptomatic laboratory abnormality.

8.5 Hospital Discharge Prior to Study Day 15

Subjects discharged from the hospital prior to the Day 15 visit are to return to a research facility when feasible for the remaining study visits. All scheduled study assessments are to be completed at these visits when conducted at a research facility.

For subjects in the brequinar treatment group discharged from the hospital prior to Day 5, the subject is to take home the remaining doses of brequinar for daily self-administration. All subjects (brequinar and SOC) should have the scheduled assessments, e.g. lab samples and the nasopharyngeal swab, on the day of discharge and enter these results on the appropriate EDC page. Following discharge, subjects are to return to the research or out-patient lab collection facility for the remaining study visits, if feasible. Out-patient lab results are to be entered into the EDC and reviewed by a member of the study team. It is important that every effort be made to have subjects return at least on Days 7 and 15, if feasible. Subjects in the brequinar group are to record brequinar dosing on the medication diary provided by the study team. The study team will arrange for the subject to return any unused study medication to the research facility.

For all subjects, if discharge occurs on Days 10, 11, or 12, ensure a hematology/chemistry sample has been obtained on the day of discharge and record these results on the appropriate EDC page. Following discharge, the subject is to return to the research or out-patient lab collection facility for the Day 15 visit, if feasible. Out-patient lab results are to be entered into the EDC and reviewed by a member of the study team.

If discharge occurs on Days 13, 14 or 15, complete the Day 15 Final Visit activities prior to discharge. No further visits are required unless follow up is needed for a study drug-related AE or an SAE; the Day 29 mortality assessment is still to take place.

If the subject is unable or not permitted to return for planned study visits, the visit activities will be conducted by contacting the subject (phone or other digital media) except for the lab draw. The lab draw will be completed at a research facility or an outpatient laboratory, if feasible, and the results entered into the EDC and reviewed by the study team.

Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF. A subject is considered completed the study if they have assessments through Day 15, whether conducted in the hospital or contacted via phone or other digital media.

8.6 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 8.9.

8.7 Treatment Compliance

Compliance will be assessed by reviewing the subject's EHR, the study medication diary when applicable, and other study records as appropriate.

8.8 Storage, Stability, Labeling and Packaging

8.8.1 Storage and Stability

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

8.8.2 Labeling and Packaging

Each brequinar bottle/dispensing container for subject use will be labeled with at least the following information:

For Clinical Trial Use Only

Study Number: CCB-CRISIS-01

Contents: Brequinar 100 mg capsules

For oral use only. Take with approximately 8 ounces water.

Subject Number: XX-XXXX

Treatment Duration: As directed

Clinical Batch Number: XXXXXXX

Expiration Date: TBD

Storage: Store at controlled room temperature

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

Caution: New Drug – Limited by US Federal Law to Investigational Use Only. To be used by Qualified Investigators only.

8.8.3 Blinding and Randomization

The trial will be conducted in an open-label manner with random assignment to standard of care or standard of care plus brequinar. The brequinar capsules will be provided to each participating institution in bulk to be dispensed by the institution's pharmacist for each subject. Randomization assignments will be provided by the sponsor.

8.8.4 Unblinding/Expectedness

It is not necessary to break the blind for this open label study as the treatment will be known for each subject.

Expectedness will be determined by establishing whether the 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.

8.8.5 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, used and discarded. It must be clear from the records whether the subject received study medication or was assigned to standard of care. 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.

Subjects in the brequinar group who are discharged prior to Day 5 will be given a study medication diary for recording at home treatment administration. The diary information will be collected by

the study team either verbally or electronically or in person during a visit to the research facility. Unused study drug at the patient's home is to be returned to the research facility.

At the end of the study, any unused study drug in the pharmacy will be returned to the Sponsor for destruction or may be destroyed locally; disposition of study drug will be documented. The study team will make arrangements for the subject to return any unused study medication to the research facility.

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.

8.9 Prohibited Medications

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

8.10 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 telephone or other digital media. Study information is to be collected from the EHR as much as possible such as NEWS2 Assessments, height, weight, hematology/chemistry, from Progress Notes for AEs, and from medication records for new or changed concomitant medications. Visits to an outpatient laboratory post hospital discharge may be required if subjects are not able or permitted to return to the research facility for follow up study visits.

