The CCB-CRISIS-04 Study: A phase II, randomized, assessor-blind, multicenter, multi-dose, placebo-controlled study assessing the safety and anti-coronavirus response of brequinar combined with dipyridamole in patients with mild to moderate SARS-CoV-2 infection.

NCT05166876

Document Date: 12/29/2021

Table of Contents

16.1.1 Protocol and protocol amendments

PROJECT NO.: 21-VIN-0372

Protocol Number	21-VIN-0372
Protocol Title	The CCB-CRISIS-04 Study: A phase II, randomized, assessor-blind, multicenter, multi-dose, placebo-controlled study assessing the safety and anti-coronavirus response of brequinar combined with dipyridamole in patients with mild to moderate SARS-CoV-2 infection.
Study Phase	II
US IND Number	149291
Sponsor Study Code	CCB-CRISIS-04
Regulatory Submission	DCGI
Version Number	01
Protocol Date	24 Sep 2021
Supersedes	None
Date of Supersedes	NA
Sponsor	Clear Creek Bio, Inc. 585 Massachusetts Ave., 4th Floor Cambridge, MA 02139 USA
Contract Research Organization (CRO)	Veeda Clinical Research Ltd., Shivalik Plaza, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India Phone: +91-79-3001 3000

Confidentiality Statement

The information contained in this document, especially unpublished data, is the property of Sponsor (or under its control), and therefore provided to you in confidence as an Investigator or consultant, for review by you, your staff and an applicable Institutional Ethics Committee. By accepting this document you agree that this information will not be disclosed to others without written authorization from Sponsor except to the extent necessary to obtain informed consent from those persons (including their legally acceptable representatives as applicable) to whom the drug may be administered.

1.0 AUTHORIZATION OF PROTOCOL

1.1 Protocol Preparation and Authorization

We, the undersigned, have read and understood this protocol and hereby agree to comply with all requirements regarding the obligations of Sponsor and all other pertinent requirements of the Ethical guidelines for biomedical research on human participants (ICMR) 2017 guidelines, New Drugs and Clinical Trials Rules (2019) of India, ICH (Step 5) 'Guidance on Good Clinical Practice' ICH Guidance E6 (R2), Declaration of Helsinki (Brazil, 2013) and with procedures oriented to Good Laboratory Practice and applicable regulatory guidelines.

We agree to comply with all relevant SOPs required for the conduct of this study. We further agree to ensure that all associates assisting in the conduct of this study are informed regarding their obligations.

Prepared by — Date: 24 Sep 2021

Name : Krunal Suthar
Associate Clinical Manager - Medical Affairs and Pharmacovigilance

Reviewed By — Date: RAVI ALAMCHANDANI 2021.09.24 15:57:17 +05'30'

Name : Dr. Ravi Alamchandani
General Manager - Medical Affairs and Pharmacovigilance

Authorized By — Date: SUMIT ARORA 2021.09.24 17:24:03 +05'30'

Name : Dr. Sumit Arora
Head - Medical Affairs and Pharmacovigilance

Address : Veeda Clinical Research Ltd.
Beside YMCA Club,
SG Highway, Ahmedabad- 380051,
Gujarat, India

Tel. No. : +91-79-3001 3000

1.2 Quality Assurance statement

The contents of the protocol were reviewed for compliance with the applicable VIN SOPs, pertinent requirements of the Ethical guidelines for biomedical research on human participants (ICMR) 2017 guidelines, New Drugs and Clinical Trial Rules (2019) of India, ICH (Step 5) 'Guidance on Good Clinical Practice' ICH Guidance E6 (R2), Declaration of Helsinki (Brazil, 2013) and with procedures oriented to Good Laboratory Practice and applicable regulatory guidelines.

Digitally signed by AMEE MILIND KANUGA
Date: 2021.09.24 17:38:45 +05'30'

Authorized signatory | Date

Name : Ms. Amee Kanuga
Head - Quality Assurance
Address : Veeda Clinical Research Ltd.
Shivalik Plaza-A,
Near I.I.M., Opp. AMA, Ambawadi,
Ahmedabad – 380015,
Gujarat, India
Tel. No. : +91-79-30013000
Email ID : Amee.Kanuga@veedacr.com

1.3 Sponsor's Review & Approval

I, on behalf of Clear Creek Bio, Inc. have read, understood and approve this protocol. We agree to comply with all requirements of the Ethical guidelines for biomedical research on human participants (ICMR) 2017 guidelines, New Drugs and Clinical Trial Rules (2019) of India, ICH (Step 5) 'Guidance on Good Clinical Practice' ICH Guidance E6 (R2), Declaration of Helsinki (Brazil, 2013) and with procedures oriented to Good Laboratory Practice guideline and other applicable regulatory guidelines.

DocuSigned by:
Vikram Kumar
D5300B17D329436...

Authorized signatory _____ Date 9/24/2021

Name : Vikram Sheel Kumar, MD

Address : Clear Creek Bio, Inc.
585 Massachusetts Ave., 4th Floor
Cambridge, MA 02139 USA

Tel. No. : +1-671-899-8944

E-mail : kumar@clearcreekbio.com

TABLE OF CONTENTS

2.0 LIST OF ABBREVIATIONS

AE	:	Adverse Event
ANOVA	:	Analysis of Variance
ATP	:	Adenosine Triphosphate
β-hCG	:	Beta-human Chorionic Gonadotropin
BA	:	Bioavailability
CBC	:	Complete Blood Count
CFR	:	Code of Federal Regulations
COA	:	Certificate of Analysis
COVID 19	:	Corona virus disease 2019
CRF	:	Case Report Form
CRO	:	Contract Research Organization
CRP	:	C-reactive protein
CTCAE	:	Common Terminology Criteria for Adverse Events
CTP	:	Cytidine Triphosphate
CYP	:	Cytochrome P
DCGI	:	Drug Controller General of India
EC	:	Ethics Committee
ECG	:	Electrocardiogram
ECMO	:	Extracorporeal membrane oxygenation
gm	:	Gram
GCP	:	Good Clinical Practice
GGT	:	Gamma glutamyl transpeptidase
GLP	:	Good Laboratory Practice
GTP	:	Guanosine Triphosphate
HbsAg	:	Hepatitis B surface Antigen
HCV	:	Hepatitis C Virus
HIV	:	Human Immunodeficiency Virus
Hrs.	:	Hours

IB	:	Investigator Brochure
ICD	:	Informed Consent Document
ICH	:	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMR	:	Indian Council of Medical Research
IMP	:	Investigational Medicinal Product
ITT	:	Intent-To-Treat
IU	:	International Unit
IUD	:	Intrauterine Device
Kg	:	Kilograms
Ltd.	:	Limited
Mg	:	milligram
mg/dL	:	milligram/deciliter
mL	:	Milliliter
No.	:	Number
OTC	:	Over the Counter
P/A	:	Postero-anterior
PD	:	Pharmacodynamic
PK	:	Pharmacokinetic
PP	:	Per protocol
PO_2	:	Partial pressure of oxygen
PCO_2	:	Partial pressure of carbon dioxide
QA	:	Quality Assurance
qPCR		Quantitative polymerase chain reaction to test SARS-CoV-2 viral load
RLD	:	Reference Listed Drug
RT-PCR		Reverse transcription polymerase chain reaction
SAE	:	Serious Adverse Event
SD	:	Standard Deviation
SGOT	:	Serum Glutamate Oxaloacetate Transaminase

SGPT	:	Serum Glutamate Pyruvate Transaminase
SOP	:	Standard Operating Procedure
TEAEs	:	Treatment Emergent Adverse Events
$t_{1/2}$	:	The time required for the drug concentration to decrease by 50 percent from the maximum concentration.
U	:	Units
UDS	:	Urine Drug Scan
UPT	:	Urine Pregnancy Test
USV	:	Unscheduled Visit
UTP	:	Uridine Triphosphate
WBC	:	White Blood Cell
WOCBP	:	Women of child bearing potential
^0C	:	Degree Celsius
^0F	:	Degree Fahrenheit
%	:	Percent

3.0 PROTOCOL SUMMARY

3.1 Synopsis

Title of Study:	The CCB-CRISIS-04 Study: A phase II, randomized, assessor-blind, multicenter, multi-dose, placebo-controlled study assessing the safety and anti-coronavirus response of brequinar combined with dipyridamole in patients with mild to moderate SARS-CoV-2 infection.
Sponsor:	Clear Creek Bio, Inc.
Clinical Study Centre(s):	Clinical facilities will be the clinics/ hospitals at different investigator sites across India.
Bio-analytical Study centre:	**For PK analysis:** Veeda Clinical Research Ltd. Rev. Sur. No. 12/1, Insignia, Corporate House, Nr. Grand Bhagvati Hotel, Sindhu Bhavan Road, S. G. Highway, Bodakdev, Ahmedabad - 380054, Gujarat, India. Phone: +91-79-67773000 **For PD analysis:** Bioneeds India Pvt. Ltd. P-3, Peenya Industrial Area, 1st Stage, Bengaluru – 560058, Karnataka, India Phone: +91-80-22658400
Statistical Centre:	Veeda Clinical Research Ltd. Shivalik Plaza, Near I.I.M., Ambawadi, Ahmedabad–380 015, India Phone: +91-79-3001 3000 Fax: +91-79-3001 3010
Type of Study:	Phase II study
Rationale:	Brequinar is a potent DHODH inhibitor that blocks *de novo* pyrimidine synthesis in the host and has been previously studied in more than 1,000 cancer, psoriasis, and organ transplant patients.

	Brequinar has potent *in vitro* antiviral activity against many RNA viruses including SARS-CoV-2. The *in vitro* antiviral activity of brequinar against SARS-CoV-2 is likely due to DHODH inhibition and shows nanomolar potency and a high selectivity index in inhibiting viral replication these studies. Brequinar has also been studied in two clinical trials in patients with confirmed SARS-CoV-2 infection. In these two studies, 25 were hospitalized (15 treated with brequinar) and 115 were non-hospitalized (56 treated with brequinar). Results in these 71 COVID-19 patients demonstrated that brequinar 100 mg x 5 days was safe and well-tolerated in these populations. Brequinar's antiviral activity was demonstrated in the out-patient study as shown by decreased viral load compared to placebo at days 12, 15, 22 and 29 and a shorter duration of viral shedding. The strong safety data in 71 COVID-19 subjects treated with daily brequinar at 100 mg for 5 days provides strong support for the further investigation of brequinar in the treatment of COVID-19. The antiviral effects of brequinar may be blunted *in vivo* by pyrimidine salvage. One approach to enhancing the antiviral effect of brequinar is to block the pyrimidine salvage pathway by combining brequinar with a pyrimidine salvage inhibitor. Dipyridamole has been shown *in vitro* to block pyrimidine salvage and may potentiate the antiviral activities of DHODH inhibition on RNA viruses (Liu et al., 2020). Blocking pyrimidine salvage via dipyridamole shows improved *in vitro* antiviral efficacy of *de novo* pyrimidine synthesis inhibition via DHODH inhibition and will be used in this study in combination with brequinar to enhance brequinar's antiviral activity. Dipyridamole is a well-tolerated, FDA-approved medication that is a nucleoside transport inhibitor and PDE3 inhibitor that inhibits blood clot formation and causes vasodilation. Dipyridamole was first approved by the US FDA in 1961 for prevention of thromboembolism in patients who have had cardiac valve replacement. It has also been widely prescribed in combination with aspirin to prevent stroke. The CCB-CRISIS-04 trial will study subjects who have mild to moderate COVID-19 infection confirmed by a positive SARS-CoV-2 RT-PCR qualitative test / rapid antigen test and have mild/moderate signs and/or symptoms ongoing at study entry. The purpose of this study is to determine if the antiviral activity of brequinar can be improved by combining brequinar with dipyridamole in patients infected with SARS-CoV-2.
Investigational Product and Combination Product Dosage:	1. Brequinar 50 mg capsules (used for the 50 mg and 150 mg doses) 2. Brequinar 100 mg capsules (used for the 100 mg, 150 mg and 200 mg doses) 3. Dipyridamole 75 mg tablets 4. Brequinar Placebo 50 mg and 100 mg capsules Note: • The subjects will take the study medication as directed on study days 1 – 5. • Treatment assignment will be randomized, assessor-blind.

	• IMP dispensing will be performed by unblinded pharmacist. • Study assessments will be performed by blinded Investigator or designate blinded site personnel. • Brequinar and brequinar placebo doses will be administered once daily. • Dipyridamole doses will be given thrice daily. • The 150 mg brequinar or brequinar placebo dose will be given as 1 capsule of 100 mg and 1 capsule of 50 mg; the 200 mg brequinar or brequinar placebo dose will be given as 2 capsules of brequinar or brequinar placebo 100 mg.
Study Design:	The first part of the study will be a phase II, randomized, assessor-blind, multicenter, multi-dose, placebo-controlled study in approximately 64 subjects with mild to moderate COVID-19 infection confirmed by a positive SARS-CoV-2 RT-PCR qualitative test /rapid antigen test and who have at least mild to moderate signs and/or symptoms ongoing at study entry. Approximately 32 subjects (50% of subjects per arm per cohort) at selected sites will be invited to participate in the "PK/PD" arm of the study until approximately 8 subjects in each cohort have been recruited after providing written informed consent for the same. PK/PD includes brequinar and dipyridamole plasma concentrations and analysis of intracellular pools of UTP/CTP/ATP/GTP. If a particular cohort meets study stopping criteria (as defined in section "Safety Criteria") or is found to be unsafe by DSMB members, then the study will not proceed with enrollment of subsequent cohorts. An expansion cohort of approximately 48 subjects will be added to the cohort with the highest brequinar dose that meets safety criteria. All subjects will receive SOC as per relevant guidelines for treatment of patients with mild to moderate COVID-19 infection. Subjects will be randomized to one of the following cohorts in Part 1: **Cohort 1:** • Arm 1: 5 days of standard of care (SOC) + brequinar 50 mg OD + dipyridamole 75 mg TID (N = 8) • Arm 2: 5 days of SOC + brequinar 50 mg OD (N = 4). • Arm 3: 5 days of SOC + brequinar placebo 50 mg OD (N = 4). **Cohort 2:** If the 50 mg brequinar OD + dipyridamole 75 mg TID meets safety criteria as pre-defined in the protocol the brequinar dose will be escalated to 100 mg. • Arm 1: 5 days of standard of care (SOC) + brequinar 100 mg OD + dipyridamole 75 mg TID (N = 8)

	• Arm 2: 5 days of SOC + brequinar 100 mg OD (N = 4). • Arm 3: 5 days of SOC + brequinar placebo 100 mg OD (N = 4). **Cohort 3:** If the 100 mg brequinar OD + dipyridamole 75 mg TID meets safety criteria as pre-defined in the protocol the brequinar dose will be escalated to 150 mg: • Arm 1: 5 days of standard of care (SOC) + brequinar 150 mg (100 mg + 50 mg) OD + dipyridamole 75 mg TID (N = 8) • Arm 2: 5 days of SOC + brequinar 150 mg (100 mg + 50 mg) OD (N = 4) • Arm 3: 5 days of SOC + brequinar placebo 150 mg (100 mg + 50 mg) OD (N = 4). **Cohort 4:** If the 150 mg brequinar OD + dipyridamole 75 mg TID meets safety criteria as pre-defined in the protocol the brequinar dose will be escalated to 200 mg: • Arm 1: 5 days of standard of care (SOC) + brequinar 200 mg (100 mg +100 mg) OD + dipyridamole 75 mg TID (N = 8) • Arm 2: 5 days of SOC + brequinar 200 mg (100 mg +100 mg) OD (N = 4) • Arm 3: 5 days of SOC + brequinar placebo 200 mg (100 mg +100 mg) OD (N = 4). **Expansion Cohort:** Approximately forty-eight (48) subjects will be added to the cohort with the highest brequinar dose that meets safety criteria in a 2 : 1 ratio of active treatment (approximately 32 SOC + brequinar + dipyridamole treated and 16 SOC + brequinar monotherapy group). Additional sites may be added if required to meet enrollment of the expansion cohort in an efficient manner.
Study Duration:	Study duration will be approximately 34 days including a maximum screening period of 5 days.
Objectives:	**Primary Objective:** • To characterize the safety and tolerability of the brequinar-dipyridamole combination in COVID-19 subjects as measured by frequencies of grade 3 and 4 toxicities and serious adverse events (SAEs) considered by the investigator to be related to the combination. **Secondary Objectives:** For subjects treated with the brequinar-dipyridamole combination compared to subjects treated with brequinar and to subjects treated with placebo through Day 29, to determine:

	• Reduction of SARS-CoV-2 levels using qPCR through Day 29 and at days 4, 8, 12, 15, 22, and 29; • Reduction in time to symptom improvement; • Reduction in percentage of subjects requiring hospital admission/re-admission as an in-patient for >24 hours; • Reduction in percentage of subjects requiring medical attended visits, e.g., hospitalization, emergency room visits, Urgent Care/Family Doctor visits; • Reduction in percentage of subjects requiring supplemental support such as oxygen. **Exploratory Objectives:** • To determine brequinar-dipyridamole combination and brequinar's pharmacokinetic profile in a subset of subjects agreeing to participate in the PK/PD aspect of the study; • To compare the effects of the brequinar-dipyridamole combination to effects with brequinar alone and placebo alone on intracellular nucleotide pools of UTP/CTP/ATP/GTP.
Study Endpoints:	**Primary Endpoints:** • Frequencies of grade 3 and 4 toxicities and serious adverse events (SAEs) considered by the investigator to be related to the combination, brequinar alone or placebo alone. **Secondary Endpoints:** • qPCR SARS-CoV-2 levels through Day 29 and at days 4, 8, 12, 15, 22, and 29; • Time to symptom improvement through Day 29; • Percentage of subjects requiring hospital admission/re-admission as an in-patient for >24 hours through Day 29; • Percentage of subjects requiring medical attended visits, e.g., hospitalization, emergency room visits, Urgent Care/Family Doctor visits through Day 29; • Percentage of subjects requiring supplemental support such as oxygen through Day 29. **Exploratory Endpoints (PK/PD):** • Analysis of brequinar's pharmacokinetic profile in a subset of patients that have received brequinar as a part of therapy and have consented to provide PK samples; • Analysis of effect on intracellular nucleotide pools of UTP/CTP/ATP/GTP in the

	subset of patients who received brequinar-dipyridamole combination with comparison to brequinar alone and placebo alone.
Study Procedure:	To be eligible for screening, subjects must have a documented positive SARS-CoV-2 test result within 5 days of first dose of study drug and have at least one ongoing symptom consistent with SARS-CoV-2 infection rated as at least mild to moderate in the opinion of the investigator. The subject's earliest symptom must have an onset date within 5 days of first dose of study drug. Subjects will undergo screening (day -4 to 0) for confirming eligibility for participation in the study. Study Day 1 includes randomization visit. Subjects will be randomized to a cohort as described above. Screening activities as well as randomization can take place on the same day as a combined Screening/Day 1 visit, if the site team is able to obtain Screening lab results on the same day. Otherwise, Day 1 is to take place as soon as Screening lab results are available. Study Day 1 and first dose of study drug must take place ≤5 days from onset of first symptom. Subjects may be hospitalized as many as 9 days in the study (day 0 to 8) or more for the PK/PD sample as per Investigator discretion. For subjects participating in the PK/PD subset, Blood samples for estimating brequinar concentrations will be drawn (PK): • Day 1: Pre-dose (within 1 hour prior to study drug administration) and post dose at 1h, 2h, 4h, and 8h; note that the 8h sample is to be obtained prior to the next dose of dipyridamole. • Days 2 – 5 pre-dose and Day 8. Blood samples for nucleotide pool analysis will be drawn (PD): • Days 1 – 5 pre-dose and Day 8. Aliquots of the NP/OP swab samples are to be stored at the testing laboratory for possible additional virological testing. Screening visit and study visits on Days 1, 8, 15, 22 and 29 will be either in person or a combination of in-person and virtual visit (telemedicine or other remote technique) or by visit to patient's home by site team. Study visits on Day 4 and 12 may be virtual visits (telemedicine or other remote technique) or in person. On Days 2, 3, 5, 6 and 7, the site will have a telephone call / or in-person communication with the subject for changes in concomitant medications and

assessment of adverse events (same will also be captured by the subject using a patient diary card or these visits will be conducted in person).

Note:

- Study procedures are presented in detail in the Schedule of Events.
- Days 1, 8, 15 and 29 require sample collection for performing laboratory tests and will be conducted at the site or via home visit.
- Any in-person visit may also have telemedicine or telephone components if all study activities cannot be completed in person.
- The visits that include bloodwork must be conducted at the study site or arrangements made for sample collection at the subject's home or other appropriate location.
- Site staff (in case of an in-person visit) or subjects (in case of a remote visit) will assess respiratory rate, heart rate, body temperature and SpO_2 (a thermometer and pulse oximeter are to be provided to subjects who are home quarantined, leave the hospital or are unable to return for study visits).
- Subjects will record details of concomitant medications, adverse events in the patient diary card (PDC).
- Subjects will complete a symptom assessment form on designated days during the study period (days 1 – 8, 12, 15, 22, and 29).
- In case the subject is hospitalized during the course of study, the activities specified in scheduled visits / time points will be carried out within the hospital facility.
- Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF.