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). Remdesivir may be used in this clinical trial as a component of standard of care of patients hospitalized with severe disease in settings where remdesivir is available via the Emergency Use Authorization (EUA) or other FDA approval.

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), 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.

Signed written informed consent must be obtained from every subject prior to any study-specific procedures. Standard procedures carried out prior to signing the informed consent but within the time constraints of the protocol may be used for baseline evaluation; they need not be repeated. An original signed informed consent form will be subject to review by the Sponsor; a copy will be given to the subject and a copy will be filed with the subject's medical notes.

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.

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

NEWS2 Assessments, laboratory assessments, SARS-CoV-2 testing, and other observations will be conducted by experienced personnel throughout the study based on the Schedule of Events. The majority of study information is to be collected from the EHR. Phone calls or other digital media and outpatient visits for hematology/chemistry samples may be required to complete some study assessments if the subject is discharged prior to Study Day 15.

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), bilirubin, total protein, albumin, glucose, serum electrolytes (sodium, potassium, chloride, carbon dioxide/bicarbonate, and calcium), lactate dehydrogenase (LDH).

Inflammatory markers including D-dimer, ferritin, CRP, ESR, troponin, fibrinogen, and procalcitonin may be collected locally if available by the Institution. Additional inflammatory markers will be collected and analyzed by a central laboratory, as specified in the Laboratory Manual. A sample is to be collected for DHO and brequinar pharmacokinetics at the timepoints specified in the Laboratory Manual.

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

If urinalysis is clinically indicated, collect results from the EHR.

Nasopharyngeal swabs for SARS-CoV-2 viral load, inflammatory markers, and DHO samples will be collected Days 1, 3, 5, 7, and 15 (standardized collection instructions available in the supplied Laboratory Manual; please use the same nostril each time). Samples may be banked for future retrospective analyses.

NEWS2 Criteria are available in Appendix C Section 15.3.

Hospitalization status is to be recorded as hospitalized not in ICU, hospitalized in ICU, or discharged.

9.5 Study Conduct

Screening Visit (Since hospital admission)

These procedures must be completed since hospital admission and prior to starting dosing. Obtain the subject's written informed consent (be sure to note time of consent), then collect baseline information from the EHR. Do not perform study specific procedures for data available from the EHR. For Screening/Day 1 use the EHR results closest to the visit to confirm subject eligibility.

- Demographics (date of birth, gender, race, ethnicity, height and weight).
- Recent (within one year unless ongoing), relevant medical/surgical history and concomitant medications.
- Date of first symptom.
- Record any new or changed adverse events and new or changed concomitant medications since signing the ICF.
- Record any clinically significant abnormal physical examination findings as recorded in EHR.
- Hematology/chemistry from EHR.

- Ensure negative pregnancy test result is present in the EHR for women of childbearing potential (WOCBP).
- Polymerase chain reaction (RT-PCR) or other FDA-cleared commercial or public health assay for SARS-CoV-2 infection (may utilize test results from external laboratory to meet entry criteria provided such results are accurately documented and can be confirmed).
- Confirm subject meets all inclusion and no exclusion criteria.

Treatment

The treatment period is up to 5 days: standard of care alone (SOC) or SOC + brequinar 100 mg daily for 5 days. Data points such as NEWS2 Assessments are to be collected from the EHR when possible, a separate visit by study staff is not to be conducted. The first dose of brequinar is to be given as soon as possible depending on availability of investigational pharmacy staff. If the subject is discharged from the hospital prior to Day 15, see Section 8.5 for how and when to conduct study assessments.