DSMB Meeting:

A Data Safety Monitoring Board (DSMB) will meet to review the safety and scientific conduct of the study. At a minimum, the DSMB will review the protocol and study design prior to study start, after the end of the first part of the study prior to the expansion phase, and at the end of the study.

At each interim meeting the DSMB members will determine whether to stop the study, amend the protocol, or continue the study per protocol. The study enrollment will not be suspended for routine DSMB meetings.

The DSMB will be convened and enrollment suspended if Cohort-Level Stopping Criteria are met. The DSMB may allow the enrollment to resume following their review if safety criteria are met.

Hospitalization:	Subjects may be hospitalized for approximately 9 days (days 0 to 8) in the study as per Investigator discretion for the PK/PD blood sample draws. Subjects may leave after this period (if medically discharged) after the Day 8 blood work has been drawn. Extended stays beyond study Day 8 are permitted if the facility is a dedicated COVID-19 unit or other relevant hospital type or if per the Investigator the extended stay facilitates study procedures; this continuation will not be considered as an SAE. However, prolongation of hospitalization due to increase in disease severity or any other safety concerns related to the subjects will be considered as an SAE. Hospitalization for the purpose of PK/PD sample collection may be done at Investigator's discretion, in this case hospitalization may be for selected few days and may not be for entire 8 days duration. Appropriate documentation of the same will be done in source file.
Treatment:	All subjects will receive standard of care (SOC) including treatment for COVID-19 signs and/or symptoms as required. Study encounters may be conducted remotely or at the study site depending on visit requirements, site facilities and subject and study team preferences.
Clinical Safety Measures:	It is the responsibility of the investigator to ensure that adequate medical supervision and care is available for the study subjects during the study to ensure their utmost safety and well being. • Demography (subject reported / measured height and weight, age, sex and race/ethnicity): At screening • Medical history (relevant within 30 days or ongoing) / History of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection): At screening • Physical Examination (subject self-reported / examiner evaluated): At screening • Vital signs (body temperature, respiratory rate, heart rate, SpO_2) assessment: At screening, Day 4 (±8 hrs), Day 8 (±8 hrs), Day 12 (± 1 day), Day 15 (±1 day), Day 22 (±1 day), End of study [EoS; Day 29 (±2 day)]. Note: If subject is hospitalized, vital signs assessment will be done on daily basis by site team during hospitalization through Day 8 then following the Vital signs visits as listed above. • Hematology, biochemistry and urine analysis: At screening, Day 1 unless same day as Screening visit, Day 8 (±8 hrs), Day 15 (±1 day), End of study [EoS; Day 29 (±2 day)]. • HCV, HbSAg, HIV Test: At screening • Serum pregnancy test (Women of child bearing potential (WOCBP)): At screening.

- Urine pregnancy test (WOCBP): End of study [EoS; Day 29 (±2 day)].

  Note: WOCBP: A premenopausal female capable of becoming pregnant

- Rapid antigen test / SARS-CoV-2 RT-PCR Qualitative (in a clinically relevant specimen (Naso-Oro-Pharyngeal as appropriate)): Screening

  Note: Test need not be repeated in those with possession of confirmed positive report. Date of positive report must be ≤5 days prior to randomization.

- RT-PCR Quantitative Viral (in a clinically relevant specimen (Naso-Oro-Pharyngeal as appropriate)): Day 1 (Prior to dosing), Day 4 (±8 hrs), Day 8 (±8 hrs), Day 12 (±1 day), Day 15 (±1 day), Day 22 (±1 day) and End of study [EoS; Day 29 (±2 day)]

- Ordinal Scale Assessment: Screening, Day 8 (±8 hrs), Day 15 (±1 day), Day 22 (±1 day) and End of study [EoS; Day 29 (±2 day)]

- Adverse events/ Serious Adverse Events: Adverse events/ Serious Adverse Events will be recorded from the time of first study drug administration till end of study safety assessments. Other medical events not related to disease condition under study and occurring before IMP administration, but after signing the informed consent form will be recorded on the medical history/current medical conditions of case report form.

- In addition to protocol-specific laboratory tests and/or clinical examinations at scheduled time points, additional tests/clinical examination may be conducted to evaluate subject safety at any time during the study, at the discretion of the Investigator (can be done in local laboratory or nearby clinic/hospital/institution).

- Medication taken prior to first dosing: All prescription medications and over-the-counter drugs (including vitamins) taken within 30 days prior to screening must be recorded in the eCRF as Medication history.

- Concomitant medications: Medications taken from time of signing of Informed Consent form until study completion (i.e. End of study) will be captured as concomitant medications.

- Prohibited medications: Any other antiviral medications or medication with antiviral potential.

Note:

- It is recommended that general precautions need to be taken by the staff caring for COVID patients during the trial.

- In case the subject is hospitalized during the course of study, the activities specified in scheduled visits / time points will be carried out within the hospital facility.

Sample Size:

In Part 1, approximately 64 subjects will be randomized to up to 4 cohorts of 5 consecutive days of one of the following regimens in addition to SOC in 2:1:1 ratio as shown below:

Treatment Arm	Day 1	Day 2	Day 3	Day 4	Day 5
Brequinar + Dipyridamole (N=8)	BRQ XX mg OD DPY 75 mg TID	BRQ XX mg OD DPY 75 mg TID	BRQ XX mg OD DPY 75 mg TID	BRQ XX mg OD DPY 75 mg TID	BRQ XX mg OD DPY 75 mg TID
Brequinar (N=4)	BRQ XX mg OD	BRQ XX mg OD	BRQ XX mg OD	BRQ XX mg OD	BRQ XX mg OD
Placebo (N=4)	PBO XX mgPlacebo OD	PBO XX mgPlacebo OD	PBO XX mgPlacebo OD	PBO XX mgPlacebo OD	PBO XX mgPlacebo OD

The brequinar dose will start at 50 mg and may be escalated to 100 mg, 150 mg, and 200 mg if safety criteria are met for each cohort (see Safety Criteria below).

The hospital pharmacist is to be unblinded. Bulk supplies of investigational medicinal product (IMP) of brequinar 50 mg, brequinar 100 mg, dipyridamole 75 mg, brequinar placebo 50 mg and brequinar placebo 100 mg will be supplied to the unblinded hospital pharmacist.

The unblinded hospital pharmacist is to prepare the assigned IMP for each individual subject at that institution and create an appropriately labeled bottle/zip lock bag of study medication sufficient for a 5-day treatment course. Randomization code will be supplied using an IWRS.

Alternatively, the hospital pharmacist and study team may decide to distribute IMP on a daily basis for each of the 5 days for brequinar and dipyridamole while the subject is hospitalized, depending on the most convenient method.

Inclusion Criteria:

Subjects will be eligible if they meet all of the following 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. Subjects between ≥18 and ≤65 years of age.
3. Subjects found positive for SARS-CoV-2 either by rapid antigen test or by reverse transcription polymerase chain reaction (RT-PCR) using ICMR-validated kit.
   Note: Test need not be repeated in those with possession of confirmed positive report but positive result test date must be ≤5 days of first dose of study drug.
4. Mild or Moderate COVID-19 as per latest updated version of CLINICAL MANAGEMENT PROTOCOL for COVID-19 (in Adults) released by Government of India Ministry of Health and Family Welfare Directorate General of Health Services (EMR Division).
5. The effects of brequinar on the developing human fetus are unknown. For this

	reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men and women treated or enrolled on this protocol must also agree to use adequate contraception for the duration of study participation, and for 90 days after completion of brequinar administration. 6. Male subjects must agree to refrain from sperm donation and female subjects must agree to refrain from ovum donation from initial study drug administration until 90 days after the last dose of brequinar. 7. At least one non-respiratory COVID-19 symptom characterized as moderate to severe by the Investigator including but not limited to fatigue, chills, fever, body aches, nasal congestion, nausea, vomiting, or other sign or symptom commonly associated with COVID-19 in the opinion of the investigator. Symptom onset must be ≤5 days prior to first dose. Subject must have one or more signs/symptoms present at first dose. 8. Willing to participate in the PK/PD subset if at one of the identified sites. 9. Able to swallow capsules.
Exclusion Criteria:	Subjects will not be eligible for this study if any of the following in present at the time of study inclusion: 1. Have an oxygen saturation of <90% while breathing ambient air. 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 subject. 3. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test. 4. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide) or other agents known to cause bone marrow suppression leading to thrombocytopenia. 5. Ongoing treatment with aspirin and or dipyridamole, famotidine or cimetidine. Remdesivir and ivermectin are prohibited through Study Day 8. Steroids are permitted per the guidelines. 6. Platelets ≤125,000 cell/mm^3. 7. Hemoglobin <10 gm/dL. 8. Absolute neutrophil count <1000 cells/mm^3. 9. Renal dysfunction, i.e., creatinine clearance <30 mL/min. 10. AST or ALT >3 x ULN, or total bilirubin >ULN. Gilbert's Syndrome is allowed. 11. Bleeding disorders or blood loss requiring transfusion in the six weeks preceding enrollment.

	12. Ongoing gastrointestinal ulcer, or gastrointestinal bleeding within 6 weeks of first dose. 13. Chronic hepatitis B infection, active hepatitis C infection, active liver disease and/or cirrhosis per subject report. 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).
PK/PD Sample Collection and Processing:	**Blood collection and processing for PK analysis:** Brequinar/Dipyridamole PK/PD blood samples are to be collected either through an indwelling intravenous cannula (Venflon or similar) or may also be collected through a fresh vein puncture at each time point. For PK samples, collect a 10 mL sample using syringe/adaptor and transfer to a pre-labelled vacutainer containing K_2EDTA as anticoagulant. Immediately following blood collection, gently invert the vacutainer 5 - 7 times to mix the anticoagulant. Place the filled vacutainer on wet ice bath (below 10 ^{0}C) during sample collection activity until storage of plasma. Centrifuge the PK blood sample at 4000 RPM for 10 minutes at 5 ± 3°C to separate plasma. Keep the samples on wet ice bath (below 10 ^{0}C) both before centrifugation and after separation. Transfer the separated plasma to pre-labeled polypropylene tubes in 2 aliquots: Aliquot 1: Approximately 1.7 mL of plasma Aliquot 2: Approximately 1.2 mL of plasma Aliquots are to be stored upright in a box containing dry ice or in a freezer at a temperature –15 °C or colder for interim storage at the sites until shipment to Veeda Clinical Research Ltd., Ahmedabad. Note: Entire activity from blood sample collection to storage in a freezer should be completed within 60 minutes time. Ship each aliquot separately. During shipment the samples are to be packed in thermocol boxes containing an adequate amount of dry ice. The temperature will be monitored using calibrated data logger during shipment. Samples will be stored at -78±8°C until completion of analysis at Veeda Clinical Research Ltd., Ahmedabad. Shipment for the backup Aliquot 2 will be carried out after confirmation of receipt of Aliquot 1. A designated person or designate from bioanalytical department will take receipt of the samples at Veeda Clinical Research Ltd., Ahmedabad. The condition of the samples is

	to be examined on arrival at Veeda Clinical Research Ltd., Ahmedabad. If any of the samples are not in a frozen condition, clinical facility and\or Sponsor is to be informed. After receiving the samples at Veeda Clinical Research Ltd., Ahmedabad, the samples will be stored at -78 ± 8 °C until completion of analysis. **Blood collection and Processing for PD analysis:** For PD (nucleotide pools) samples, collect a 10 mL blood sample in a K_2EDTA vaccutainer per subject per time point is required to process for isolating the PBMCs in order to analyse the intracellular nucleotide content. The filled vacutainer tube is slowly inverted 2-3 times to ensure the collected blood mixes with the anticoagulant. No centrifugation will be performed on the PD samples at the site. Freshly collected blood samples are to be shipped once daily in 2-8 °C shipment condtions to Bioneeds laboratory for further processing. The blood should reach the laboratory within 24-36 hours. Note: Samples of patients enrolled in Arm 3 (SOC + Placebo) of each cohort will not be analysed.
Quantitative PCR (qPCR)	• Obtain a NP/OP swab sample to be processed as outlined in the laboratory manual and sent to a central lab for analysis of quantitative PCR.
Drug and Nucleotide Pool Analysis:	• Plasma concentration of brequinar and dipyridamole will be quantified at the Bioanalytical facility of Veeda Clinical Research Ltd. • Intracellular nucleotide pool concentration (ATP/GTP/UTP/CTP) from isolated PBMCs will be estimated at the Bioanalytical facility of Bioneeds India Private Limited, Bengaluru.
Safety Criteria:	An independent, unblinded study physician (from CRO) will assess each cohort for safety. A cohort will be declared safe are as soon as all results are available for the Day 15 visit if the following conditions are met: • No toxic deaths (deaths judged by the investigator to be related to either study drug); • Not more than 1 toxic SAE (SAEs judged by the investigator to be related to either study drug); • No Grade 3 or higher toxicities (including laboratory AEs as per CTCAE version 5.0 or higher) (AEs judged by the investigator to be related to either study drug); • <4 subjects with any grade toxicity (AEs judged by the investigator to be related to either study drug). In addition to the cohort-level safety, the independent study physician (from CRO) will determine if any subjects meet Individual Stopping Criteria: • Subjects who develop a Grade 3 toxicity that is assessed by the investigator to

	be related to the study drug are to be permanently discontinued from study treatment but will continue in the study for safety assessments. • Subjects who develop a Grade 4 toxicity, regardless of relatedness to study drug, are to be permanently discontinued from study treatment but will continue in the study for safety assessments. In addition to the individual subject-level safety, the independent study physician (from CRO) will determine if a cohort meets Cohort-level Stopping Criteria prior to completing the 16 subjects, in which case no additional subjects will be enrolled into that cohort and no higher brequinar doses will be assessed: • ≥3 brequinar-treated or combination-treated subjects meet the individual stopping criteria; • ≥5 brequinar-treated or combination-treated subjects develop a Grade 3 or higher AE regardless of relationship to study drug.
Statistical methods:	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, standard error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the 95% CI, when appropriate. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.4 or higher). Safety and tolerability will be assessed in terms of AEs, SAEs, and safety laboratory data. Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of treatment-emergent adverse events, defined as TEAEs occurring after first dose will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results and other clinical measures will be summarized using appropriate descriptive statistics.
Ethical Issues:	The study will commence only after a written approval is obtained from the Institutional Ethics Committee and applicable regulatory authorities. The trial will be conducted as per the biomedical research on human participants (ICMR) 2017 guidelines, New Drugs and Clinical Trial Rules (2019) of India, ICH (Step 5) 'Guidance on Good Clinical Practice' ICH Guidance E6 (R2), Declaration of Helsinki (Brazil, 2013) and with procedures oriented to Good Laboratory Practice and applicable regulatory guidelines.

3.2 Schedule of Activities

Windows are relative to time of first dose Procedures	Screening[a]/ Day 1 (Day -4 to 0)	Day 2, 3 (± 8 hrs)	Day 4 (± 8 hrs)	Day 5, 6, 7 (±8 hrs)	Day 8 (±8 hrs)	Day 12 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Final Visit[k] Day 29 (±2 days)
Type of visit[g]	IPV[f]	TC[f]	TM	TC	IPV+TM	TM	IPV+TM	IPV+TM	IPV+TM
Informed Consent (note Date and Time)	X								
AE/Concomitant Medications (dose, route, duration or ongoing)	X	X	X	X	X	X	X	X	X
Medical history (relevant within 30 days or ongoing)/ History of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection)	X								
Demographics (subject reported/ measured height and weight, age, sex, race/ethnicity)	X								
Check for Physical Exam abnormalities (subject self-reported/examiner evaluated)	X								
Pregnancy Test (WOCBP) (serum at Screen and urine at D29)	X								X
Hematology / Biochemistry / Urine Analysis[j]	X	X[m]			X		X		X
HCV, HbSAg, HIV Test	X								
Vital Signs[b]	X		X		X	X	X	X	X
Symptom Assessment[c]	X	X	X	X	X	X	X	X	X
Rapid antigen test/SARS-CoV-2 RT-PCR Qualitative[d]	X								
RT-PCR Quantitative Viral Load[l]	X		X		X	X	X	X	X
PK/PD Sampling (subset of subjects)[h]	X	X	X	X	X				
Hospitalized Days 0 to 8[i]	Day 0	X	X	X	X				
Hospital/Healthcare utilization Status							X	X	X
Ordinal Scale Assessment	X				X		X	X	X
Confirm Eligibility	3								
Randomize subject and dispense Study Medication	X								
Study drug administration (Days 1 – 5 only)[f]	X	X	X	X					

Windows are relative to time of first dose Procedures	Screening[a]/ Day 1 (Day -4 to 0)	Day 2, 3 (± 8 hrs)	Day 4 (± 8 hrs)	Day 5, 6, 7 (±8 hrs)	Day 8 (±8 hrs)	Day 12 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Final Visit[k] Day 29 (±2 days)
Type of visit[g]	IPV[f]	TC[f]	TM	TC	IPV+TM	TM	IPV+TM	IPV+TM	IPV+TM
Drug Accountability (Unblinded pharmacist)					X				
PDC distribution		X			X		X	X	
PDC collection and review					X		X	X	X
Symptom assessment form distribution		X			X		X	X	
Symptom assessment form collection and review					X		X	X	X

a. Day -4 to 0 includes screening activities.
b. Vital signs (include heart rate, respiratory rate, body temperature, SpO_2) assessment will be done at screening, Day 4 (±8 hrs), Day 8 (±8 hrs), Day 12 (± 1 day), Day 15 (±1 day), Day 22 (±1 day), End of study [EoS; Day 29 (±2 day)]. Subjects who leave the hospital will be provided with a thermometer and pulse oximeter with heart rate monitoring capability. Training will be provided during the first home visit. Vital signs parameters will be observed and recorded by study staff via telemedicine or in-person visit (IPV) (at the study site or home visit).
   Note: If subject is hospitalized, vital signs assessment will be done on daily basis by site team during hospitalization through day 8 then following the Vital signs visits as listed above.
c. Symptom Assessment will capture respiratory symptoms as well as sore throat, cough, GI symptoms (vomiting, diarrhea), fatigue, anosmia, dysgeusia, other (specify), etc. Severity None, Mild, Moderate, or Severe will be collected. Longest symptom(s) onset date must be within 5 days of first dose.
d. Documentation of a positive SARS-CoV-2 result from Rapid antigen test/RT-PCR or other regulatory agency-approved test is required to qualify for Screening. Test need not be repeated in those with possession of confirmed positive report. Date of positive report must be ≤5 days prior to randomization.
e. Day 1 PK/PD baseline sample must be obtained prior to dosing.
f. Subject will take study drug once daily Days 1 – 5 and record doses in a medication diary. Note that some visits/visit activities post hospital discharge may be conducted via telephone, telemedicine, or digital media other than serum pregnancy test and chemistry/hematology/PK/PD sample collections. These labs may be collected at the clinical site or another designated out-patient facility/laboratory or collected via home visit.
g. IPV= in-person visit (subject's home or at clinical site, may also include TM or TC if all study visit activities cannot be completed by the in-person personnel); TC = Telephone Call with site and subject; TM = Telemedicine with site and subject.
h. PK/PD Sampling: For PK, day 1 samples will be drawn pre-dose, and after dosing at 1h, 2h, 4h, and 8h (Note: 8h sample is to be obtained prior to the next dose of dipyridamole), and pre-dose days 2, 3, 4, 5 and on day 8. For PD, samples will be drawn pre-dose days 1-5 and on day 8. One 10 mL sample is required for PK at each timepoint; one 10 mL sample is required for PD at each time point.
i. Subjects hospitalization will be based on the discretion of the Investigator. Hospitalization for the purpose of PK/PD sample collection can be done at Investigator's discretion, in this case hospitalization may be for selected few days and may not be for entire 8 days duration. Subjects may leave the hospital

after the Day 8 samples have been obtained if medically able to be discharged. In case the subject is hospitalized during the course of study, the activities specified in scheduled visits / time points will be carried out within the hospital facility.

j. Sample collection for performing laboratory tests on days 1, 8, 15 and 29 will be conducted at the site or via home visit.

k. If a study subject is discontinued from the study during an unscheduled visit, the unscheduled visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for End of Study Visit will be performed.

l. RT-PCR Quantitative Viral will be done at Day 1 (Prior to dosing), Day 4 (±8 hrs), Day 8 (±8 hrs), Day 12 (±1 day), Day 15 (±1 day), Day 22 (±1 day) and End of study [EoS; Day 29 (±2 day)]

m. Day 1 unless same day as Screening visit.

Note:

- If the unscheduled visit is not an Early Discontinuation Visit (i.e., the study subject will continue to take part in the study), then the reason for unscheduled visit is to be documented and required procedures at the discretion of investigator considering the reason for visit, will be performed.

4.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

4.1 Clinical Facilities

Clinical facilities will be the clinics/ hospitals of investigators' site.

4.2 Biostatistics Services and Quality Assurance

Biostatistics	:	Dr. Ghanshyam Patel
Quality Assurance	:	Mrs. Amee Kanuga
Authorised Signatory	:	Dr. Sumit Arora

Veeda clinical research Ltd.,

Shivalik Plaza, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India.

Phone No.: +91-79-3001 3000

4.3 Medical Experts

Veeda's Medical Expert:	Sponsor's Medical Expert:
Dr. Ravi Alamchandani Veeda Clinical Research Ltd., Shivalik Plaza, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India. Phone No.: +91-79-3001 3000 E-mail: Ravi.A1950@veedacr.com	John Pottage, MD E-mail: John.pottagemd@gmail.com Phone No: +1-610-761-0840

5.0 BACKGROUND INFORMATION

5.1 Introduction

Coronaviruses are large group of viruses that cause illness in humans and animals. Rarely, animal coronaviruses can evolve and infect people and then spread between people such as has been seen with MERS and SARS. The current outbreak of novel coronavirus disease (COVID-19) was initially noticed in Wuhan city in Hubei Province of China in mid December, 2019 has now spread to 215 countries/territories/areas worldwide. WHO (under International Health Regulations) has declared this outbreak as a "Public Health Emergency of International Concern" (PHEIC) on 30th January 2020. WHO subsequently declared COVID- 19 a pandemic on 11th March, 2020.

Pathophysiology of COVID 19:

Most adult patients with COVID-19 predominantly have a respiratory tract infection associated with SARS-CoV-2 infection. However, in a small proportion of cases, the disease can progress to a more severe stage characterized by a dysregulated immune response with hyperinflammation with subsequent development of ARDS.

Clinical Features:

COVID-19 patients reporting to various COVID-19 treatment facilities have reported the following signs and symptoms:

- Fever,
- cough,
- general weakness/ fatigue,
- headache,
- myalgia,
- sore throat, coryza,
- dyspnoea,
- anorexia/nausea/vomiting,
- diarrhoea,
- altered mental status.
- loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms has also been reported.

Older people and immune-suppressed patients in particular may present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, delirium, and absence of fever.

Diagnosis of COVID 19:

COVID-19 diagnosis is currently based on using a reverse transcriptase polymerase chain reaction (RT-PCR)

assay to detect viral RNA in respiratory samples. The high specificity of RT-PCR removes the need for lower respiratory tract samples to diagnose COVID-19 when a nasopharyngeal swab is positive for a patient with recent onset of the disease.

5.2 Safety of brequinar

Introduction:

Brequinar is an orally available and potent inhibitor of dihydroorotate dehydrogenase (DHODH). DHODH catalyzes the fourth step in pyrimidine synthesis, the conversion of dihydroorotate (DHO) to orotate. DHODH inhibitors, including brequinar, inhibit *de novo* pyrimidine synthesis thereby leading to a depletion of the cellular pool of uridine, cytidine, and thymidine ribonucleotides and deoxyribonucleotides. Brequinar has previously been evaluated for the treatment of hematologic malignancies, autoimmune disorders and COVID 19. There are other DHODH inhibitors that have been approved for use in the treatment of rheumatoid arthritis and multiple sclerosis.

Brequinar has been shown to have significant *in vitro* antiviral activity against several RNA viruses, including SARS-CoV-2, the cause of COVID-19 disease. As RNA viruses cannot synthesize their own ribonucleotides, they depend upon the host intracellular pool of ribonucleotides as the source for viral gene expression and replication. By transiently depleting the pool of host of pyrimidines, DHODH inhibition denies a virus of its source of ribonucleotide building blocks and thereby suppresses viral replication. This antiviral strategy targeting a host rather than viral protein also is less likely to select for resistant viruses.

Preclinical study data:

Initial nonclinical pharmacology studies of brequinar confirmed that its mechanism of action is the inhibition of *de novo* pyrimidine synthesis. Further studies with partially purified enzymes isolated from L1210 cells showed that brequinar inhibited DHODH activity, the fourth biochemical step in pyrimidine synthesis

Clinical study data:

Brequinar has been studied under FDA IND 149,291 in 138 patients in two studies as an antiviral for coronavirus disease 2019 (COVID-19); 71 of these patients were treated with brequinar. Brequinar was administered as a single daily dose for five consecutive days with standard of care (SOC) in these COVID-19 studies.

Brequinar has also been previously studied in more than 1,000 patients in 30 clinical trials for treatment of solid tumors, psoriasis, and organ transplant. More recently Clear Creek Bio has studied brequinar use for acute myeloid leukemia (AML). In the oncology, psoriasis and organ transplant studies brequinar was administered as a single dose and as multiple courses with once weekly, twice weekly, single dose every 3 weeks, daily times 5 every 4 weeks, and daily times 21 days regimens. The maximum single intravenous dose of 3250 mg/m^2 was administered in an oncology study; the maximum oral dose of 950 mg/m^2 twice weekly was also dosed during an oncology study.

5.3 Brequinar COVID-19 Studies

CCB-CRISIS-01 in Hospitalized Patients

The CRISIS-01 trial studied standard of care (SOC) and SOC with 5 days of brequinar administration in patients hospitalized for treatment of COVID-19. This was a phase 1 randomized, open label, multi-center study designed to enroll approximately 24 subjects. All subjects received SOC per institutional guidelines for treatment of patients with SARS-CoV-2 infection. In addition to SOC, the brequinar group received brequinar 100 mg as an oral capsule once daily for 5 days.

A total of 25 subjects were randomized in study CRISIS-01 at 5 sites. Two subjects assigned to the SOC plus brequinar group were randomized but withdrew consent and were never treated with brequinar. The modified Intent-to-Treat (mITT) population which was used for all study analyses included all 23 randomized subjects who had at least one post-randomization assessment, and who received at least one dose of study medication if randomized to the SOC plus brequinar group. A total of 15 subjects were exposed to SOC plus brequinar and 8 subjects had SOC treatment only.

Brequinar was generally safe and well-tolerated in this population. No subjects discontinued study drug treatment due to an AE. No subjects died. 4 subjects (17.4%) experienced a total of 6 SAEs (1 in the SOC + brequinar group and three in the SOC only group). 12 subjects (52.2%) experienced a total of 28 treatment emergent AEs (TEAEs); 10/15 subjects (66.7%) reported 22 TEAEs in the SOC plus brequinar group; 2/8 (25.0%) reported 6 TEAEs in the SOC only group. The most common TEAE was hyperglycaemia reported in 3 subjects (20.0%) in the SOC plus brequinar group. Increased ALT was experienced by 2 subjects (13.3%) in the SOC plus brequinar group in subjects who had also received remdesivir. No other AEs were reported for more than one subject in either treatment group.

CCB-CRISIS-02 in Non-Hospitalized Patients

The CRISIS-02 trial: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2.

The CRISIS-02 trial studied outpatients (non-hospitalized patients) who had a positive SARS-CoV-2 RT-PCR test using a saliva sample and were symptomatic. Subjects were randomized to receive SOC + 5 days of brequinar or SOC + 5 days of placebo. The purpose of this study was to determine if the *in vitro* antiviral activity of brequinar translated to patients infected with SARS-CoV-2 by measuring the effect of treatment with brequinar on SARS-CoV-2 RNA levels (henceforth called “viral load”).

The study enrolled 115 subjects (56 in the SOC plus brequinar group and 59 in the SOC plus placebo group). All subjects received SOC for treatment of patients with COVID-19 infection. In addition to SOC, the subjects self-administered one capsule of brequinar or placebo once daily for 5 days. Subjects were randomly assigned in a 1:1 ratio to SOC plus brequinar or SOC plus placebo.

The median decrease in viral load was higher in the SOC plus brequinar group beginning at Day 12 (Days 12, 15, 22, and 29). None of the comparisons to placebo reached statistical significance. None of the other efficacy endpoints showed a difference between the SOC plus brequinar compared to the SOC plus placebo treatments.

There was no effect in reducing the time to clinical symptom resolution, however the majority of patients had very mild disease making improvements difficult to assess.

Brequinar was safe and well-tolerated in this population. No subjects discontinued study drug treatment or discontinued from the study due to an AE. No subjects died. One subject in the brequinar plus SOC group (1.8%) experienced one non-study-drug-related SAE (admitted to hospital for COVID-19 penumonia). A total of 23 subjects (52.2%) experienced a total of 28 TEAEs; 10/56 subjects (17.9%) reported 22 TEAEs in the SOC plus brequinar group; 13/59 (22.0%) reported 6 TEAEs in the SOC plus placebo group. AEs were experienced by one subject only with the exceptions of nausea and rash each of which were experienced by two subjects. The majority of AEs were mild or moderate; there was one subject (1.8%) with a non-related Grade 3 AE in the SOC plus brequinar group (COVID-19 pneumonia) and 3 subjects with Grade 3 AEs in the SOC plus placebo group (chills, pain, injury and breast pain); all of the related AEs were considered Mild (Grade 1) by the investigators. There were no Grade 4 or higher AEs in either treatment group.

A total of 6 subjects had AEs considered possibly related to treatment, 3 in each group.

5.4 Rationale

Rationale for the use of brequinar and dipyridamole in COVID-19 disease:

Brequinar is a potent DHODH inhibitor that blocks *de novo* pyrimidine synthesis in the host and has been previously studied in more than 1,000 cancer, psoriasis, and organ transplant patients.

Brequinar has potent *in vitro* antiviral activity against many RNA viruses including SARS-CoV-2. The *in vitro* antiviral activity of brequinar against SARS-CoV-2 is likely due to DHODH inhibition and shows nanomolar potency and a high selectivity index in inhibiting viral replication these studies. Brequinar has also been studied in two clinical trials in patients with confirmed SARS-CoV-2 infection. In these two studies, 25 were hospitalized (15 treated with brequinar) and 115 were non-hospitalized (56 treated with brequinar). Results in these 71 COVID-19 patients demonstrated that brequinar 100 mg x 5 days was safe and well-tolerated in these populations. Brequinar's antiviral activity was demonstrated in the out-patient study as shown by decreased viral load compared to placebo at days 12, 15, 22 and 29 and a shorter duration of viral shedding. The strong safety data in 71 COVID-19 subjects treated with daily brequinar at 100 mg for 5 days provides strong support for the further investigation of brequinar in the treatment of COVID-19.

The antiviral effects of brequinar may be blunted *in vivo* by pyrimidine salvage. One approach to enhancing the antiviral effect of brequinar is to block the pyrimidine salvage pathway by combining brequinar with a pyrimidine salvage inhibitor. Dipyridamole has been shown *in vitro* to block pyrimidine salvage and may potentiate the antiviral activities of DHODH inhibition on RNA viruses (Liu et al., 2020). Blocking pyrimidine salvage via dipyridamole shows improved *in vitro* antiviral efficacy of *de novo* pyrimidine synthesis inhibition via DHODH inhibition and will be used in this study in combination with brequinar to enhance brequinar's antiviral activity.

Dipyridamole is a well-tolerated, FDA-approved medication that is a nucleoside transport inhibitor and PDE3 inhibitor that inhibits blood clot formation and causes vasodilation. Dipyridamole was first approved by the US

FDA in 1961 for prevention of thromboembolism in patients who have had cardiac valve replacement. It has also been widely prescribed in combination with aspirin to prevent stroke.

The CCB-CRISIS-04 trial will study subjects who have mild to moderate COVID-19 infection confirmed by a positive SARS-CoV-2 RT-PCR qualitative test / rapid antigen test and have mild/moderate signs and/or symptoms ongoing at study entry. The purpose of this study is to determine if the antiviral activity of brequinar can be improved by combining brequinar with dipyridamole in patients infected with SARS-CoV-2.

5.5 Hypothesis

Treatment with brequinar combined with dipyridamole in patients with SARS-CoV-2 viral infection will reduce viral load, decrease time to resolution of COVID-19-related clinical signs and/or symptoms and improve clinical outcomes compared with current standard care.

6.0 STUDY OBJECTIVE

Primary Objective:

- To characterize the safety and tolerability of the brequinar-dipyridamole combination in COVID-19 subjects as measured by frequencies of grade 3 and 4 toxicities and serious adverse events (SAEs) considered by the investigator to be related to the combination.

Secondary Objectives:

For subjects treated with the brequinar-dipyridamole combination compared to subjects treated with brequinar and to subjects treated with placebo through Day 29, to determine:

- Reduction of qPCR SARS-CoV-2 levels through Day 29 and at days 4, 8, 12, 15, 22, and 29;
- Reduction in time to symptom improvement;
- Reduction in percentage of subjects requiring hospital admission/re-admission as an in-patient for >24 hours;
- Reduction in percentage of subjects requiring medical attended visits, e.g., hospitalization, emergency room visits, Urgent Care/Family Doctor visits;
- Reduction in percentage of subjects requiring supplemental support such as oxygen.

Exploratory Objectives:

- To determine brequinar-dipyridamole combination and brequinar's pharmacokinetic profile in a subset of subjects agreeing to participate in the PK/PD aspect of the study;
- To compare the effects of the brequinar-dipyridamole combination to effects with brequinar alone and placebo alone on intracellular nucleotide pools of UTP/CTP/ATP/GTP.

7.0 STUDY ENDPOINTS

Primary Endpoints:

- Frequencies of grade 3 and 4 toxicities and serious adverse events (SAEs) considered by the investigator to be related to the combination, brequinar alone or placebo alone.

Secondary Endpoints:

- qPCR SARS-CoV-2 levels through Day 29 and at days 4, 8, 12, 15, 22, and 29;
- Time to symptom improvement through Day 29;
- Percentage of subjects requiring hospital admission/re-admission as an in-patient for >24 hours through Day 29;
- Percentage of subjects requiring medical attended visits, e.g., hospitalization, emergency room visits, Urgent Care/Family Doctor visits through Day 29;
- Percentage of subjects requiring supplemental support such as oxygen through Day 29.

Exploratory Endpoints (PK/PD):

- Analysis of brequinar's pharmacokinetic profile in a subset of patients that have received brequinar as a part of therapy and have consented to provide PK samples.
- Analysis of effect on intracellular nucleotide pools of UTP/CTP/ATP/GTP in the subset of patients who received brequinar-dipyridamole combination with comparison to brequinar alone and placebo alone.

Clinical improvement will be defined as a 2-point or greater improvement on an 8-point WHO ordinal scale in every subject measured on each designated day, from the date of randomization through day 29. This scale has been used in the current COVID-19 outbreak.

Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitaion of activities	1
	Limitation of activities	2
Hospitalized	Hospitalized, no oxygen therapy	3
Mild disease	Oxygen by mask or nasal prongs	4
Hospitalized	Non-invasive ventilation or high-flow oxygen	5
Severe Disease	Intubation and mechanical ventilation	6

	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

8.0 SELECTION AND WITHDRAWAL OF PATIENTS

Subjects will be selected on the basis of the following inclusion and exclusion criteria.

8.1 Inclusion Criteria

Subjects will be eligible if they meet all of the following 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. Subjects between ≥18 and ≤65 years of age.
3. Subjects found positive for SARS-CoV-2 either by rapid antigen test or by reverse transcription polymerase chain reaction (RT-PCR) using ICMR-validated kit.
   Note: Test need not be repeated in those with possession of confirmed positive report but positive result test date must be ≤5 days of first dose of study drug.
4. Mild or Moderate COVID-19 as per latest updated version of CLINICAL MANAGEMENT PROTOCOL for COVID-19 (in Adults) released by Government of India Ministry of Health and Family Welfare Directorate General of Health Services (EMR Division).
5. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men and women treated or enrolled on this protocol must also agree to use adequate contraception for the duration of study participation, and for 90 days after completion of brequinar administration.
6. Male subjects must agree to refrain from sperm donation and female subjects must agree to refrain from ovum donation from initial study drug administration until 90 days after the last dose of brequinar.
7. At least one non-respiratory COVID-19 symptom characterized as moderate to severe by the Investigator including but not limited to fatigue, chills, fever, body aches, nasal congestion, nausea, vomiting, or other sign or symptom commonly associated with COVID-19 in the opinion of the investigator. Symptom onset must be ≤5 days prior to first dose. Subject must have one or more signs/symptoms present at first dose.
8. Willing to participate in the PK/PD subset if at one of the identified sites.
9. Able to swallow capsules.

8.2 Exclusion Criteria

Subjects will not be eligible for this study if any of the following in present at the time of study inclusion:

1. Have an oxygen saturation of <90% while breathing ambient air.
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 subject.

3. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test.
4. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide) or other agents known to cause bone marrow suppression leading to thrombocytopenia.
5. Ongoing treatment with aspirin and or dipyridamole, famotidine or cimetidine. Remdesivir and ivermectin are prohibited through Study Day 8. Steroids are permitted per the guidelines.
6. Platelets ≤125,000 cell/mm^3.
7. Hemoglobin <10 gm/dL.
8. Absolute neutrophil count <1000 cells/mm^3.
9. Renal dysfunction, i.e., creatinine clearance <30 mL/min.
10. AST or ALT >3 x ULN, or total bilirubin >ULN. Gilbert's Syndrome is allowed.
11. Bleeding disorders or blood loss requiring transfusion in the six weeks preceding enrollment.
12. Ongoing gastrointestinal ulcer, or gastrointestinal bleeding within 6 weeks of first dose.
13. Chronic hepatitis B infection, active hepatitis C infection, active liver disease and/or cirrhosis per subject report.
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).

8.3 Withdrawal Criteria

Subjects may voluntarily withdraw from the study at any time without assigning any reason thereof by withdrawing their consent. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason.

If premature withdrawal occurs for any reason, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information in the CRF. For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, other means of communication even though patient is unwilling to attend further visits etc.

If study participation is discontinued, the final evaluation will be performed as completely as possible. Any comments (spontaneous or elicited) or complaints made by the patient and the reason for termination, date of stopping the study medication and the total amount of study medication must be recorded in the source documents or CRFs.

Criteria for a withdrawal of patients from clinical study:

The subject may be withdrawn from the trial at the discretion of the investigator or the sponsor, if judged non-compliant with trial procedures or due to safety concern.

A subject must in addition be withdrawn from treatment with IMP if the following applies:

- AE requiring permanent discontinuation of study drug.
- The subject suffers from significant intercurrent illness or undergoes surgery requiring study discontinuation during the course of the study.
- Any subject who requires the use of an unacceptable concomitant medicine.
- If the Investigator believes it is not in the subject's best interest to continue.
- The subject wishes to withdraw his/her consent.
- Any other justifiable reason, which should be adequately documented.
- Any subject whose condition worsens, requiring treatment with immunomodulators including but not limited to tocilizumab and / or antiviral drugs including but not limited to remdesivir as per the best judgement of the Investigator.
- Non-compliance: The participant may be withdrawn from the trial at the discretion of the Investigator if it is judged that participant is non-compliant to study assessment and schedule leading to safety concerns.
- Positive pregnancy test: A female participant with a positive pregnancy test will be withdrawn from the trial.

The sponsor or its representative may be contacted for clarification as required on a case-by case basis.

Handling of Withdrawals:

In the case of premature discontinuation of study subject, the investigator should schedule a study discontinuation visit to complete all assessment according to End of Study / Early Termination visit requirements. All reasons for ending participation must be recorded in the source documents or in the CRF.

If the subject discontinues because of an adverse event (serious or non-serious), the investigator must follow up patient's recovery until resolution or stabilization of AEs or up to 30 days after administration of last dose of IMP, whichever is earlier.

This visit should be documented in the appropriate section of the Case Report Form (CRF). The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up for such subjects, and document the course of the subject's condition. In addition, the investigator will report the subject's withdrawal to the responsible study monitor immediately.

Subjects withdrawn from investigational product treatment will be treated as routine subjects. The investigator will discuss the appropriate therapy with each subject who withdraws early from this study. Determination of the appropriate follow-on therapy will be left to the discretion of the investigator and investigator could treat such subjects as per his/her routine practice.

9.0 STUDY PROCEDURE

9.1 Study Design

The first part of the study will be a phase II, randomized, assessor-blind, multicenter, multi-dose, placebo-controlled study in approximately 64 subjects with mild to moderate COVID-19 infection confirmed by a

positive SARS-CoV-2 RT-PCR qualitative test /rapid antigen test and who have at least mild to moderate signs and/or symptoms ongoing at study entry.

Approximately 32 subjects (50% of subjects per arm per cohort) at selected sites will be invited to participate in the "PK/PD" arm of the study until approximately 8 subjects in each cohort have been recruited after providing written informed consent for the same. PK/PD includes brequinar and dipyridamole plasma concentrations and analysis of intracellular pools of UTP/CTP/ATP/GTP.

If a particular cohort meets study stopping criteria (as defined in section "Stopping Criteria") or is found to be unsafe by DSMB members, then the study will not proceed with enrollment of subsequent cohorts.

An expansion cohort of approximately 48 subjects will be added to the cohort with the highest brequinar dose that meets safety criteria.

All subjects will receive SOC as per relevant guidelines for treatment of patients with mild to moderate COVID-19 infection.

Subjects will be randomized to one of the following cohorts in Part 1:

Cohort 1:

- Arm 1: 5 days of standard of care (SOC) + brequinar 50 mg OD + dipyridamole 75 mg TID (N = 8)
- Arm 2: 5 days of SOC + brequinar 50 mg OD (N = 4).
- Arm 3: 5 days of SOC + brequinar placebo 50 mg OD (N = 4).

Cohort 2:

If the 50 mg brequinar OD + dipyridamole 75 mg TID meets safety criteria as pre-defined in the protocol the brequinar dose will be escalated to 100 mg.