It is understood that some assessments may not be conducted if the subject is unable to return to the clinic after discharge due to restricted travel or if the study visit cannot be conducted remotely; this will not be counted as a protocol deviation. Collect information from the EHR, medication records and Progress Notes whenever possible

Days 1 - 7 (8 AM ± 8 hours)

- If Day 1 is a different date from Screening, confirm subject continues to meet all inclusion and no exclusion criteria.
- Randomize the subject (record date and time of randomization).
- Review Progress Notes and medication records to collect any new or changes to ongoing adverse events or new or changed concomitant medications since previous visit (may be omitted on Day 1 if Screening visit was conducted on same day as Study Day 1). Repeat daily until discharge.
- Collect SOC hematology/chemistry results from the EHR beginning on Day 1 (pre-dose) (may be omitted for Day 1 if Screening visit conducted on same date as Study Day 1) then daily through Day 7 or until the clinician decides daily testing is no longer necessary. Ensure that Day 1 samples are obtained prior to first dose of study drug, if applicable.
- Days 1 (pre-dose), 3, 5, 7:
  - Collect NEWS2 Assessments from the EHR.
  - Collect results for inflammatory markers from EHR for those analyzed locally; collect, process and ship samples for DHO/brequinar PK and cytokine panel to be analyzed at the central laboratory per the Laboratory Manual.
  - Collect and process SARS-CoV-2 nasopharyngeal viral load samples.
  - Record hospitalization status (hospitalized, hospitalized in ICU, discharged) (Day 1 already recorded as part of Inclusion criteria, do not record again).
- Dispense study medication (Days 1 through 5 if in brequinar group) and record date and time of brequinar administration. Keep the drug administration interval as close as possible

to 24 hours. Ensure Day 1 labs are drawn prior to first brequinar dose on Day 1. If a subject taking brequinar is discharged prior to Day 5, give the subject adequate study drug to take home along with a diary to record daily treatment administration through Day 5.

- Drug accountability Day 7 ± 2 days.

Final Visit Day 15 (8 AM ± 2 days)

- Review Progress Notes and the medication record to collect information for any adverse events or new concomitant medications since Day 7 (from EHR if subject still hospitalized, otherwise by phone or other digital media).
- Collect results for SOC hematology/chemistry from the EHR if subject still hospitalized.
- Collect inflammatory markers from EHR for those analyzed locally; collect samples for DHO and cytokine panel to be analyzed at the central laboratory if subject still hospitalized.
- Collect NEWS2 Assessments from the EHR.
- Collect nasopharyngeal viral load sample.
- Collect hospital status (hospitalized, hospitalized in ICU, discharged).

Day 29 (8 AM ± 3 days)

- Determine survival status from EHR if available or contact the subject by phone call/digital media as acceptable to the institution.

If the subject is being discharged before Day 15, follow the procedures outlined in Section 8.5.

9.5.1 Unscheduled Visits

Unscheduled visits and tests to assess AEs/SAEs are permitted as needed providing the AE related to study drug or SAE onset occurs within two (2) weeks after the final study dose.

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. Provided that activities are carried out within the identified windows it will not be necessary to file a protocol deviation. It is understood that some scheduled study assessments may not be able to be conducted if the subject is unable to return to the clinic after discharge due to COVID-19 restricted travel; it is also understood that crowded hospital conditions/lack of personnel may make it impossible to carry out all requested study procedures; this will not be counted as a protocol deviation. The Day 7 and 15 visits are to be conducted via telephone if the subject has been discharged from the hospital with lab draws for subjects in the brequinar treatment group as described in Section 8.5.

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 be withdrawn from the study 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 evaluations for subjects who withdraw from the study 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).

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 15. After Day 15, collect/record only Serious Adverse Events (SAEs) or those judged 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.

Any serious adverse events (SAEs) experienced after 30 days post the last dose of study drug should only be reported to the sponsor if the investigator suspects a causal relationship to the 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, or require therapy.

Death due to disease progression should not be reported as an SAE. Report death from disease progression on the appropriate electronic data capture form.

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 progression of the disease under study.

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 descriptions and grading scales found in the revised National Cancer Institute (NCI) Common Terminology *Criteria for Adverse Events (CTCAE) version 4.03* will be utilized for adverse event reporting. *(http://ctep.cancer.gov/reporting/ctc.html)*.

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 descriptions and grading scales found in the revised NCI CTCAE version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the criteria. The CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program (CTEP) web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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:

- 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, or
- is a congenital anomaly / birth defect;
- all other events that are 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 the studied indication, 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;
- Note that 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 is not an SAE.