- Arm 1: 5 days of standard of care (SOC) + brequinar 100 mg OD + dipyridamole 75 mg TID (N = 8)
- Arm 2: 5 days of SOC + brequinar 100 mg OD (N = 4).
- Arm 3: 5 days of SOC + brequinar placebo 100 mg OD (N = 4).

Cohort 3:

If the 100 mg brequinar OD + dipyridamole 75 mg TID meets safety criteria as pre-defined in the protocol the brequinar dose will be escalated to 150 mg:

- Arm 1: 5 days of standard of care (SOC) + brequinar 150 mg (100 mg + 50 mg) OD + dipyridamole 75 mg TID (N = 8)
- Arm 2: 5 days of SOC + brequinar 150 mg (100 mg + 50 mg) OD (N = 4)
- Arm 3: 5 days of SOC + brequinar placebo 150 mg (100 mg + 50 mg) OD (N = 4).

Cohort 4:

If the 150 mg brequinar OD + dipyridamole 75 mg TID meets safety criteria as pre-defined in the protocol the brequinar dose will be escalated to 200 mg:

- Arm 1: 5 days of standard of care (SOC) + brequinar 200 mg (100 mg +100 mg) OD + dipyridamole 75 mg TID (N = 8)
- Arm 2: 5 days of SOC + brequinar 200 mg (100 mg +100 mg) OD (N = 4)
- Arm 3: 5 days of SOC + brequinar placebo (100 mg + 100 mg) OD (N = 4).

Expansion Cohort:

Approximately forty-eight (48) subjects will be added to the cohort with the highest brequinar dose that meets safety criteria in a 2 : 1 ratio of active treatment (approximately 32 in SOC + brequinar + dipyridamole treated and 16 in SOC + brequinar monotherapy group). Additional sites may be added if required to meet enrollment of the expansion cohort in an efficient manner.

9.2 Study Procedure

To be eligible for screening, subjects must have a documented positive SARS-CoV-2 test result within 5 days of first dose of study drug and have at least one ongoing symptom consistent with SARS-CoV-2 infection rated as at least mild to moderate in the opinion of the investigator. The subject's earliest symptom must have an onset date within 5 days of first dose of study drug.

Subjects will undergo screening (day -4 to 0) for confirming eligibility for participation in the study. Study Day 1 includes randomization visit.

Subjects will be randomized to a cohort as described above.

Screening activities as well as randomization can take place on the same day as a combined Screening/Day 1 visit, if the site team is able to obtain Screening lab results on the same day. Otherwise, Day 1 is to take place as soon as Screening lab results are available.

Study Day 1 and first dose of study drug must take place ≤5 days from onset of first symptom.

Subjects may be hospitalized as many as 9 days in the study (day 0 to 8) or more for the PK/PD sample as per Investigator discretion.

For subjects participating in the PK/PD subset,

Blood samples for estimating brequinar concentrations will be drawn (PK):

- Day 1: Pre-dose (within 1 hour prior to study drug administration) and post dose at 1h, 2h, 4h, and 8h; note that the 8h sample is to be obtained prior to the next dose of dipyridamole;
- Days 2 – 5 pre-dose and Day 8.

Blood samples for nucleotide pool analysis will be drawn (PD):

- Days 1 – 5 pre-dose and Day 8.

Aliquots of the NP/OP swab samples are to be stored at the testing laboratory for possible additional virological testing.

Screening visit and study visits on Days 1, 8, 15, 22 and 29 will be either in person or a combination of in-person and virtual visit (telemedicine or other remote technique) or by visit to patient's home by site team.

Study visits on Day 4 and 12 may be virtual visits (telemedicine or other remote technique) or in person.

On Days 2, 3, 5, 6 and 7, the site will have a telephone call / or in-person communication with the subject for changes in concomitant medications and assessment of adverse events (same will also be captured by the subject using a patient diary card or these visits will be conducted in person).

Note:

- Study procedures are presented in detail in the Schedule of Events.
- Days 1, 8, 15 and 29 require sample collection for performing laboratory tests and will be conducted at the site or via home visit.
- Any in-person visit may also have telemedicine or telephone components if all study activities cannot be completed in person.
- The visits that include bloodwork must be conducted at the study site or arrangements made for sample collection at the subject's home or other appropriate location.
- Site staff (in case of an in-person visit) or subjects (in case of a remote visit) will assess respiratory rate, heart rate, body temperature and SpO_2 (a thermometer and pulse oximeter are to be provided to subjects who are home quarantined, leave the hospital or are unable to return for study visits).
- Subjects will record details of concomitant medications, adverse events in the patient diary card (PDC).
- Subjects will complete a symptom assessment form on designated days daily during the study period (days 1 – 8, 12, 15, 22, and 29).
- In case the subject is hospitalized during the course of study, the activities specified in scheduled visits / time points will be carried out within the hospital facility.
- Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF.

DSMB Meeting:

A Data Safety Monitoring Board (DSMB) will meet to review the safety and scientific conduct of the study. At a minimum, the DSMB will review the protocol and study design prior to study start, after the end of the first part of the study prior to the expansion phase, and at the end of the study.

At each interim meeting the DSMB members will determine whether to stop the study, amend the protocol, or continue the study per protocol. The study enrollment will not be suspended for routine DSMB meetings.

The DSMB will be convened and enrollment suspended if Cohort-Level Stopping Criteria are met. The DSMB may allow the enrollment to resume following their review if safety criteria are met.

9.3 Hospitalization

Subjects may be hospitalized for approximately 9 days (day 0 to 8) in the study as per Investigator discretion for the PK/PD blood sample draws. Subjects may leave after this period (if medically discharged) after the Day 8 blood work has been drawn. Extended stays beyond study Day 8 are permitted if the facility is a dedicated COVID-19 unit or other relevant hospital type or if per the Investigator the extended stay facilitates study procedures; this continuation will not be considered as an SAE. However, prolongation of hospitalization due to increase in disease severity or any other safety concerns related to the subjects will be considered as an SAE.

Hospitalization for the purpose of PK/PD sample collection may be done at Investigator's discretion, in this case hospitalization may be for selected few days and may not be for entire 8 days duration. Appropriate documentation of the same will be done in source file.

9.4 Unscheduled Visits and Early Discontinuation Visit

An Unscheduled Visit is allowed at any time, for any reason, if in the Investigator's opinion it is warranted. If the Unscheduled Visit is due to an AE, the Investigator will determine whether additional visits are needed.

If a subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for End of Study visit will be performed.

If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the subject will continue to take part in the study), then the reason for unscheduled visit is documented and required procedures at the discretion of investigator considering the reason for visit will be performed.

If the Investigator determines that the subject's condition has worsened to the degree that it is unsafe for the subject to continue in the study, the subject may be discontinued from the study as treatment failure and a standard of care treatment may be advised at the Investigator's discretion.

In case of ongoing AEs, telephonic safety follow up will be continued until resolution or stabilization of AEs or up to 30 days after administration of last dose of IMP, whichever is earlier.

9.5 Sample Collection Procedure

Blood collection for PK analysis:

PK blood samples will be collected through an indwelling intravenous cannula (Venflon or similar) placed in the forearm vein of the subjects for up to 24 hours or may also be collected through a fresh vein puncture at each time point. A 10 mL of blood per sample will be obtained using syringe/adaptor and transferred in to pre-labelled vacutainers containing K_2EDTA as anticoagulant. Filled vacutainers will be placed on wet ice bath (below 10 ^{0}C) during sample collection activity and until storage of plasma.

Time of collection of each blood sample (as displayed in the calibrated digital clock) will be recorded in 24-hour clock format (hh:mm) on the PK blood sample collection log and same will be transcribed to eCRFs.

If an intravenous indwelling cannula is placed, maintain this as long as possible by injecting 0.5 mL of 5 IU/mL of heparin in normal saline solution or per hospital's usual practice to maintain the cannula patentcy. When sampling through the cannula, collect study blood samples after discarding the first 0.5 mL of heparinised blood from the cannula. If insertion of cannula is not possible, alternatively blood samples may be drawn by a fresh venipuncture or in case of blockade in an existing cannula, extra heparinised saline will be injected to stimulate the cannula and later blood samples will be collected after discarding the heparinised blood or central line. If the time window does not allow, it is recommended to directly use a disposable syringe for extraction, and appropriately dispose of the retained needle after blood collection.

The blood samples will be withdrawn using syringe or adaptor and transferred into pre-chilled (maintained at temperature below 10 °C), pre-labelled (mentioning Site number, Protocol number, Subject number, Period number, Sampling time point and Sample ID) sample collection tubes containing K_2EDTA as an anticoagulant kept on wet ice bath (below 10 ^{0}C) until centrifugation. Immediately following blood collection, the vacutainers are to be gently inverted 5 - 7 times to mix the anticoagulant.

It is recommended that collected blood samples be placed on wet ice bath (below 10 ^{0}C) from the point of collection until storage of plasma.

Blood collection for PD analysis:

PD (nucleotide pools) blood samples are to be collected in a K_2EDTA vaccutainer. Approximately 10 mL blood sample per subject pre-dose on days 1-5 and on day 8 is required to process for the isolating the PBMCs in order to analyse the intracellular nucleotide content.

Freshly collected blood samples are to be shipped once daily in 2-8 °C shipment condtions to Bioneeds laboratory for further processing. The blood should reach the laboratory within 24-36 hours.

Blood samples will be collected through an indwelling intravenous cannula (Venflon) placed in the forearm vein of the subjects or through a fresh vein puncture. The filled vacutainer tube is slowly inverted 2-3 times to ensure the collected blood mixes with the anticoagulant. This will prevent partial clotting of the samples which is generally seen due to improper mixing. No centrifugation will be done at investigation site.

NP/OP Sample Collection for qPCR

The Laboratory Manual will provide details regarding collection, processing, storage and shipment for qPCR samples.

9.6 Sample Size

No statistical powering has been performed for this study. The number of subjects is designed to provide information on the safety, tolerability, and efficacy of the IMP tested in this study. In Part 1, approximately 64

subjects will be randomized to up to 4 cohorts of 5 consecutive days of one of the following regimens in addition to SOC in 2:1:1 ratio as shown below:

Treatment Arm	Day 1	Day 2	Day 3	Day 4	Day 5
Brequinar + Dipyridamole (N=8)	BRQ XX mg OD DPY 75 mg TID	BRQ XX mg OD DPY 75 mg TID	BRQ XX mg OD DPY 75 mg TID	BRQ XX mg OD DPY 75 mg TID	BRQ XX mg OD DPY 75 mg TID
Brequinar (N=4)	BRQ XX mg OD	BRQ XX mg OD	BRQ XX mg OD	BRQ XX mg OD	BRQ XX mg OD
Placebo (N=4)	PBO XX mg OD	PBO XX mg OD	PBO XX mg OD	PBO XX mg OD	PBO XX mg OD

The brequinar dose will start at 50 mg and may be escalated to 100 mg, 150 mg, and 200 mg if safety criteria are met for each cohort (see Safety Criteria below).

The hospital pharmacist is to be unblinded. Bulk supplies of investigational medicinal product (IMP) of brequinar 50 mg, brequinar 100 mg, dipyridamole 75 mg, brequinar placebo 50 mg and brequinar placebo 100 mg will be supplied to the unblinded hospital pharmacist.

The unblinded hospital pharmacist is to prepare the assigned IMP for each individual subject at that institution and create an appropriately labeled bottle/zip lock bag of study medication sufficient for a 5-day treatment course. The randomization assignment will be provided via an IWRS.

Alternatively, the hospital pharmacist and study team may decide to distribute IMP on a daily basis for 5 days for brequinar and dipyridamole while the subject is hospitalized, depending on the most convenient method.

9.7 Patient identification and Randomisation

Randomization will be carried out using SAS® (SAS Institute Inc., USA) version 9.4 or higher. Randomization will be done in blocks using PROC PLAN such that the design is unstructured. The treatment allocation will be determined according to the randomization schedule and randomization schedule will be done per cohort.

Screening and Randomization Numbering

Each subject will be assigned a unique number that will serve to identify laboratory specimens and all documents, and if randomized throughout the study. If a subject fails to qualify for allocation to the study i.e. is a screen failure, the subject's unique number will not be used for another subject.

Screening number will be a combination of center number, project number and subject number. The center number will be assigned by Veeda to the investigative site (e.g. A, B, C, D) and subsequent sites are assigned consecutive alphabet numbers. Upon signing the informed consent form, the subject will be assigned a screening number by the Investigator. At each site the first subject consented is assigned screening number e.g. A-21-0372-001, and subsequent subjects are assigned consecutive numbers (e.g., the second subject consented is assigned screening number A-21-0372-002, the third subject is assigned screening number A-21-0372-003).

Once a screening number is assigned to a subject, that number will not be reused.

If the subject is deemed eligible for enrollment into the study and will commence dosing, then a randomization number will be assigned via IWRS as defined in the randomization plan. Subjects will be randomized with the next qualifying subject given the next available randomization number.

A source document maintained at the site will link the screening number to the randomization assignment number (once assigned) and the same will be reflected in screening and enrollment log of Investigator site file.

The assigned subject number will be recorded in the CRF of the subject.

The personnel involved in dispensing of study drug and verification of dispensed study drugs will be accountable for ensuring compliance to randomization schedule.

9.8 Blinding

Instructions provided in this section are a general description of operational procedures. Investigators are instructed to always refer to latest version of respective study plans/manuals for detailed and latest information.

The intent of blinding is to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study. The essential aim of blinding, therefore, is to prevent identification of the treatments by the Investigator and others associated with the conduct of the study until all such opportunities for bias have passed.

Due to unavailability of a matching dipyridamole placebo, subjects in the brequinar-dipyridamole treatment arm will have a daily dose of one brequinar capsule of appropriate strength and three 75 mg dipyridamole tablets whereas subjects in the SOC + brequinar only arm will receive only brequinar capsule(s) daily at the appropriate strength. Subjects in the SOC + brequnar placebo arm will receive only brequinar placebo capsule(s) daily at the appropriate strength. No dipyridamole placebo tablets will be provided to the subjects assigned to the brequinar only or brequninar placebo treatment arms.

The Sponsor will provide investigational medicinal product (IMP) bulk drug supplies to the ThermoFisher depot. ThermoFisher will supply each site with bulk supplies of brequinar 50 mg and 100 mg capsules (50 count bottles) and dipyridamole (100 count bottles). An unblinded independent site staff member (e.g., hospital pharmacist) will dispense the IMP for each subject according to the assigned cohort and randomization schedule, and perform IMP accountability by collecting used and unused products. The unblinded pharmacist will not participate in the clinical trial assessments in order to minimize potential bias, and will be instructed not to discuss the IMP with assessors and other blinded study personnel.

The unblinded pharmacist should use an opaque bottle or envelope to ensure that the blinded study team is not able to see the IMP. The subjects will be instructed not to reveal the contents of the bottle(s)/envelope(s) to the blinded investigator or study staff.

The blinded investigational staff performing the assessments and data analysts (with the exception of the biostatistician who will undertake the generation of the randomisation scheme) will remain blinded to the identity of the treatment assignments for individual subjects from the time of randomization until database lock, using the following methods:

- Randomization data will be kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study.
- Only the unblinded pharmacist or designate will be involved in dispensing, administering and collecting the study medication.
- Unblinding of blinded study personnel will be permitted only in the case of patient in emergency condition and at the conclusion of the study.

Data that may potentially unblind the intervention assignment (i.e., study intervention preparation/accountability data, intervention allocation or other specific laboratory data) will be handled with special care to ensure that the integrity of the blinding is maintained and the potential for bias is minimized.

Site specific randomization schedule, drug dispensing logs, drug accountability forms and other papers identifying treatment allocation are kept in a separate binder in a locked cupboard to which the investigators does not have access. Trial staff is provided training in the importance of maintaining blinding, and trial medication delegates/trial coordinators are also helped to set up systems at the clinic.

Every effort must be made to limit the number of unblinded study personnel to ensure the integrity of this study.

In the event of a Quality Assurance audit after the study has been unblinded, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

9.8.1 Unblinding of treatment assignment

If necessary, the Investigator may be required to unblind a participant if an adverse event (AE) meets criteria in order to fulfill expedited regulatory reporting requirements. In this event, Investigator will inform the same to sponsor or its designee/study medical monitor if possible to discuss the particular situation, before breaking the blinding unless this could delay emergency treatment of the participant. Telephone contact with the medical monitor will be available 24 hours per day, 7 days per week. The Sponsor/CRO PV and/or safety review team will access the AE report and conclude whether unblinding is required. Once Sponsor/CRO PV and/or safety review team conclude that study participant requires the unblinding, Investigator will ask unblinded study personnel to provide the treatment sequence.

Investigators are instructed to always refer to latest version of respective unblinding procedure manuals for detailed and latest information.

9.8.2 Emergency unblinding of treatment assignment

Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. While the responsibility to break the intervention code in emergency situations resides solely with the evaluating investigator, it is recommended that the investigator contact the sponsor or its designee/study medical monitor if possible to discuss the particular situation, before breaking the blinding unless this could delay emergency treatment of the participant. Telephone contact with the medical monitor will be available 24 hours per day, 7 days per week. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind.

The investigator will inform the participant how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, study drug name if available, participant number, and instructions for contacting the sponsor (or any entity to which it has delegated responsibility for emergency code breaks) to the participant in case emergency unblinding is required at a time when the investigator and backup are unavailable.

An assessment will be done by the appropriate site personnel and the Study Lead after an emergency unblinding to assess whether or not study drug should be discontinued for a given participant.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed.

9.9 Study Duration

Study duration will be approximately 34 days including a maximum screening period of 5 days.

9.10Treatment

All subjects will receive standard of care (SOC) including treatment for COVID-19 signs and/or symptoms as required. Study encounters may be conducted remotely or at the study site depending on visit requirements, site facilities and subject and study team preferences.

9.11Clinical Safety Measures

It is the responsibility of the investigator to ensure that adequate medical supervision and care is available for the study subjects during the study to ensure their utmost safety and well being.

- Demography (subject reported / measured height and weight, age, sex and race/ethnicity): At screening
- Medical history (relevant within 30 days or ongoing) / History of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection): At screening
- Physical Examination (subject self-reported / examiner evaluated): At screening
- Vital signs (body temperature, respiratory rate, heart rate, SpO_2) assessment: At screening, Day 4 (±8 hrs),

Day 8 (±8 hrs), Day 12 (± 1 day), Day 15 (±1 day), Day 22 (±1 day), End of study [EoS; Day 29 (±2 day)].

Note: If subject is hospitalized, Vital signs assessment will be done on daily basis by site team during hospitalization through Day 8 then following the Vital signs visits as listed above.

- Hematology, biochemistry and urine analysis: At screening, Day 1 unless same day as Screening visit, Day 8 (±8 hrs), Day 15 (±1 day), End of study [EoS; Day 29 (±2 day)].
- HCV, HbSAg, HIV Test: At screening
- Serum pregnancy test (Women of child bearing potential (WOCBP)): At screening.
- Urine pregnancy test (WOCBP): End of study [EoS; Day 29 (±2 day)].

  Note: WOCBP: A premenopausal female capable of becoming pregnant
- Rapid antigen test / SARS-CoV-2 RT-PCR Qualitative (in a clinically relevant specimen (Naso-Oro-Pharyngeal as appropriate)): Screening

  Note: Test need not be repeated in those with possession of confirmed positive report. Date of positive report must be ≤5 days prior to randomization.
- RT-PCR Quantitative Viral (in a clinically relevant specimen (Naso-Oro-Pharyngeal as appropriate)): Day 1 (Prior to dosing), Day 4 (±8 hrs), Day 8 (±8 hrs), Day 12 (±1 day), Day 15 (±1 day), Day 22 (±1 day) and End of study [EoS; Day 29 (±2 day)]
- Ordinal Scale Assessment: Screening, Day 8 (±8 hrs), Day 15 (±1 day), Day 22 (±1 day) and End of study [EoS; Day 29 (±2 day)]
- Adverse events/ Serious Adverse Events: Adverse events/ Serious Adverse Events will be recorded from the time of first study drug administration till end of study safety assessments. Other medical events not related to disease condition under study and occurring before IMP administration, but after signing the informed consent form will be recorded on the medical history/current medical conditions of case report form.
- In addition to protocol-specific laboratory tests and/or clinical examinations at scheduled time points, additional tests/clinical examination may be conducted to evaluate subject safety at any time during the study, at the discretion of the Investigator (can be done in local laboratory or nearby clinic/hospital/institution).
- Medication taken prior to first dosing: All prescription medications and over-the-counter drugs (including vitamins) taken within 30 days prior to screening must be recorded in the eCRF as Medication history.
- Concomitant medications: Medications taken from time of signing of Informed Consent form until study completion (i.e. End of study) will be captured as concomitant medications.
- Prohibited medications: Any other antiviral medications or medication with antiviral potential.

Note:

- It is recommended that general precautions need to be taken by the staff caring for COVID patients during

the trial.

- In case the subject is hospitalized during the course of study, the activities specified in scheduled visits / time points will be carried out within the hospital facility.