Death due to disease progression is considered to be an Expected event in patients with severe SARS-CoV-2 infection and does not require reporting on an expedited basis.

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 the Sponsor contact until the event has subsided or, in case of permanent impairment, it stabilizes, and the overall clinical outcome has been ascertained.

SAE REPORTING EMAIL: Safety-CCB-CRISIS-01@prosoftclinical.com

Medical Monitor:

Sharon Levy, MD	Telephone:	O: (484) 320-2062

Sponsor Representative:

Barbara Powers, MSN, Ph.D.	Telephone:	M: 484-686-0545
	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 Medical Monitor 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 is to 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 the Medical Monitor/Sponsor. Follow-up information is to be subsequently communicated to the relevant Regulatory Authority within an additional eight calendar days.

All other SUSARs are to 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 knowledge by the Medical Monitor/Sponsor.

The Medical Monitor/Sponsor or designee must 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 the Sponsor Contact 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 pregnancy is due to a subject's failure to comply with the contraceptive requirements of this protocol, this should also be documented as a protocol deviation.

Complications of pregnancy or congenital abnormalities in the newborn child will be reported appropriately as 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-up with 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 initially be hospitalized as in-patients and will be under the care of highly qualified infectious disease, critical care, and associated medical personnel. As is standard of care for moderately to severely ill in-patients, daily samples will be obtained for hematology assessments including complete blood count with full differential (WBC, RBC, hemoglobin, hematocrit, platelet count, absolute neutrophils, absolute lymphocytes, absolute monocytes, absolute eosinophils, and absolute basophils). Any clinically significant out-of-range laboratory values will be assessed by hospital staff in a timely manner and treatment needs addressed as appropriate. 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 Clear Creek Medical Monitor will assess the available hematology data on a weekly 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, the Sponsor, and the Medical Monitor. In addition, the Data Safety Monitoring Board 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.

Subjects who are discharged from the hospital before Day 7 will have follow up contacts with study staff (phone calls or other digital media) on Days 7, 15 and 29. Early discharge subjects in the brequinar treatment group will also have samples for safety labs (hematology and chemistry) obtained either at the research facility or at an outpatient laboratory on Study Days 7 ± 2 and 15 ± 2. The safety laboratory results are to be initially assessed in real time by the Principal Investigator or designated person and the Medical Monitor. 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-hospital assessments and phone call visits will specifically ask about possible hematologic toxicity including any evidence of the list below. Early discharge 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 Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be established to provide independent oversight to this trial. The primary responsibility of the DSMB 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 DSMB will be detailed in a separate DSMB charter. The DSMB 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 DSMB Chair will advise the Sponsor that the study be stopped, the design changed, or that the study may continue per protocol.

10.9.1 DSMB Safety Review Schedule

The DSMB is to review adverse events and safety laboratory assessments after the first six subjects complete Day 5 of treatment, and again after the first 12 subjects complete Day 5 of treatment.

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 analyses will be based on the ITT population, which is defined as all randomized subjects.

11.2 Safety Analyses

Safety and tolerability will be assessed in terms of AEs, SAEs, NEWS2 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 NEWS2 Assessments will be summarized using appropriate descriptive statistics.

11.3 Efficacy Analyses

Efficacy will be assessed in terms of mortality, hospitalization status and duration, NEWS2 score, viral load (plasma and nasopharyngeal), and inflammatory markers.

11.4 DHO and Brequinar Concentration Levels

DHO and brequinar concentrations levels will be summarized using descriptive statistics.

11.5 Sample Size Considerations

Formal sample size calculations are not applicable for this phase 1a, open label study. Up to 24 subjects are planned to be entered in this trial. Additional subjects may be enrolled following data review.

11.6 Randomization

A randomization scheme will be provided by the Sponsor to ensure subjects are randomly assigned to SOC or SOC + brequinar in a 1:2 ratio.

11.7 Pooling of Study Centers

Not applicable to this small, early phase study.

11.8 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.

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) 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.