9.12Discontinuation/ Termination of Study

Investigator reserves the right to discontinue the study for safety reasons at any time. Ethics Committee (EC) and/or Regulatory Authority may ask to terminate the study, if there are major violations of ethical considerations or due to any serious adverse event(s). Reasons for termination of study will be provided to subjects. In case sponsor/PI decides to terminate the study, reason for the same will be notified to Central Licensing Authority within thirty working days of such termination and/or notified to EC as applicable.

Note: In case of IMP termination, ongoing subjects will continue with standard treatment based on PI's discretion.

Discontinuation of the trial at one particular centre:

The sponsor may stop this trial at one particular centre for any of the following reasons or more:

- Serious and/or persistent non-compliance with the protocol
- False documentation in the source
- Inadequate co-operation with the sponsor, or its representatives
- Non-compliance with GCP and/or regulatory requirements
- The investigator requests discontinuation.

10.0 STUDY TREATMENT

10.1 Investigational Medicinal Product and Combination Product Dosage

1. Brequinar 50 mg capsules (used for the 50 mg and 150 mg doses)
2. Brequinar 100 mg capsules (used for the 100 mg, 150 mg and 200 mg doses)
3. Dipyridamole 75 mg tablets
4. Brequinar Placebo 50 mg and 100 mg capsules

Note:

- The subjects will take the study medication as directed on study days 1 – 5.
- Treatment assignment will be randomized, assessor-blind.
- IMP dispensing will be performed by an unblinded pharmacist.
- Study assessments will be performed by blinded Investigator or other designed blinded site personnel.
- Brequinar and brequinar placebo doses will be administered once daily.
- Dipyridamole doses will be given thrice daily.

- The 150 mg brequinar or brequinar placebo dose will be given as 1 capsule of 100 mg and 1 capsule of 50 mg; the 200 mg brequinar or brequinar placebo dose will be given as 2 capsules of brequinar or placebo 100 mg.

10.1.1 Assessment of Compliance

Compliance for dosing at home will be captured using a patient diary card.

10.2 Procurement, Storage and Accountability Procedures for Investigational Products

10.2.1 Receipt and storage of investigational products

Adequate supplies of investigational medicinal products for dosing will be distributed to the sites in bulk from the chosen depot. Investigational medicinal products will be stored per the storage condition supplied by sponsor. Certificates of analysis (COA) containing required product information will be received from sponsor. The hospital pharmacist will receive bulk supplies of IMP (brequinar 50 mg, brequinar 100 mg, dipyridamole 75 mg and brequinar placebo 50 mg and 100 mg) and will be unblinded to treatment. For each individual subject, the hospital pharmacist will use the IWRS to assign the randomization subject numbers. Hospital pharmacist will create an opaque, labeled zip lock bag or bottle for IMPs as assigned for individual subjects either per day or for all 5 days in the requisite packaging.

10.2.2 Accountability of investigational products

Sites will maintain accountability of IMPs received, stored, administered and returned to CRO/ destroyed at site. Only subjects enrolled in the study should be administered IMP per this protocol. Investigator/ designee supervising the dosing will be responsible for compliance to randomization schedule at site. Overall responsibility of IMP accountability at the site lies with the Investigator.

10.2.3 Handling of Unused Investigational products

Unused IMPs will be returned to the CRO or destroyed locally (per IMP plan).

10.2.4 Maintenance of Dispensing Record

A copy of site-specific dispensing record will be maintained in the Site Investigator File as well as in Central Investigator File.

10.2.5 Concomitant medication

Any allowable concomitant medication being taken by the subject should be continued on same dose during the study. Any change in the dose needs to be documented and subjects can continue in the study if the investigator deems proper. Administration of the following medications is not permitted after screening until after the end of each subject's study participation.

Prohibited Medications:

The following concomitant medications, products or procedures will not be allowed while enrolled in the study:

- Hydroxychloroquine
- Ivermectin
- Immunomodulators such as tocilizumab
- Antiviral drugs or drugs with antiviral potential including but not limited to remdesivir

The use of any of the above mentioned medications/procedure will result in withdrawal of the subject from the study.

Note: This list of drug is not exhaustive. However, any drug which is not mentioned above and having a possible on study drug *efficacy and safety, should be confirmed with Medical Monitor/Medical Expert.*

Permissible Medications: Other than those prohibited.

Standard treatment [(Standard Of Care (SOC)] provided in all the arms will be per the latest updated version of CLINICAL MANAGEMENT PROTOCOL for COVID-19 (in adults) released by Government of India Ministry of Health and Family Welfare Directorate General of Health Services (EMR Division).

If drug therapy other than that specified in the protocol is required prior to or during the study period, decisions shall be taken by the investigator to continue or discontinue the subject based on the following:

- The pharmacology and pharmacokinetic of the non-study medication.
- The likelihood of a drug–drug interaction.
- The time and duration of administration of the non-study medicine.

The start and stop date of concomitant medication use during the study should be recorded in source data. All such instances will be recorded and reported in the final report with details of start date, stop date and reason for medication use.

11.0 EFFICACY ASSESSMENT

Efficacy will primarily be assessed by reduction in SARS-CoV-2 RNA levels as measured by the quantitative RTPCR test for SARS COV2 in brequinar-dipyridamole treated subjects compared to brequinar-only and placebo-treated subjects through Day 29.

Symptom improvement will be defined in the SAP. Clinical improvement for the ordinal scale will be defined as defined as a 2-point or greater improvement on an 8-point WHO ordinal scale in every subject measured on each designated day (i.e Screening, Days 1, 4, 8, 12, 15, 22, 29), until Day 29 from the date of randomization. This scale has been used in the current COVID-19 outbreak.

Ordinal Scale for Clinical Improvement

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

12.0 SAFETY ASSESSMENT

The study will include the following evaluations of safety and tolerability according to the time points provided in the 3.2 Schedule of Activities.

12.1 Demographic Characteristics

Demographic data (subject reported / measured height and weight, age, sex and race/ethnicity) will be captured as specified in the 3.2 Schedule of Activities.

12.2 Medical and Medication History

The Investigator or his/her designee will obtain a detailed medical history and medication history as specified in the 3.2 Schedule of Activities.

Medical history includes clinically significant diseases within 30 days or ongoing and history of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection).

Information on all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 30 days prior to baseline visit will be recorded on the CRF.

Concomitant medications administered from screening to randomization will be recorded as a medication

history on the CRF.

12.3 Physical Examination

This evaluation will include an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system evaluation. Information about the physical examination must be present in the source documentation at the study site. If any abnormalities are noted during the study, the participant may be referred to another doctor. The investigator should use his or her clinical judgment for appropriate treatment and/or medical referral.

Clinically significant findings/abnormalities prior to the signing of ICF must be included in the relevant medical history/current medical conditions section of the CRF. Significant findings after the start of the IMPs that meet the definition of an AE must be recorded in the Adverse Event section of the CRF. Physical examination should be done at specified in the 3.2 Schedule of Activities. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event CRF.

12.4 Vital Signs

Vital signs will include measurements of body temperature, respiratory rate, heart rate and SpO_2 taken with the participant in a seated position after resting for 5 minutes. Vital signs will be measured at specified in the 3.2 Schedule of Activities. If the subject needs to be assessed remotely due to COVID-19 restrictions or for other reasons, the subject is to be provided with a pulse oximeter and digital thermometer.

12.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia)
- Is clinically significant in the investigator's judgment
- Requires a change in concomitant therapy (i.e. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event CRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event CRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

12.6 Clinical Safety Laboratory Assessments

Clinical laboratory tests will be performed at specified in the 3.2 Schedule of Activities. (Refer to section 26.0: for the list of clinical laboratory tests).

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during the study or within 30 days after the last dose of study intervention should be documented as AE. The abnormal test should be repeated until the values return to normal or baseline or are no longer considered clinically significant.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

12.7 Other safety evaluations as appropriate and as indicated in the schedule of activities

- Pregnancy test (Serum and Urine): At specified in the 3.2 Schedule of Activities.

12.8 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia)
- Is clinically significant in the investigator's judgment
- Requiring a change in concomitant therapy (i.e. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

It is the responsibility of the investigator to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse

event. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the adverse event CRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the adverse event CRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., “elevated potassium,” as opposed to “abnormal potassium”).

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the adverse event CRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

For each laboratory abnormality reported as an AE, the following laboratory values should be reported in the laboratory section of the CRF: the value indicative of the onset of each toxicity grade; the most abnormal value observed during the AE, and the value supporting recovery to Grade ≤1 or to baseline values. The CTCAE version 5 scale will be used to grade AEs including laboratory AEs.

12.9 Handling and Reporting of Adverse Events

An adverse event is any untoward medical occurrence (including a symptom or disease or an abnormal laboratory finding) during treatment with an investigational drug or a pharmaceutical product in a subject that does not necessarily have a relationship with the treatment being given.

*Abnormalities based on laboratory parameters, vital signs, and 12-Lead ECG will be called AE, if they are associated with at least one of the following:

- Interruption or stoppage of the study medication
- Associated with signs or symptoms
- Requiring treatment
- Considered clinically significant by the investigator

Safety Criteria:

An independent, unblinded study physician (from CRO) will assess each cohort for safety. A cohort will be declared safe are as soon as all results are available for the Day 15 visit if the following conditions are met:

- No toxic deaths (deaths judged by the investigator to be related to either study drug);
- Not more than 1 toxic SAE (SAEs judged by the investigator to be related to either study drug);

- No Grade 3 or higher toxicities (including laboratory AEs as per CTCAE version 5.0 or higher) (AEs judged by the investigator to be related to either study drug);
- <4 subjects with any grade toxicity (AEs judged by the investigator to be related to either study drug).

In addition to the cohort-level safety, the independent study physician (from CRO) will determine if any subjects meet Individual Stopping Criteria:

- Subjects who develop a Grade 3 toxicity that is assessed by the investigator to be related to the study drug are to be permanently discontinued from study treatment but will continue in the study for safety assessments.
- Subjects who develop a Grade 4 toxicity, regardless of relatedness to study drug, are to be permanently discontinued from study treatment but will continue in the study for safety assessments.

In addition to the individual subject-level safety, the independent study physician (from CRO) will determine if a cohort meets Cohort-level Stopping Criteria prior to completing the 16 subjects, in which case no additional subjects will be enrolled into that cohort and no higher brequinar doses will be assessed:

- ≥3 brequinar-treated or combination-treated subjects meet the individual stopping criteria.
- ≥5 brequinar-treated or combination-treated subjects develop a Grade 3 or higher AE regardless of relationship to study drug.

Adverse Drug Reaction is a noxious and unintended response to a medicinal product related to any dose. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

An **Unexpected Adverse Drug Reaction (UADR)** is an adverse reaction, the nature or severity of which is not consistent with the applicable product information [e.g., investigator's brochure for an unapproved investigational medicinal product or company core data sheet or package insert for marketed product].

Subjects will be monitored throughout the study period for adverse events. Subjects will be instructed to bring to the notice of study personnel any adverse event that may occur during the entire study period.

The following information is to be recorded for each adverse event individually in Adverse Event Reporting Form.

- Type of adverse event*
- Is it serious or non-serious?
- Date of onset/reporting
- Date of onset and resolution
- Severity (as per section 12.12)

- Association with the study medication (as per section 12.13)
- Action taken
- Outcome of adverse event (as per section 12.14)
- Further details of the AE, if any.

*The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

For the recording of signs and symptoms, the subject will be required to report spontaneously any AEs as well as the intensity of these events. In addition, each subject will be asked by the investigator for AEs during vital signs and physical examination. All AEs including both observed and volunteered ones will be recorded in the Adverse Event Reporting Form, irrespective of its association with study medications. All findings considered clinically relevant and reportable as AE by investigator will be reported on the "Adverse event" page in the CRF and in the subject's medical records.

Each AE will be evaluated for duration, severity and action taken, outcome and association with study medication.

Adverse events/ Serious Adverse Events will be recorded from signing informed consent form through the end of the study safety assessments. Other medical events not related to study screening occurring before first dose administration, but after signing the informed consent form will be recorded on the medical history/current medical conditions of case report form.

12.10 Serious Adverse Events (SAEs)

A serious adverse event is any untoward medical occurrence during a study which satisfies one or more of the following conditions:

- resulting in death or
- permanent disability, or
- hospitalisation of the trial subject, or
- prolongation of hospitalisation, or
- significant disability, or
- incapacity, congenital anomaly, birth defect ,or

- life threatening event.

The term 'Life threatening' refers to an event in which the subject was at immediate risk of death at the time of event. It does not refer to an event which may have caused death if it was more severe.

The Investigator will be responsible to report all SAE to the central regulatory (e.g. DCGI-Central Licensing Authority), Sponsor's representative and respective Ethics Committee within 24 hours of SAE occurrence/knowledge of occurrence if required. Investigator will be responsible for reporting the detailed report to the local regulatory (e.g. DCGI), chairman of the Ethics Committee and the head of the institution where the trial has been conducted within 14 days of SAE occurrence if required. Each AE will be evaluated for duration, severity, action taken, outcome and association with Investigational Medicinal Product. The study may be suspended or terminated depending upon the seriousness of SAEs.

12.11 Reporting and Follow-up

The investigator must complete SAE form, verify the accuracy of the information recorded in corresponding source documents, and send a copy (by fax /mail) to sponsor/representative/CRO.

Investigator:

The investigator shall report all serious adverse events (SAE) to the central licensing authority (DCGI), the Sponsor/CRO and chairperson of ethics committee within 24 hour of SAE occurrence, if required.

The investigator shall report all SAE after due analysis to the central licensing authority (DCGI), chairperson of ethics committee and head of the institution where the trial has been conducted within fourteen days of SAE occurrence, if required. Subsequent follow-up information shall be reported to all stakeholders as mentioned above.

In case, Investigator fails to report any SAE within stipulated period, the investigator shall have to furnish the reason for the delay to the satisfaction of central licensing authority along with the report of SAE.

Sponsor or Sponsor's Representative:

In case of SAE the Sponsor and/or CRO will be responsible for reporting the due analysis report of SAE to chairman of the Ethics Committee, the central licensing authority and the head of the institution where the trial has been conducted within 14 days of SAE occurrence, if required.

Note: In case if SAE occurrence time and reporting time by subject to investigator is not same, investigator may fail to report such serious adverse event within the stipulated period. In such case Investigator shall have to furnish the reason for the delay to the satisfaction of the central licensing authority along with the report of the serious adverse event.

Name of the sponsor representative:

Barbara Powers, MSN, Ph.D.

E-mail: bpowers@clearcreekbio.com

Sponsor Medical Monitor:

John Pottage, MD

E-mail: John.pottagemd@gmail.com

CRO contact details:

Veeda Clinical Research Ltd.

E-mail: safety@veedacr.com

Fax: +91-79-3001 3010

Follow-up of Adverse Events:

All AEs (serious or not) will be followed to resolution (the subject's health has returned to his/her baseline status or all variables have returned to normal or clinically acceptable level), an outcome is reached, stabilization (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained regardless of whether the subject is still participating in the study. Where appropriate, medical tests and examinations will be performed to document resolution of event(s).

The Investigator should institute any supplemental investigations of SAE based on their clinical judgment of likely causative factors.

If required, a follow-up report including all relevant new or reassessed information (e.g., concomitant treatment, medical history) obtained on the SAE will be prepared and same will be marked “Follow-up report”. Follow up reports are to be sequentially numbered to allow tracking. These reports will be sent to the sponsor/CRO.

Adverse events occurring between informed consent and the last visit

The investigator should follow up on all AEs which occurred from signature of study-specific informed consent until the last visit of the subject, at which point the outcome assessment is documented in the CRF.

Ongoing serious adverse events at the time of last visit

For any SAEs still ongoing at the time of last visit considered to be related to IMP, the investigator should continue to follow-up until the SAE has resolved or has stabilized / is judged permanent for SAEs, and for up to 30 days after the last visit of subject for non-related SAEs. Where appropriate, medical tests and examinations

will be performed to document resolution of event(s). The investigator should send SAE follow-up reports including all relevant new or reassessed information (e.g., concomitant treatment, medical history) obtained on the SAE /pregnancy to the sponsor/CRO.

If a subject dies during participation in the study and an autopsy is performed, a copy of the report must be submitted.

Serious adverse events occurring after the last visit

Any SAEs experienced after the last visit should only be reported to sponsor if the investigator suspects a causal relationship to study treatment. The investigator must report the SADR to recipients as per the 'SAE Reporting' section 12.10.

Pregnancy Reporting:

Pregnancy recorded for any trial participant after study drug administration should be reported immediately to the sponsor/representative. The subject will be withdrawn from the trial and every effort will be made to gather information regarding the pregnancy outcome until 8 weeks post-partum/termination of pregnancy. It will be the responsibility of the Investigator to obtain this information. Pregnancy recorded after screening but before randomization will be reported and subject will be withdrawn from the study and further follow up will not be done. In case of pregnancy, separate pregnancy form should be filled. Cases of pregnancy exposure associated with SAE and/or abnormal pregnancy outcome should be reported as per SAE reporting timelines. If any congenital anomaly is observed in offspring then the follow up should be conducted till six months after birth, if applicable.

Ethics Committee Timelines for Reporting of SAE:

In case of SAE, the Ethics Committee shall forward its report along with its opinion on the financial compensation (if any) to the licensing authority within 30 days of the occurrence of the SAE, if required.

12.12 Classification of Severity of Adverse Event

Adverse event will be assessed for onset time, occurrence (single or repeat) and intensity. In terms of grade,

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care ADL**.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

*Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

12.13 Causality Assessment/Association with the Study Medication

Every effort will be made to obtain all the required information to determine whether the Adverse Event is related or unrelated to the study procedure or Investigational Medicinal Product (causal relationship).

In terms of relationship

Causality term	Assessment criteria
Definite*	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Re-challenge satisfactory, if necessary
Probable*	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Re-challenge not required
Possible*	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear

Unlikely[#]	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Not Related[#]	• The AE is clearly NOT related to the study treatment

Note: [#]Unlikely and Not Related will be considered as Not Related.

[*]Definite, Probable and Possible will be considered as Related.

12.14 Outcome Categories

The outcome of adverse event will be categorized as following:

- Recovered/ Resolved
- Recovering/ Resolving
- Recovered with sequelae/ Resolved with sequelae
- Not recovered/ Not Resolved
- Fatal
- Unknown

13.0 SAMPLE PROCESSING AND TRANSFER PROCEDURES

Clinical Laboratory Samples:

All clinical laboratory blood and urine samples will be transferred to the central laboratory in controlled temperature and in pre validated laboratory kits which will be supplied to all the sites by the central laboratory. In case of emergency, samples can be sent to local laboratory for safety assessment at the discretion of the investigator.

Pharmacokinetic (PK) samples:

After collection of PK blood samples from all subjects at each time point, they will be centrifuged at 4000 RPM for 10 minutes at 5 ± 3 °C to separate plasma. For precaution purpose, the blood samples will be kept on wet ice bath (below 10 ^{0}C) both before centrifugation and after separation.

The separated plasma will be transferred to pre-labeled polypropylene tubes in 2 aliquots:

For Brequinar and Dipyridamol PK:

Aliquot 1: Approximately 1.7 mL of plasma

Aliquot 2: Approximately 1.2 mL of plasma

Aliquot will be stored upright in a box containing dry ice or in a freezer at a temperature –15 °C or colder for interim storage at different investigator sites until shipment to Veeda Clinical Research Ltd., Ahmedabad, for analysis.

Note: Entire activity from blood sample collection to storage in a freezer should be completed within 60 minutes time.

During shipment the samples will be packed in thermocol boxes containing adequate amount of dry ice. The temperature will be monitored using calibrated data logger during shipment. Samples will then be stored at -78 ± 8 °C until completion of analysis at Veeda Clinical Research Ltd., Ahmedabad.

Shipment for each aliquot will be carried out separately.

A designated person from bioanalytical department will receive the samples at Veeda Clinical Research Ltd., Ahmedabad or designate on arrival. The condition of the samples will be examined on arrival at Veeda Clinical Research Ltd., Ahmedabad and if any of the samples are not in a frozen condition, clinical facility and\or Sponsor will be informed for the same. After receiving the samples at Veeda Clinical Research Ltd., Ahmedabad, the samples will be stored at –78 ± 8 °C until completion of analysis.

Pharmacodynamic (PD) samples:

The PD blood samples will be centrifuged at 3500 RPM for 30 minutes at 5 ± 3°C to separate plasma. For precaution purpose, the blood samples will be kept on wet ice bath (below 10 ^{0}C) both before centrifugation.

The plasma samples separated are to be transfeered to pre-labeled cryovials in 2 aliquots

Aliquot 1: 2.5 mL of plasma- Primary Sample

Aliquot 2: 2.5 mL of plasma- Backup sample

Both the aliquots will be stored upright in a box containing dry ice or in a freezer at a temperature –20°C for interim storage at different investigator sites until shipment to Bioneeds India Private Limited, Bengaluru for analysis.

During shipment, primary aliquot and backup aliquots are to be separately shipped in dry ice with data logger to Bioneeds, Bnagalore with necessary sample shipment documents.

Note: Samples of patients enrolled in Arm 3 (SOC + Placebo) of each cohort will not be analysed.

qPCR Samples

The qPCR samples are to be collected, processed, stored, and shipped as per the instructions in the Laboratory Manual.