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15 APPENDICES

15.1 Appendix A: CCB-CRISIS-01 Schedule of Events

CCB-CRISIS-01 Schedule of Events **Procedures**	**Screen**	**D1**	**D2 - D7 (± 8 hours)**	**Final Visit D15 (± 2 days)**	**F/U Phone Call 2 weeks/ Survival (± 3 days)**
Informed Consent	X				
AE/Concomitant Medications (daily until discharge)	X	X	D1-7	X	
Medical history / History of current illness	X				
Demographics, collect Height and weight	X				
Check for Physical Exam abnormalities	X				
Pregnancy Test (urine or serum)	X				
Hematology/Chemistry	X	X (pre-dose)	D1-7	X	
Inflammatory Markers*		X (pre-dose)	D3, D5, D7	X	
DHO/brequinar PK Sample Collection & Processing		X (pre-dose)	D3, D5, D7	X (DHO only)	
Swab collection for nasopharyngeal viral load		X (pre-dose)	D3, D5, D7	X	
Clinical SARS-CoV-2 testing RT-PCR	X				
Hospital Status			D3, D5, D7	X	
NEWS2 Assessments		X	D3, D5, D7	X	
Dispense Study Medication if assigned to brequinar**		X	D2 – 5		
Drug Accountability			D7		
Survival Assessment Day 29					X

Collect information from available electronic health record (EHR), Progress Notes, and medication records; a special visit by research staff is not to be performed. Results for Hematology, Chemistry and available inflammatory markers analyzed locally are to be obtained from the EHR; do not draw another set of labs. Missed samples due to hospital staff too busy or for technical reasons unable to obtain samples will not be counted as protocol deviations. Record urinalysis results if urinalysis is clinically indicated and results are available in the EHR. Note that if the subject is discharged before Day 15, follow instructions provided in Section 8.5.

Note that any visits other than Screening/Day 1 may be conducted via telephone or digital media. Missed samples/assessments when phone visits occur will not be counted as protocol deviations.

*Inflammatory markers are to be collected from the EHR when available; otherwise process and ship samples to the central laboratory per the Laboratory Manual. DHO and brequinar samples will also be sent to the central laboratory.

**If a subject in the brequinar group is discharged prior to Day 5 (has not completed taking brequinar all 5 days) the subject may be dispensed study medication to take at home on a daily basis. In this instance the subject is also to be provided with the study medication diary for drug accountability purposes.

15.2 Appendix B: Investigator's Statement and Agreement

STUDY NUMBER: CCB-CRISIS-01

STUDY TITLE: The CRISIS Study: A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19).

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:** _____

Site Address:

_____

_____

15.3 Appendix C: National Early Warning Score (NEWS2)

Chart 1: The NEWS scoring system

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

Use SpO_2 Scale 2 if target range is 88 – 92%, e.g., in hypercapnic respiratory failure.

National Early Warning System Score (NEWS) 2 Royal College of Physicians 2017 [14].

15.4 Appendix D: Massachusetts General Hospital COVID-19 Treatment Guidance.

Recommended daily labs: • CBC with diff • CMP • CPK (creatine kinase)	If Clinically Indicated: • Blood cultures • For acute kidney injury- urinalysis and spot urine protein creatinine • Procalcitonin • IL-6
Recommended repeated labs q 2-3 days: • D-dimer • Ferritin/CRP/ESR • LDH • Troponin • Baseline ECG	Radiology: • Chest X-ray at admission
Viral Serologies: • HBV serologies (sAb, cAb, sAg) • HCV antibody • HIV ½ Ab/Ag	

Risk Factors for COVID-19 Progression:

Epidemiological - Category 1	
Age > 65	Vital Signs – Category 2
Pre-existing pulmonary disease	Respiratory Rate > 24 breaths per minute
Chronic kidney disease	Heart rate > 125 beats per minute
Diabetes with A1c > 7.6%	Sp02 ≤ 93%
History of hypertension	
History of cardiovascular disease	Labs – Category 3
Obesity (BMI > 30)	D-dimer > 1000 ng/mL
Use of biologics	CRP > 100
History of transplant or other immunosuppression	LDH > 245 U/L
HIV, CD4 cell count < 200 or unknown CD4 count	Elevated troponin
	Admission absolute lymphocyte count < 0.8
	Ferritin > 500 µg/L