14.0 BIOANALYTICAL PROCEDURES

The Bioanalytical procedures will be performed at Bioanalytical facility of Veeda Clinical Research Ltd. Validated analytical method will be used for the PK analysis of the plasma samples.

14.1 Method Validation

Bioanalytical method will be validated at Veeda clinical research Ltd., which is in accordance with the regulatory guidelines on validation of bioanalytical methods.

Method validations of Brequinar and Dipyridamol will be carried out by using analytical method developed at Veeda Clinical Research Ltd. This analytical methods will be validated for the sensitivity, specificity, matrix effect, linearity, ruggedness, accuracy and precision (repeatability and reproducibility), percent recovery and stability of samples (bench-top stability, autosampler stability, short-term, long-term stability of stock solution and internal standard) and effect of concomitant medications, if any.

14.2 Assay of Samples

The Brequinar and Dipyridamol will be quantified using a validated method. All available plasma samples of all subjects in the study will be analyzed as per approved protocol irrespective of withdrawn or dropped out from the study.

The analysis of subject's samples will be done using calibration curve with quality control samples, distributed throughout each batch. The details for the preparation of the calibration curve and quality control samples and the analytical batch acceptance criteria will be discussed in the respective in-house procedure. The analyst will not have access to the randomization schedule until analysis is completed.

Note: Samples of patients enrolled in Arm 3 (SOC + Placebo) of each cohort will not be analysed.

14.3 Incurred Study Sample Re-analysis

Incurred Study Sample Re-analysis will be performed to ensure method reproducibility as per SOP (VIN-BRD-092).

15.0 STATISTICAL ANALYSIS

15.1 Statistical Analysis Plan

A statistical analysis plan (SAP) will be prepared and finalized prior to the database lock. Detailed description of the statistical methodology, population and handling of missing data will be described in this document.

Mock tables and listings will be provided with the SAP.

15.2 Sample Size Estimation

There is no prospective powering in this study. The sample size was chosen to provide an adequate number of subjects to provide reasonable safety and efficacy data for this type of study.

15.3 Study Population for Analysis

- Intent-to-treat population:

Intent-to-treat (ITT) analysis set will include all the subjects who undergo randomization.

- Safety Population:

The safety population will include all randomized subjects who receive at least one dose of the study product.

15.4 Analysis of Efficacy Data

All statistical analysis will be done using SAS® Version 9.4 or higher (SAS Institute Inc., USA).

For continuous variables, the summary statistics will be the number of observations, mean, standard deviation, median, minimum and maximum values. Categorical values will be summarized using frequencies and percentages.

Primary Endpoints:

- Frequencies of grade 3 and 4 toxicities and serious adverse events (SAEs) considered by the investigator to be related to the combination, brequinar alone or placebo alone.

  Because the primary study endpoint is a safety parameter no formal statistical testing will be performed for this parameter.

Secondary Endpoints:

For subjects treated with the brequinar-dipyridamole combination compared to subjects treated with the brequinar and to subjects treated with the placebo combination through Day 29, to determine:

- SARS-CoV-2 levels through Day 29 and at days 4, 8, 12, 15, 22, and 29 will be analyzed using analysis of covariance (ANCOVA) test;
- Time to symptom improvement through Day 29 will be analyzed using Kaplan-Meier time-to-event analysis;
- Percentage of subjects requiring hospital admission/re-admission as an in-patient for >24 hours through Day 29 will be analyzed using Fisher exact / chi square test;

- Percentage of subjects requiring medical attended visits, e.g., hospitalization, emergency room visits, Urgent Care/Family Doctor visits through Day 29 will be analyzed using Fisher exact / chi square test ;
- Percentage of subjects requiring supplemental support such as oxygen through Day 29 will be analyzed using Fisher exact / chi square test..

Exploratory Endpoints:

- Brequinar's pharmacokinetic profile in a subset of patients that have received brequinar as a part of therapy and have consented to provide PK samples will be analyzed descriptively.
- Effect on intracellular nucleotide pools of UTP/CTP/ATP/GTP in the subset of patients who received brequinar-dipyridamole combination with comparison to brequinar alone and placebo alone will be analyzed using an appropriate statistical method.

15.5 Safety Analysis

All safety analysis will be conducted using the safety population set.

Frequency distribution or summary statistics of all demographics variable and baseline characteristics will be generated by treatment arm.

The evaluation of the drug safety will be based on clinical AEs, vital signs, physical examination, concomitant medications and laboratory abnormalities reported during the study and incidence of adverse events and treatment emergent adverse events in each arm during the study. All safety presentations will include subjects who receive at least one dose of the study medication and will group subjects by treatment received. Frequency distributions and individual listings of all adverse events will be generated. Changes in clinical laboratory test results from baseline will be listed.

A treatment emergent adverse event is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terms using the version that is current at the time the first subjects is enrolled and will be summarized by system organ class (SOC) and preferred term within SOC. The Common Terminology Criteria for Adverse Events CTCAE 5.0 will be used to grade the severity of adverse events.

Adverse Events will be summarized by treatment and overall. AE summary tables will include counts of subjects and the number of events. If a subject experiences more than one episode of a particular AE, that subject will be conducted only once for that event. If a subject has more than one AE that coded to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than one AE within a SOC, the subject will be counted only once in that SOC.

16.0 AMENDMENT TO THE PROTOCOL

Any significant change in the study procedure or study design will only be effected upon mutual agreement between the Sponsor, CRO and Investigator and after obtaining a favorable opinion from the Ethics Committee and regulatory authority(ies). All such changes will be documented in the amended version of the protocol and a list of changes with reference to the previous version will be generated and submitted to the IEC and regulatory authorities as soon as possible. In cases where there is an immediate safety hazard to the subjects, the amended protocol will be effective immediately and approval of the IEC will be obtained as soon as possible.

17.0 SOURCE DATA ACCESSIBILITY

Quality Assurance (QA) auditors and study monitors of Veeda Clinical Research Ltd. as well as sponsor's monitors, IEC and Regulatory agency(ies) will have access to raw data during inspection and audits.

18.0 STUDY MONITORING

Monitoring procedures developed by Veeda will be followed in order to comply with GCP guidelines and to ensure acceptability of the study data for national registration purposes. During the course of the study, a monitor from Veeda will perform site visits to review protocol compliance, compare CRFs to individual subject's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. CRF entries will be verified with source documentation.

The Sponsor or its representative may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study.

This clinical trial is to be conducted at Investigator sites and the Investigators should permit the different stakeholders for monitoring/ auditing/ inspections at their site.

19.0 QUALITY CONTROL AND QUALITY ASSURANCE AUDITS

Auditing procedures developed by Veeda will be followed in order to comply with GCP guidelines and to ensure accuracy, completeness and authenticity of the data generated, recorded and reported and acceptability of the study data for international registration purposes.

The raw data generated during the course of the study as well as reports will undergo a random quality assurance process for conformance to this protocol and all the governing SOPs by the Monitors and the auditors of Veeda Clinical Research Ltd, respectively. The final report will contain a statement of quality assurance duly signed by the Head, Quality Assurance department.

20.0 ETHICS

20.1 Ethics Committee

This protocol and corresponding informed consent Document (ICD) (containing information about the study to be given to subjects) to be used to obtain written informed consent of study subjects will be reviewed by IEC and subjects will not be enrolled into the study until IEC approves the protocol and ICD.

The study will be conducted according to the current version of the IEC approved protocol, Relevant SOPs, [New Drugs & Clinical Trial Rules, 2019 of CDSCO (Central Drugs Standard Control Organization), Ministry of health and family welfare, Government of India], [Ethical guidelines for biomedical research on human participants, ICMR (Indian Council of Medical Research (2006)], [ICH (The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) E6 (R2) 'Guideline for Good Clinical Practice' 2016], Declaration of Helsinki – Brazil, October 2013].

20.2 Written Informed Consent

Investigator or designated study personnel before initiation of any study related procedure will inform the subject (in a language best understood by the subject) through an oral presentation regarding the purpose, procedures to be carried out, information on the investigational medicinal products, potential hazards, benefits and rights of the study subjects with maintaining adequate social distancing. Subjects will be encouraged to ask questions and clarify their doubts regarding any aspect of the study and the same would be documented in the source notes with sign and date. The ample time after completion of ICF discussion will be given to the subjects to think and take an informed and voluntary decision. Investigator will ensure that the entire process of informed consent is followed as per local regulatory requirement for each subject at the respective site maintaining the confidentiality of subject's personal information and all relevant records will be maintained in source file. The responsibility for taking informed consent must remain with that of a medically qualified person and cannot be delegated to a non-medically qualified person.

Subject (or legally acceptable representative) should be present during the entire informed consent process and will also append his/her signatures on the informed consent form. If subject or subject's legally acceptable representative is unable to read/write, an impartial witness should be present during the entire informed consent process, and will append his/her signatures on the informed consent form. In both the above cases, subjects will be required to give a thumb impression on the informed consent form. Only those subjects who are able to understand the ICF and able to communicate with the study personnel will be enrolled in the study.

The subjects will give their written consent for participation in the trial by signing or by putting a thumb impression on the informed consent form, which will also be signed by the Investigator or his/her designate.

If any new information becomes available during the course of the study that may be relevant to the subject's willingness to continue participating in the trial, the Investigator must inform the subject in a timely manner, and a revised written informed consent must be obtained.

Investigator will ensure that all the subject are handed over a signed and dated copy of the informed consent form immediately once the informed consent process is completed.

21.0 DATA HANDLING AND RECORD KEEPING

All clinical data generated during the conduct of the study will be entered in the source notes and will be transcribed in the respective CRF. All raw data and transcribed data forms compiled by the study personnel assisting in the study will be checked for completeness. All data related to the project will be in the custody of the Investigator or Project Manager until transferred to archives.

All raw data generated during the conduct of the project compiled by the study personnel assisting in the study will be checked for completeness. Biostatistics department after receipt of the raw data will perform a statistical analysis and statistical data will be generated which will be further sent for compilation of the final clinical study report of the study.

22.0 STUDY REPORTS AND SUPPLEMENTARY DOCUMENTS

The final report will be compiled and sent as per eCTD (Module 5) format. All copies of supplementary documents such as approved final version of Protocol along with all appendices, IEC approval letter, List of IEC members, CVs of Investigators, all subject CRFs, adverse event form (if any), Investigational Product Accountability records, Randomization list, Summary report of statistical analysis, protocol deviations, demographics and baseline characteristics and safety data will be submitted to sponsor with the final study report.

23.0 ARCHIVING

All data generated in connection with this study, together with the copy of this protocol and the audited final report will be archived according to the ICH guideline for good clinical practice and regulatory requirement and the TMF plan agreed with the Sponsor. Subject files, original source notes with Signed informed consent form and Patient Information Sheet (PIS), CRFs (If paper CRF has been used) and the Site Investigator File will be retained at individual study site as per applicable regulatory guidelines.

All other data generated will be retained at Veeda as mentioned in Research Service Agreement. The sponsor will then arrange for the maintenance of these documents.

24.0 INSURANCE POLICY

The sponsor has a clinical trial insurance policy to cover the risks to subjects and/or any other eventualities pertaining to study.

25.0 CONFIDENTIALITY OF DATA

The data identifying each subject by name will be kept confidential and will be accessible to the study personnel and if necessary, to the QA auditors, IEC, Sponsor representative and Regulatory agency(ies).

Information related to COVID-19 infection may be highly sensitive in nature with a lot of scope for stigmatization, discrimination, violence etc. Maintaining confidentiality of research related data and its publication is important to protect the privacy of individuals and avoid any discrimination against them.

26.0 PUBLICATION POLICY

The results of the study including all data obtained will be the property of sponsor of this study. For any publication pertaining to the data or results of the study, a written approval of the sponsor will be obtained prior to communicating for publication and the manuscript will be sent for sponsor's approval, if the sponsor asks to do so.

27.0 REFERENCES

1. CLINICAL MANAGEMENT PROTOCOL: COVID-19 released by Government of India Ministry of Health and Family Welfare Directorate General of Health Services (EMR Division). Version 6. Released on: 24.05.21
2. WHO R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis. February 18, 2020, Geneva, Switzerland
3. Declaration of Helsinki, Fortaleza, Brazil, October 2013.
4. International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use- Good Clinical Practice (ICH-GCP) E6 (R2).
5. Ethical Guidelines for Biomedical Research On Human Participants, Indian Council of Medical Research, 2017.

28.0 CLINICAL LABORATORY TESTS

HEMATOLOGY		
Hemoglobin		
Absolute WBC Counts (Neutrophils, Lymphocyte, Eosinophils, Monocyte, Basophils)		
Complete Blood Counts, hematocrit, RBC count and indices		
White blood cell (WBC) count, Differential Leucocyte count, Platelet count		
BIOCHEMICAL PARAMETERS		
SGOT (AST)	Alkaline Phosphatase	Serum Magnesium
SGPT (ALT)	Random Blood Glucose	Serum Potassium
Total Bilirubin	Serum Cholesterol	Total Protein
Direct Bilirubin	Serum Triglyceride	
Indirect Bilirubin	Serum Creatinine	
Blood urea nitrogen (BUN)	Creatinine clearance	
Pregnancy test by β-hCG Method (for all females of child bearing potential)	Urea	
SEROLOGY		
HIV	HbsAg (Hepatitis B surface antigen)	HCV antibodies
URINE ANALYSIS		
Color	Glucose	WBC
Odor	Bilirubin	Epithelial Cells
Clarity	Blood	Casts
Specific gravity	Ketones	Crystals
pH	Urobilinogen	Bacteria
Protein	Nitrite	

- Any laboratory test, if required for adverse event management, may be performed at a local clinical laboratory at the discretion of Investigator.

SIGNATURE(S) OF INVESTIGATOR(S)

I, the undersigned, have read and understood this protocol, entitled

"The CRISIS-04 Study: A phase II, randomized, assessor-blind, multicenter, multi-dose, placebo-controlled study assessing the safety and anti-coronavirus response of brequinar combined with dipyridamole in patients with mild to moderate SARS-CoV-2 infection."

and hereby agree to conduct the study in accordance with this protocol and to comply with all the requirements regarding the obligations of Investigators and all other pertinent requirements of the Ethical guidelines for biomedical research on human participants (ICMR) 2017 guidelines, New Drugs and Clinical Trial Rules (2019) of India, ICH (Step 5) 'Guidance on Good Clinical Practice' ICH Guidance E6 (R2), Declaration of Helsinki (Brazil, 2013) and with procedures oriented to Good Laboratory Practice and applicable regulatory guidelines.

I agree to comply with all relevant SOPs required for the conduct of this study. I further agree to ensure that all associates assisting in the conduct of this study are informed regarding their obligations.

_____ Date: _____
Investigator

Name:

Address: _____

_____

_____

_____

Tel. No.: _____

Fax: _____

E-mail: _____

PROJECT NO.: 21-VIN-0372

Protocol Number	21-VIN-0372
Protocol Title	The CCB-CRISIS-04 Study: A phase II, randomized, assessor-blind, multicenter, multi-dose, placebo-controlled study assessing the safety and anti-coronavirus response of brequinar combined with dipyridamole in patients with mild to moderate SARS-CoV-2 infection.
Study Phase	II
US IND Number	149291
Sponsor Study Code	CCB-CRISIS-04
Regulatory Submission	DCGI
Version Number	2.1
Protocol Date	29 Dec 2021
Supersedes	02
Date of Supersedes	30 Sep 2021
Sponsor	Clear Creek Bio, Inc. 585 Massachusetts Ave., 4th Floor Cambridge, MA 02139 USA
Contract Research Organization (CRO)	Veeda Clinical Research Ltd., Shivalik Plaza, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India Phone: +91-79-3001 3000

Confidentiality Statement

The information contained in this document, especially unpublished data, is the property of Sponsor (or under its control), and therefore provided to you in confidence as an Investigator or consultant, for review by you, your staff and an applicable Institutional Ethics Committee. By accepting this document you agree that this information will not be disclosed to others without written authorization from Sponsor except to the extent necessary to obtain informed consent from those persons (including their legally acceptable representatives as applicable) to whom the drug may be administered.

1.0 AUTHORIZATION OF PROTOCOL

1.1 Protocol Preparation and Authorization

We, the undersigned, have read and understood this protocol and hereby agree to comply with all requirements regarding the obligations of Sponsor and all other pertinent requirements of the Ethical guidelines for biomedical research on human participants (ICMR) 2017 guidelines, New Drugs and Clinical Trials Rules (2019) of India, ICH (Step 5) 'Guidance on Good Clinical Practice' ICH Guidance E6 (R2), Declaration of Helsinki (Brazil, 2013) and with procedures oriented to Good Laboratory Practice and applicable regulatory guidelines.

We agree to comply with all relevant SOPs required for the conduct of this study. We further agree to ensure that all associates assisting in the conduct of this study are informed regarding their obligations.

29 Dec 2021

Prepared by — Date

Name : Krunal Suthar
Associate Clinical Manager - Medical Affairs and Pharmacovigilance

RAVI ALAMCHANDANI
2021.12.29 17:26:54 +05'30'

Reviewed By — Date

Name : Dr. Ravi Alamchandani
General Manager - Medical Affairs and Pharmacovigilance

SUMIT ARORA
2021.12.29 18:37:49 +05'30'

Authorized By — Date

Name : Dr. Sumit Arora
Head - Medical Affairs and Pharmacovigilance

Address : Veeda Clinical Research Ltd.
Beside YMCA Club,
SG Highway, Ahmedabad- 380051,
Gujarat, India

Tel. No. : +91-79-3001 3000

1.2 Quality Assurance statement

The contents of the protocol were reviewed for compliance with the applicable VIN SOPs, pertinent requirements of the Ethical guidelines for biomedical research on human participants (ICMR) 2017 guidelines, New Drugs and Clinical Trial Rules (2019) of India, ICH (Step 5) 'Guidance on Good Clinical Practice' ICH Guidance E6 (R2), Declaration of Helsinki (Brazil, 2013) and with procedures oriented to Good Laboratory Practice and applicable regulatory guidelines.

Amee

Digitally signed by
AMEE MILIND KANUGA
Date: 2021.12.30
09:16:53 +05'30'

Authorized signatory | Date

Name : Ms. Amee Kanuga
Head - Quality Assurance
Address : Veeda Clinical Research Ltd.
Shivalik Plaza-A,
Near I.I.M., Opp. AMA, Ambawadi,
Ahmedabad – 380015,
Gujarat, India
Tel. No. : +91-79-30013000
Email ID : Amee.Kanuga@veedacr.com

1.3 Sponsor's Review & Approval

I, on behalf of Clear Creek Bio, Inc. have read, understood and approve this protocol. We agree to comply with all requirements of the Ethical guidelines for biomedical research on human participants (ICMR) 2017 guidelines, New Drugs and Clinical Trial Rules (2019) of India, ICH (Step 5) 'Guidance on Good Clinical Practice' ICH Guidance E6 (R2), Declaration of Helsinki (Brazil, 2013) and with procedures oriented to Good Laboratory Practice guideline and other applicable regulatory guidelines.

DocuSigned by:
Vikram Sheel Kumar
D5300B17D329436...

12/30/2021

Authorized signatory | Date

Name : Vikram Sheel Kumar, MD

Address : Clear Creek Bio, Inc.
585 Massachusetts Ave., 4th Floor
Cambridge, MA 02139 USA

Tel. No. : +1-671-899-8944

E-mail : kumar@clearcreekbio.com

TABLE OF CONTENTS

2.0 LIST OF ABBREVIATIONS

AE	:	Adverse Event
ANOVA	:	Analysis of Variance
β-hCG	:	Beta-human Chorionic Gonadotropin
BA	:	Bioavailability
CBC	:	Complete Blood Count
CFR	:	Code of Federal Regulations
COA	:	Certificate of Analysis
COVID 19	:	Corona virus disease 2019
CRF	:	Case Report Form
CRO	:	Contract Research Organization
CRP	:	C-reactive protein
CTCAE	:	Common Terminology Criteria for Adverse Events
CYP	:	Cytochrome P
DCGI	:	Drug Controller General of India
EC	:	Ethics Committee
ECG	:	Electrocardiogram
ECMO	:	Extracorporeal membrane oxygenation
gm	:	Gram
GCP	:	Good Clinical Practice
GGT	:	Gamma glutamyl transpeptidase
GLP	:	Good Laboratory Practice
HbsAg	:	Hepatitis B surface Antigen
HCV	:	Hepatitis C Virus
HIV	:	Human Immunodeficiency Virus
Hrs.	:	Hours
IB	:	Investigator Brochure
ICD	:	Informed Consent Document
ICH	:	International Council for Harmonization of Technical Requirements for Registration of

		Pharmaceuticals for Human Use
ICMR	:	Indian Council of Medical Research
IMP	:	Investigational Medicinal Product
ITT	:	Intent-To-Treat
IU	:	International Unit
IUD	:	Intrauterine Device
Kg	:	Kilograms
Ltd.	:	Limited
Mg	:	milligram
mg/dL	:	milligram/deciliter
mL	:	Milliliter
No.	:	Number
OTC	:	Over the Counter
P/A	:	Postero-anterior
PK	:	Pharmacokinetic
PP	:	Per protocol
PO_2	:	Partial pressure of oxygen
PCO_2	:	Partial pressure of carbon dioxide
QA	:	Quality Assurance
qPCR		Quantitative polymerase chain reaction to test SARS-CoV-2 viral load
RLD	:	Reference Listed Drug
RT-PCR		Reverse transcription polymerase chain reaction
SAE	:	Serious Adverse Event
SD	:	Standard Deviation
SGOT	:	Serum Glutamate Oxaloacetate Transaminase
SGPT	:	Serum Glutamate Pyruvate Transaminase
SOP	:	Standard Operating Procedure
TEAEs	:	Treatment Emergent Adverse Events
$t_{1/2}$	:	The time required for the drug concentration to decrease by 50 percent from the

		maximum concentration.
U	:	Units
UDS	:	Urine Drug Scan
UPT	:	Urine Pregnancy Test
USV	:	Unscheduled Visit
WBC	:	White Blood Cell
WOCBP	:	Women of child bearing potential
^{0}C	:	Degree Celsius
^{0}F	:	Degree Fahrenheit
%	:	Percent

3.0 PROTOCOL SUMMARY

3.1 Synopsis

Title of Study:	The CCB-CRISIS-04 Study: A phase II, randomized, assessor-blind, multicenter, multi-dose, placebo-controlled study assessing the safety and anti-coronavirus response of brequinar combined with dipyridamole in patients with mild to moderate SARS-CoV-2 infection.
Sponsor:	Clear Creek Bio, Inc.
Clinical Study Centre(s):	Clinical facilities will be the clinics/ hospitals at different investigator sites across India.
Bio-analytical Study centre:	**For PK analysis:** Veeda Clinical Research Ltd. Rev. Sur. No. 12/1, Insignia, Corporate House, Nr. Grand Bhagvati Hotel, Sindhu Bhavan Road, S. G. Highway, Bodakdev, Ahmedabad - 380054, Gujarat, India. Phone: +91-79-67773000
Statistical Centre:	Veeda Clinical Research Ltd. Shivalik Plaza, Near I.I.M., Ambawadi, Ahmedabad–380 015, India Phone: +91-79-3001 3000 Fax: +91-79-3001 3010
Type of Study:	Phase II study
Rationale:	Brequinar is a potent DHODH inhibitor that blocks *de novo* pyrimidine synthesis in the host and has been previously studied in more than 1,000 cancer, psoriasis, and organ transplant patients. Brequinar has potent *in vitro* antiviral activity against many RNA viruses including SARS-CoV-2. The *in vitro* antiviral activity of brequinar against SARS-CoV-2 is likely due to DHODH inhibition and shows nanomolar potency and a high selectivity index in inhibiting viral replication these studies. Brequinar has also been studied in two clinical trials in patients with confirmed SARS-CoV-2 infection. In these two studies, 25 were hospitalized (15 treated with brequinar) and 115 were non-hospitalized (56 treated with brequinar). Results in these 71 COVID-19 patients demonstrated that brequinar 100 mg x 5 days was safe and well-tolerated in these populations.

	Brequinar's antiviral activity was demonstrated in the out-patient study as shown by decreased viral load compared to placebo at days 12, 15, 22 and 29 and a shorter duration of viral shedding. The strong safety data in 71 COVID-19 subjects treated with daily brequinar at 100 mg for 5 days provides strong support for the further investigation of brequinar in the treatment of COVID-19. The antiviral effects of brequinar may be blunted *in vivo* by pyrimidine salvage. One approach to enhancing the antiviral effect of brequinar is to block the pyrimidine salvage pathway by combining brequinar with a pyrimidine salvage inhibitor. Dipyridamole has been shown *in vitro* to block pyrimidine salvage and may potentiate the antiviral activities of DHODH inhibition on RNA viruses (Liu et al., 2020). Blocking pyrimidine salvage via dipyridamole shows improved *in vitro* antiviral efficacy of *de novo* pyrimidine synthesis inhibition via DHODH inhibition and will be used in this study in combination with brequinar to enhance brequinar's antiviral activity. Dipyridamole is a well-tolerated, FDA-approved medication that is a nucleoside transport inhibitor and PDE3 inhibitor that inhibits blood clot formation and causes vasodilation. Dipyridamole was first approved by the US FDA in 1961 for prevention of thromboembolism in patients who have had cardiac valve replacement. It has also been widely prescribed in combination with aspirin to prevent stroke. The CCB-CRISIS-04 trial will study subjects who have mild to moderate COVID-19 infection confirmed by a positive SARS-CoV-2 RT-PCR qualitative test / rapid antigen test and have mild/moderate signs and/or symptoms ongoing at study entry. The purpose of this study is to determine if the antiviral activity of brequinar can be improved by combining brequinar with dipyridamole in patients infected with SARS-CoV-2.
Investigational Product and Combination Product Dosage:	1. Brequinar 50 mg capsules (used for the 50 mg and 150 mg doses) 2. Brequinar 100 mg capsules (used for the 100 mg, 150 mg and 200 mg doses) 3. Dipyridamole 75 mg tablets 4. Brequinar Placebo 50 mg and 100 mg capsules Note: • The subjects will take the study medication as directed on study days 1 – 5. • Treatment assignment will be randomized, assessor-blind. • IMP dispensing will be performed by unblinded pharmacist. • Study assessments will be performed by blinded Investigator or designate blinded site personnel. • Brequinar and brequinar placebo doses will be administered once daily. • Dipyridamole doses will be given thrice daily.

	• The 150 mg brequinar or brequinar placebo dose will be given as 1 capsule of 100 mg and 1 capsule of 50 mg; the 200 mg brequinar or brequinar placebo dose will be given as 2 capsules of brequinar or brequinar placebo 100 mg.
Study Design:	The first part of the study will be a phase II, randomized, assessor-blind, multicenter, multi-dose, placebo-controlled study in approximately 64 subjects with mild to moderate COVID-19 infection confirmed by a positive SARS-CoV-2 RT-PCR qualitative test /rapid antigen test and who have at least mild to moderate signs and/or symptoms ongoing at study entry. Approximately 32 subjects (50% of subjects per arm per cohort) at selected sites will be invited to participate in the "PK" arm of the study until approximately 8 subjects in each cohort have been recruited after providing written informed consent for the same. PK includes brequinar and dipyridamole plasma concentrations. If a particular cohort meets study stopping criteria (as defined in section "Safety Criteria") or is found to be unsafe by DSMB members, then the study will not proceed with enrollment of subsequent cohorts. An expansion cohort of approximately 48 subjects will be added to the cohort with the highest brequinar dose that meets safety criteria. Safety data of cohort 1 to cohort 4 (or highest dose cohort evaluated) will be submitted to the regulators and their approval will be obtained prior to commencing recruitment in the expansion cohort. All subjects will receive SOC as per relevant guidelines for treatment of patients with mild to moderate COVID-19 infection. Subjects will be randomized to one of the following cohorts in Part 1: **Cohort 1:** • Arm 1: 5 days of standard of care (SOC) + brequinar 50 mg OD + dipyridamole 75 mg TID (N = 8) • Arm 2: 5 days of SOC + brequinar 50 mg OD (N = 4). • Arm 3: 5 days of SOC + brequinar placebo 50 mg OD (N = 4). **Cohort 2:** If the 50 mg brequinar OD + dipyridamole 75 mg TID meets safety criteria as pre-defined in the protocol the brequinar dose will be escalated to 100 mg. • Arm 1: 5 days of standard of care (SOC) + brequinar 100 mg OD + dipyridamole 75 mg TID (N = 8) • Arm 2: 5 days of SOC + brequinar 100 mg OD (N = 4). • Arm 3: 5 days of SOC + brequinar placebo 100 mg OD (N = 4).

	Cohort 3: If the 100 mg brequinar OD + dipyridamole 75 mg TID meets safety criteria as pre-defined in the protocol the brequinar dose will be escalated to 150 mg: • Arm 1: 5 days of standard of care (SOC) + brequinar 150 mg (100 mg + 50 mg) OD + dipyridamole 75 mg TID (N = 8) • Arm 2: 5 days of SOC + brequinar 150 mg (100 mg + 50 mg) OD (N = 4) • Arm 3: 5 days of SOC + brequinar placebo 150 mg (100 mg + 50 mg) OD (N = 4). **Cohort 4:** If the 150 mg brequinar OD + dipyridamole 75 mg TID meets safety criteria as pre-defined in the protocol the brequinar dose will be escalated to 200 mg: • Arm 1: 5 days of standard of care (SOC) + brequinar 200 mg (100 mg +100 mg) OD + dipyridamole 75 mg TID (N = 8) • Arm 2: 5 days of SOC + brequinar 200 mg (100 mg +100 mg) OD (N = 4) • Arm 3: 5 days of SOC + brequinar placebo 200 mg (100 mg +100 mg) OD (N = 4). **Expansion Cohort:** Approximately forty-eight (48) subjects will be added to the cohort with the highest brequinar dose that meets safety criteria in a 2 : 1 ratio of active treatment (approximately 32 SOC + brequinar + dipyridamole treated and 16 SOC + brequinar monotherapy group). Additional sites may be added if required to meet enrollment of the expansion cohort in an efficient manner.
Study Duration:	Study duration will be approximately 34 days including a maximum screening period of 5 days.
Objectives:	**Primary Objective:** • To characterize the safety and tolerability of the brequinar-dipyridamole combination in COVID-19 subjects as measured by frequencies of grade 3 and 4 toxicities and serious adverse events (SAEs) considered by the investigator to be related to the combination. **Secondary Objectives:** For subjects treated with the brequinar-dipyridamole combination compared to subjects treated with brequinar and to subjects treated with placebo through Day 29, to determine: • Reduction of SARS-CoV-2 levels using qPCR through Day 29 and at days 4, 8, 12, 15, 22, and 29;

	• Reduction in time to symptom improvement; • Reduction in percentage of subjects requiring hospital admission/re-admission as an in-patient for >24 hours; • Reduction in percentage of subjects requiring medical attended visits, e.g., hospitalization, emergency room visits, Urgent Care/Family Doctor visits; • Reduction in percentage of subjects requiring supplemental support such as oxygen. **Exploratory Objectives:** • To determine brequinar-dipyridamole combination and brequinar's pharmacokinetic profile in a subset of subjects agreeing to participate in the PK aspect of the study.
Study Endpoints:	**Primary Endpoints:** • Frequencies of grade 3 and 4 toxicities and serious adverse events (SAEs) considered by the investigator to be related to the combination, brequinar alone or placebo alone. **Secondary Endpoints:** • qPCR SARS-CoV-2 levels through Day 29 and at days 4, 8, 12, 15, 22, and 29; • Time to symptom improvement through Day 29; • Percentage of subjects requiring hospital admission/re-admission as an in-patient for >24 hours through Day 29; • Percentage of subjects requiring medical attended visits, e.g., hospitalization, emergency room visits, Urgent Care/Family Doctor visits through Day 29; • Percentage of subjects requiring supplemental support such as oxygen through Day 29. **Exploratory Endpoints (PK):** • Analysis of brequinar's pharmacokinetic profile in a subset of patients that have received brequinar as a part of therapy and have consented to provide PK samples.
Study Procedure:	To be eligible for screening, subjects must have a documented positive SARS-CoV-2 test result within 5 days of first dose of study drug and have at least one ongoing symptom consistent with SARS-CoV-2 infection rated as at least mild to moderate in the opinion of the investigator. The subject's earliest symptom must have an onset date within 5 days of first dose of study drug. Subjects will undergo screening (day -4 to 0) for confirming eligibility for participation

in the study. Study Day 1 includes randomization visit.

Subjects will be randomized to a cohort as described above.

Screening activities as well as randomization can take place on the same day as a combined Screening/Day 1 visit, if the site team is able to obtain Screening lab results on the same day. Otherwise, Day 1 is to take place as soon as Screening lab results are available.

Study Day 1 and first dose of study drug must take place ≤5 days from onset of first symptom.

Subjects may be hospitalized as many as 9 days in the study (day 0 to 8) or more for the PK sample as per Investigator discretion.

For subjects participating in the PK subset,

Blood samples for estimating brequinar concentrations will be drawn (PK):

- Day 1: Pre-dose (within 1 hour prior to study drug administration) and post dose at 1h, 2h, 4h, and 8h; note that the 8h sample is to be obtained prior to the next dose of dipyridamole.
- Days 2 – 5 pre-dose and Day 8.

Aliquots of the NP/OP swab samples are to be stored at the testing laboratory for possible additional virological testing.

Screening visit and study visits on Days 1, 8, 15, 22 and 29 will be either in person or a combination of in-person and virtual visit (telemedicine or other remote technique) or by visit to patient's home by site team.

Study visits on Day 4 and 12 may be virtual visits (telemedicine or other remote technique) or in person.

On Days 2, 3, 5, 6 and 7, the site will have a telephone call / or in-person communication with the subject for changes in concomitant medications and assessment of adverse events (same will also be captured by the subject using a patient diary card or these visits will be conducted in person).

Note:

- Study procedures are presented in detail in the Schedule of Events.
- Days 1, 8, 15 and 29 require sample collection for performing laboratory tests and will be conducted at the site or via home visit.
- Any in-person visit may also have telemedicine or telephone components if all study activities cannot be completed in person.
- The visits that include bloodwork must be conducted at the study site or

	arrangements made for sample collection at the subject's home or other appropriate location. • Site staff (in case of an in-person visit) or subjects (in case of a remote visit) will assess respiratory rate, heart rate, body temperature and SpO_2 (a thermometer and pulse oximeter are to be provided to subjects who are home quarantined, leave the hospital or are unable to return for study visits). • Subjects will record details of concomitant medications, adverse events in the patient diary card (PDC). • Subjects will complete a symptom assessment form on designated days during the study period (days 1 – 8, 12, 15, 22, and 29). • In case the subject is hospitalized during the course of study, the activities specified in scheduled visits / time points will be carried out within the hospital facility. • Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF. **DSMB Meeting:** A Data Safety Monitoring Board (DSMB) will meet to review the safety and scientific conduct of the study. At a minimum, the DSMB will review the protocol and study design prior to study start, after the end of the first part of the study prior to the expansion phase, and at the end of the study. At each interim meeting the DSMB members will determine whether to stop the study, amend the protocol, or continue the study per protocol. The study enrollment will not be suspended for routine DSMB meetings. The DSMB will be convened and enrollment suspended if Cohort-Level Stopping Criteria are met. The DSMB may allow the enrollment to resume following their review if safety criteria are met.
Hospitalization:	Subjects may be hospitalized for approximately 9 days (days 0 to 8) in the study as per Investigator discretion for the PK blood sample draws. Subjects may leave after this period (if medically discharged) after the Day 8 blood work has been drawn. Extended stays beyond study Day 8 are permitted if the facility is a dedicated COVID-19 unit or other relevant hospital type or if per the Investigator the extended stay facilitates study procedures; this continuation will not be considered as an SAE. However, prolongation of hospitalization due to increase in disease severity or any other safety concerns related to the subjects will be considered as an SAE. Hospitalization for the purpose of PK sample collection may be done at Investigator's discretion, in this case hospitalization may be for selected few days and may not be for entire 8 days duration. Appropriate documentation of the same will be done in source

	file.
Treatment:	All subjects will receive standard of care (SOC) including treatment for COVID-19 signs and/or symptoms as required. Study encounters may be conducted remotely or at the study site depending on visit requirements, site facilities and subject and study team preferences.
Clinical Safety Measures:	It is the responsibility of the investigator to ensure that adequate medical supervision and care is available for the study subjects during the study to ensure their utmost safety and well being. • Demography (subject reported / measured height and weight, age, sex and race/ethnicity): At screening • Medical history (relevant within 30 days or ongoing) / History of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection): At screening • Physical Examination (subject self-reported / examiner evaluated): At screening • Vital signs (body temperature, respiratory rate, heart rate, SpO_2) assessment: At screening, Day 4 (±8 hrs), Day 8 (±8 hrs), Day 12 (± 1 day), Day 15 (±1 day), Day 22 (±1 day), End of study [EoS; Day 29 (±2 day)]. Note: If subject is hospitalized, vital signs assessment will be done on daily basis by site team during hospitalization through Day 8 then following the Vital signs visits as listed above. • Hematology, biochemistry and urine analysis: At screening, Day 1 unless same day as Screening visit, Day 8 (±8 hrs), Day 15 (±1 day), End of study [EoS; Day 29 (±2 day)]. • HCV, HbSAg, HIV Test: At screening • Serum pregnancy test (Women of child bearing potential (WOCBP)): At screening. • Urine pregnancy test (WOCBP): End of study [EoS; Day 29 (±2 day)]. Note: WOCBP: A premenopausal female capable of becoming pregnant • Rapid antigen test / SARS-CoV-2 RT-PCR Qualitative (in a clinically relevant specimen (Naso-Oro-Pharyngeal as appropriate)): Screening Note: Test need not be repeated in those with possession of confirmed positive report. Date of positive report must be ≤5 days prior to randomization. • RT-PCR Quantitative Viral (in a clinically relevant specimen (Naso-Oro-Pharyngeal as appropriate)): Day 1 (Prior to dosing), Day 4 (±8 hrs), Day 8 (±8 hrs), Day 12 (±1 day), Day 15 (±1 day), Day 22 (±1 day) and End of study [EoS;

Day 29 (±2 day)]

- Ordinal Scale Assessment: Screening, Day 8 (±8 hrs), Day 15 (±1 day), Day 22 (±1 day) and End of study [EoS; Day 29 (±2 day)]
- Adverse events/ Serious Adverse Events: Adverse events/ Serious Adverse Events will be recorded from the time of first study drug administration till end of study safety assessments. Other medical events not related to disease condition under study and occurring before IMP administration, but after signing the informed consent form will be recorded on the medical history/current medical conditions of case report form.
- In addition to protocol-specific laboratory tests and/or clinical examinations at scheduled time points, additional tests/clinical examination may be conducted to evaluate subject safety at any time during the study, at the discretion of the Investigator (can be done in local laboratory or nearby clinic/hospital/institution).
- Medication taken prior to first dosing: All prescription medications and over-the-counter drugs (including vitamins) taken within 30 days prior to screening must be recorded in the eCRF as Medication history.
- Concomitant medications: Medications taken from time of signing of Informed Consent form until study completion (i.e. End of study) will be captured as concomitant medications.
- Prohibited medications: Any other antiviral medications or medication with antiviral potential.

Note:

- It is recommended that general precautions need to be taken by the staff caring for COVID patients during the trial.
- In case the subject is hospitalized during the course of study, the activities specified in scheduled visits / time points will be carried out within the hospital facility.

Sample Size:

In Part 1, approximately 64 subjects will be randomized to up to 4 cohorts of 5 consecutive days of one of the following regimens in addition to SOC in 2:1:1 ratio as shown below:

Treatment Arm[a]	Day 1	Day 2	Day 3	Day 4	Day 5
Brequinar + Dipyridamole (N=8)	BRQ XX mg OD DPY 75 mg TID	BRQ XX mg OD DPY 75 mg TID	BRQ XX mg OD DPY 75 mg TID	BRQ XX mg OD DPY 75 mg TID	BRQ XX mg OD DPY 75 mg TID
Brequinar (N=4)	BRQ XX mg OD	BRQ XX mg OD	BRQ XX mg OD	BRQ XX mg OD	BRQ XX mg OD

	<table><tr><td>Placebo (N=4)</td><td>PBO XX mgPlacebo OD</td><td>PBO XX mgPlacebo OD</td><td>PBO XX mgPlacebo OD</td><td>PBO XX mgPlacebo OD</td><td>PBO XX mgPlacebo OD</td></tr></table> [a]All subjects in the study will also receive standard of care (SOC). The brequinar dose will start at 50 mg and may be escalated to 100 mg, 150 mg, and 200 mg if safety criteria are met for each cohort (see Safety Criteria below). The hospital pharmacist is to be unblinded. Bulk supplies of investigational medicinal product (IMP) of brequinar 50 mg, brequinar 100 mg, dipyridamole 75 mg, brequinar placebo 50 mg and brequinar placebo 100 mg will be supplied to the unblinded hospital pharmacist. The unblinded hospital pharmacist is to prepare the assigned IMP for each individual subject at that institution and create an appropriately labeled bottle/zip lock bag of study medication sufficient for a 5-day treatment course. Randomization code will be supplied using an IWRS. Alternatively, the hospital pharmacist and study team may decide to distribute IMP on a daily basis for each of the 5 days for brequinar and dipyridamole while the subject is hospitalized, depending on the most convenient method.
Inclusion Criteria:	Subjects will be eligible if they meet all of the following 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. Subjects between ≥18 and ≤65 years of age. 3. Subjects found positive for SARS-CoV-2 either by rapid antigen test or by reverse transcription polymerase chain reaction (RT-PCR) using ICMR-validated kit. Note: Test need not be repeated in those with possession of confirmed positive report but positive result test date must be ≤5 days of first dose of study drug. 4. Mild or Moderate COVID-19 as per latest updated version of CLINICAL MANAGEMENT PROTOCOL for COVID-19 (in Adults) released by Government of India Ministry of Health and Family Welfare Directorate General of Health Services (EMR Division). 5. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men and women treated or enrolled on this protocol must also agree to use adequate contraception for the duration of study participation, and for 90 days after completion of brequinar administration. 6. Male subjects must agree to refrain from sperm donation and female subjects must

	agree to refrain from ovum donation from initial study drug administration until 90 days after the last dose of brequinar. 7. At least one non-respiratory COVID-19 symptom characterized as mild to moderate by the Investigator including but not limited to fatigue, chills, fever, body aches, nasal congestion, nausea, vomiting, or other sign or symptom commonly associated with COVID-19 in the opinion of the investigator. Symptom onset must be ≤5 days prior to first dose. Subject must have one or more signs/symptoms present at first dose. 8. Willing to participate in the PK subset if at one of the identified sites. 9. Able to swallow capsules.
Exclusion Criteria:	Subjects will not be eligible for this study if any of the following in present at the time of study inclusion: 1. Have an oxygen saturation of <90% while breathing ambient air. 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 subject. 3. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test. 4. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide) or other agents known to cause bone marrow suppression leading to thrombocytopenia. 5. Ongoing treatment with aspirin and or dipyridamole, famotidine or cimetidine. Remdesivir and ivermectin are prohibited through Study Day 8. Steroids are permitted per the guidelines. 6. Platelets ≤125,000 cell/mm^3. 7. Hemoglobin <10 gm/dL. 8. Absolute neutrophil count <1000 cells/mm^3. 9. Renal dysfunction, i.e., creatinine clearance <30 mL/min. 10. AST or ALT >3 x ULN, or total bilirubin >ULN. Gilbert's Syndrome is allowed. 11. Bleeding disorders or blood loss requiring transfusion in the six weeks preceding enrollment. 12. Ongoing gastrointestinal ulcer, or gastrointestinal bleeding within 6 weeks of first dose. 13. HIV, Chronic hepatitis B infection, active hepatitis C infection, active liver disease and/or cirrhosis per subject report. 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).

PK Sample Collection and Processing:	**Blood collection and processing for PK analysis:** Brequinar/Dipyridamole PK blood samples are to be collected either through an indwelling intravenous cannula (Venflon or similar) or may also be collected through a fresh vein puncture at each time point. For PK samples, collect a 10 mL sample using syringe/adaptor and transfer to a pre-labelled vacutainer containing K_2EDTA as anticoagulant. Immediately following blood collection, gently invert the vacutainer 5 - 7 times to mix the anticoagulant. Place the filled vacutainer on wet ice bath (below 10 ^{0}C) during sample collection activity until storage of plasma. Centrifuge the PK blood sample at 4000 RPM for 10 minutes at 5 ± 3°C to separate plasma. Keep the samples on wet ice bath (below 10 ^{0}C) both before centrifugation and after separation. Transfer the separated plasma to pre-labeled polypropylene tubes in 2 aliquots: Aliquot 1: Approximately 1.7 mL of plasma Aliquot 2: Approximately 1.2 mL of plasma Aliquots are to be stored upright in a box containing dry ice or in a freezer at a temperature –15 °C or colder for interim storage at the sites until shipment to Veeda Clinical Research Ltd., Ahmedabad. Note: Entire activity from blood sample collection to storage in a freezer should be completed within 60 minutes time. Ship each aliquot separately. During shipment the samples are to be packed in thermocol boxes containing an adequate amount of dry ice. The temperature will be monitored using calibrated data logger during shipment. Samples will be stored at -78 ± 8°C until completion of analysis at Veeda Clinical Research Ltd., Ahmedabad. Shipment for the backup Aliquot 2 will be carried out after confirmation of receipt of Aliquot 1. A designated person or designate from bioanalytical department will take receipt of the samples at Veeda Clinical Research Ltd., Ahmedabad. The condition of the samples is to be examined on arrival at Veeda Clinical Research Ltd., Ahmedabad. If any of the samples are not in a frozen condition, clinical facility and\or Sponsor is to be informed. After receiving the samples at Veeda Clinical Research Ltd., Ahmedabad, the samples will be stored at -78 ± 8 °C until completion of analysis. Note: Samples of patients enrolled in Arm 3 (SOC + Placebo) of each cohort will not be analysed.
Quantitative PCR (qPCR)	Obtain a NP/OP swab sample to be processed as outlined in the laboratory manual and sent to a central lab for analysis of quantitative PCR.

Drug Analysis:	Plasma concentration of brequinar and dipyridamole will be quantified at the Bioanalytical facility of Veeda Clinical Research Ltd.
Safety Criteria:	An independent, unblinded study physician (from CRO) will assess each cohort for safety. A cohort will be declared safe are as soon as all results are available for the Day 15 visit if the following conditions are met: • No toxic deaths (deaths judged by the investigator to be related to either study drug); • Not more than 1 toxic SAE (SAEs judged by the investigator to be related to either study drug); • No Grade 3 or higher toxicities (including laboratory AEs as per CTCAE version 5.0 or higher) (AEs judged by the investigator to be related to either study drug); • <4 subjects with any grade toxicity (AEs judged by the investigator to be related to either study drug). In addition to the cohort-level safety, the independent study physician (from CRO) will determine if any subjects meet Individual Stopping Criteria: • Subjects who develop a Grade 3 toxicity that is assessed by the investigator to be related to the study drug are to be permanently discontinued from study treatment but will continue in the study for safety assessments. • Subjects who develop a Grade 4 toxicity, regardless of relatedness to study drug, are to be permanently discontinued from study treatment but will continue in the study for safety assessments. In addition to the individual subject-level safety, the independent study physician (from CRO) will determine if a cohort meets Cohort-level Stopping Criteria prior to completing the 16 subjects, in which case no additional subjects will be enrolled into that cohort and no higher brequinar doses will be assessed: • ≥3 brequinar-treated or combination-treated subjects meet the individual stopping criteria; • ≥5 brequinar-treated or combination-treated subjects develop a Grade 3 or higher AE regardless of relationship to study drug.
Statistical methods:	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, standard error, minimum, and maximum. For qualitative variables, the summaries will include the number and percentage of subjects for each outcome, and the 95% CI, when

	appropriate. Any statistical testing will be considered exploratory and descriptive. All computations will be performed using SAS® (Version 9.4 or higher). Safety and tolerability will be assessed in terms of AEs, SAEs, and safety laboratory data. Adverse event data will be descriptively evaluated. All AEs will be reported in data listings. The incidence of treatment-emergent adverse events, defined as TEAEs occurring after first dose will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class, and by severity and relationship to study treatment. All laboratory results and other clinical measures will be summarized using appropriate descriptive statistics.
Ethical Issues:	The study will commence only after a written approval is obtained from the Institutional Ethics Committee and applicable regulatory authorities. The trial will be conducted as per the biomedical research on human participants (ICMR) 2017 guidelines, New Drugs and Clinical Trial Rules (2019) of India, ICH (Step 5) 'Guidance on Good Clinical Practice' ICH Guidance E6 (R2), Declaration of Helsinki (Brazil, 2013) and with procedures oriented to Good Laboratory Practice and applicable regulatory guidelines.

3.2 Schedule of Activities

Windows are relative to time of first dose Procedures	Screening[a]/ Day 1 (Day -4 to 0)	Day 2, 3 (± 8 hrs)	Day 4 (± 8 hrs)	Day 5, 6, 7 (±8 hrs)	Day 8 (±8 hrs)	Day 12 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Final Visit[k] Day 29 (±2 days)
Type of visit[g]	IPV[f]	TC[f]	TM	TC	IPV+TM	TM	IPV+TM	IPV+TM	IPV+TM
Informed Consent (note Date and Time)	X								
AE/Concomitant Medications (dose, route, duration or ongoing)	X	X	X	X	X	X	X	X	X
Medical history (relevant within 30 days or ongoing)/ History of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection)	X								
Demographics (subject reported/ measured height and weight, age, sex, race/ethnicity)	X								
Check for Physical Exam abnormalities (subject self-reported/examiner evaluated)	X								
Pregnancy Test (WOCBP) (serum at Screen and urine at D29)	X								X
Hematology / Biochemistry / Urine Analysis[j]	X	X[m]			X		X		X
HCV, HbSAg, HIV Test	X								
Vital Signs[b]	X		X		X	X	X	X	X
Symptom Assessment[c]	X	X	X	X	X	X	X	X	X
Rapid antigen test/SARS-CoV-2 RT-PCR Qualitative[d]	X								
RT-PCR Quantitative Viral Load[l]	X		X		X	X	X	X	X
PK Sampling (subset of subjects)[h]	X	X	X	X	X				
Hospitalized Days 0 to 8[i]	Day 0	X	X	X	X				
Hospital/Healthcare utilization Status							X	X	X
Ordinal Scale Assessment	X				X		X	X	X
Confirm Eligibility	3								
Randomize subject and dispense Study Medication	X								
Study drug administration (Days 1 – 5 only)[f]	X	X	X	X					

Windows are relative to time of first dose Procedures	Screening[a]/ Day 1 (Day -4 to 0)	Day 2, 3 (± 8 hrs)	Day 4 (± 8 hrs)	Day 5, 6, 7 (±8 hrs)	Day 8 (±8 hrs)	Day 12 (±1 day)	Day 15 (±1 day)	Day 22 (±1 day)	Final Visit[k] Day 29 (±2 days)
Type of visit[g]	IPV[f]	TC[f]	TM	TC	IPV+TM	TM	IPV+TM	IPV+TM	IPV+TM
Drug Accountability (Unblinded pharmacist)					X				
PDC distribution		X			X		X	X	
PDC collection and review					X		X	X	X
Symptom assessment form distribution		X			X		X	X	
Symptom assessment form collection and review					X		X	X	X

a. Day -4 to 0 includes screening activities.
b. Vital signs (include heart rate, respiratory rate, body temperature, SpO_2) assessment will be done at screening, Day 4 (±8 hrs), Day 8 (±8 hrs), Day 12 (± 1 day), Day 15 (±1 day), Day 22 (±1 day), End of study [EoS; Day 29 (±2 day)]. Subjects who leave the hospital will be provided with a thermometer and pulse oximeter with heart rate monitoring capability. Training will be provided during the first home visit. Vital signs parameters will be observed and recorded by study staff via telemedicine or in-person visit (IPV) (at the study site or home visit).
   Note: If subject is hospitalized, vital signs assessment will be done on daily basis by site team during hospitalization through day 8 then following the Vital signs visits as listed above.
c. Symptom Assessment will capture respiratory symptoms as well as sore throat, cough, GI symptoms (vomiting, diarrhea), fatigue, anosmia, dysgeusia, other (specify), etc. Severity None, Mild, Moderate, or Severe will be collected. Longest symptom(s) onset date must be within 5 days of first dose.
d. Documentation of a positive SARS-CoV-2 result from Rapid antigen test/RT-PCR or other regulatory agency-approved test is required to qualify for Screening. Test need not be repeated in those with possession of confirmed positive report. Date of positive report must be ≤5 days prior to randomization.
e. Day 1 PK baseline sample must be obtained prior to dosing.
f. Subject will take study drug once daily Days 1 – 5 and record doses in a medication diary. Note that some visits/visit activities post hospital discharge may be conducted via telephone, telemedicine, or digital media other than serum pregnancy test and chemistry/hematology/PK sample collections. These labs may be collected at the clinical site or another designated out-patient facility/laboratory or collected via home visit.
g. IPV= in-person visit (subject's home or at clinical site, may also include TM or TC if all study visit activities cannot be completed by the in-person personnel); TC = Telephone Call with site and subject; TM = Telemedicine with site and subject.
h. PK Sampling: For PK, day 1 samples will be drawn pre-dose, and after dosing at 1h, 2h, 4h, and 8h (Note: 8h sample is to be obtained prior to the next dose of dipyridamole), and pre-dose days 2, 3, 4, 5 and on day 8. One 10 mL sample is required for PK at each timepoint.
i. Subjects hospitalization will be based on the discretion of the Investigator. Hospitalization for the purpose of PK sample collection can be done at Investigator's discretion, in this case hospitalization may be for selected few days and may not be for entire 8 days duration. Subjects may leave the hospital after the Day 8 samples have been obtained if medically able to be discharged. In case the subject is hospitalized during the course of study, the activities specified in scheduled visits / time points will be carried out within the hospital facility.

j. Sample collection for performing laboratory tests on days 1, 8, 15 and 29 will be conducted at the site or via home visit.
k. If a study subject is discontinued from the study during an unscheduled visit, the unscheduled visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for End of Study Visit will be performed.
l. RT-PCR Quantitative Viral will be done at Day 1 (Prior to dosing), Day 4 (±8 hrs), Day 8 (±8 hrs), Day 12 (±1 day), Day 15 (±1 day), Day 22 (±1 day) and End of study [EoS; Day 29 (±2 day)]
m. Day 1 unless same day as Screening visit.

Note:

- If the unscheduled visit is not an Early Discontinuation Visit (i.e., the study subject will continue to take part in the study), then the reason for unscheduled visit is to be documented and required procedures at the discretion of investigator considering the reason for visit, will be performed.

4.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

4.1 Clinical Facilities

Clinical facilities will be the clinics/ hospitals of investigators' site.

4.2 Biostatistics Services and Quality Assurance

Biostatistics	:	Dr. Ghanshyam Patel
Quality Assurance	:	Mrs. Amee Kanuga
Authorised Signatory	:	Dr. Sumit Arora

Veeda clinical research Ltd.,

Shivalik Plaza, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India.

Phone No.: +91-79-3001 3000

4.3 Medical Experts

Veeda's Medical Expert:	Sponsor's Medical Expert:
Dr. Ravi Alamchandani Veeda Clinical Research Ltd., Shivalik Plaza, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India. Phone No.: +91-79-3001 3000 E-mail: Ravi.A1950@veedacr.com	John Pottage, MD Phone No: +1-610-761-0840 E-mail: John.pottagemd@gmail.com

5.0 BACKGROUND INFORMATION

5.1 Introduction

Coronaviruses are large group of viruses that cause illness in humans and animals. Rarely, animal coronaviruses can evolve and infect people and then spread between people such as has been seen with MERS and SARS. The current outbreak of novel coronavirus disease (COVID-19) was initially noticed in Wuhan city in Hubei Province of China in mid December, 2019 has now spread to 215 countries/territories/areas worldwide. WHO (under International Health Regulations) has declared this outbreak as a "Public Health Emergency of International Concern" (PHEIC) on 30th January 2020. WHO subsequently declared COVID- 19 a pandemic on 11th March, 2020.

Pathophysiology of COVID 19:

Most adult patients with COVID-19 predominantly have a respiratory tract infection associated with SARS-CoV-2 infection. However, in a small proportion of cases, the disease can progress to a more severe stage characterized by a dysregulated immune response with hyperinflammation with subsequent development of ARDS.

Clinical Features:

COVID-19 patients reporting to various COVID-19 treatment facilities have reported the following signs and symptoms:

- Fever,
- cough,
- general weakness/ fatigue,
- headache,
- myalgia,
- sore throat, coryza,
- dyspnoea,
- anorexia/nausea/vomiting,
- diarrhoea,
- altered mental status.
- loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms has also been reported.

Older people and immune-suppressed patients in particular may present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, delirium, and absence of fever.

Diagnosis of COVID 19:

COVID-19 diagnosis is currently based on using a reverse transcriptase polymerase chain reaction (RT-PCR)

assay to detect viral RNA in respiratory samples. The high specificity of RT-PCR removes the need for lower respiratory tract samples to diagnose COVID-19 when a nasopharyngeal swab is positive for a patient with recent onset of the disease.

5.2 Safety of brequinar

Introduction:

Brequinar is an orally available and potent inhibitor of dihydroorotate dehydrogenase (DHODH). DHODH catalyzes the fourth step in pyrimidine synthesis, the conversion of dihydroorotate (DHO) to orotate. DHODH inhibitors, including brequinar, inhibit *de novo* pyrimidine synthesis thereby leading to a depletion of the cellular pool of uridine, cytidine, and thymidine ribonucleotides and deoxyribonucleotides. Brequinar has previously been evaluated for the treatment of hematologic malignancies, autoimmune disorders and COVID 19. There are other DHODH inhibitors that have been approved for use in the treatment of rheumatoid arthritis and multiple sclerosis.

Brequinar has been shown to have significant *in vitro* antiviral activity against several RNA viruses, including SARS-CoV-2, the cause of COVID-19 disease. As RNA viruses cannot synthesize their own ribonucleotides, they depend upon the host intracellular pool of ribonucleotides as the source for viral gene expression and replication. By transiently depleting the pool of host of pyrimidines, DHODH inhibition denies a virus of its source of ribonucleotide building blocks and thereby suppresses viral replication. This antiviral strategy targeting a host rather than viral protein also is less likely to select for resistant viruses.

Preclinical study data:

Initial nonclinical pharmacology studies of brequinar confirmed that its mechanism of action is the inhibition of *de novo* pyrimidine synthesis. Further studies with partially purified enzymes isolated from L1210 cells showed that brequinar inhibited DHODH activity, the fourth biochemical step in pyrimidine synthesis

Clinical study data:

Brequinar has been studied under FDA IND 149,291 in 138 patients in two studies as an antiviral for coronavirus disease 2019 (COVID-19); 71 of these patients were treated with brequinar. Brequinar was administered as a single daily dose for five consecutive days with standard of care (SOC) in these COVID-19 studies.

Brequinar has also been previously studied in more than 1,000 patients in 30 clinical trials for treatment of solid tumors, psoriasis, and organ transplant. More recently Clear Creek Bio has studied brequinar use for acute myeloid leukemia (AML). In the oncology, psoriasis and organ transplant studies brequinar was administered as a single dose and as multiple courses with once weekly, twice weekly, single dose every 3 weeks, daily times 5 every 4 weeks, and daily times 21 days regimens. The maximum single intravenous dose of 3250 mg/m^2 was administered in an oncology study; the maximum oral dose of 950 mg/m^2 twice weekly was also dosed during an oncology study.

5.3 Safety of Dipyridamole

Introduction:

Dipyridamole was first approved for use in 1961 as an adjunct to coumarin anticoagulants in the prevention of postoperative thromboembolic complications of cardiac valve replacement. The primary therapeutic actions of dipyridamole relate to its activity in (1) inhibiting platelet function and aggregation and (2) vasodilatation.

Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells and erythrocytes in vitro and in vivo; the inhibition occurs in a dose-dependent manner at therapeutic concentrations (0.5−1.9 µg/mL). This inhibition results in an increase in local concentrations of adenosine which acts on the platelet A_2-receptor thereby stimulating platelet adenylate cyclase and increasing platelet cyclic-3',5'-adenosine monophosphate (cAMP) levels. Via this mechanism, platelet aggregation is inhibited in response to various stimuli such as platelet activating factor (PAF), collagen and adenosine diphosphate (ADP).

Dipyridamole also inhibits phosphodiesterase (PDE) in various tissues. While the inhibition of cAMP-PDE is weak, therapeutic levels of dipyridamole inhibit cyclic-3',5'-guanosine monophosphate-PDE (cGMP-PDE), thereby augmenting the increase in cGMP produced by EDRF (endothelium-derived relaxing factor, now identified as nitric oxide).

Preclinical study data:

In addition to the effects upon platelet function, dipyridamole can cause vasodilatation.

Hemodynamics:

In dogs intraduodenal doses of dipyridamole of 0.5 to 4.0 mg/kg produced dose-related decreases in systemic and coronary vascular resistance leading to decreases in systemic blood pressure and increases in coronary blood flow. Onset of action was in about 24 minutes and effects persisted for about 3 hours.

Similar effects were observed following intravenous dipyridamole in doses ranging from 0.025 to 2.0 mg/kg.

In man the same qualitative hemodynamic effects have been observed. However, acute intravenous administration of dipyridamole may worsen regional myocardial perfusion distal to partial occlusion of coronary arteries.

5.4 Brequinar COVID-19 Studies

CCB-CRISIS-01 in Hospitalized Patients

The CRISIS-01 trial studied standard of care (SOC) and SOC with 5 days of brequinar administration in patients hospitalized for treatment of COVID-19. This was a phase 1 randomized, open label, multi-center study designed to enroll approximately 24 subjects. All subjects received SOC per institutional guidelines for treatment of patients with SARS-CoV-2 infection. In addition to SOC, the brequinar group received brequinar 100 mg as an oral capsule once daily for 5 days.

A total of 25 subjects were randomized in study CRISIS-01 at 5 sites. Two subjects assigned to the SOC plus brequinar group were randomized but withdrew consent and were never treated with brequinar. The modified Intent-to-Treat (mITT) population which was used for all study analyses included all 23 randomized subjects who had at least one post-randomization assessment, and who received at least one dose of study medication if randomized to the SOC plus brequinar group. A total of 15 subjects were exposed to SOC plus brequinar and 8 subjects had SOC treatment only.

Brequinar was generally safe and well-tolerated in this population. No subjects discontinued study drug treatment due to an AE. No subjects died. 4 subjects (17.4%) experienced a total of 6 SAEs (1 in the SOC + brequinar group and three in the SOC only group). 12 subjects (52.2%) experienced a total of 28 treatment emergent AEs (TEAEs); 10/15 subjects (66.7%) reported 22 TEAEs in the SOC plus brequinar group; 2/8 (25.0%) reported 6 TEAEs in the SOC only group. The most common TEAE was hyperglycaemia reported in 3 subjects (20.0%) in the SOC plus brequinar group. Increased ALT was experienced by 2 subjects (13.3%) in the SOC plus brequinar group in subjects who had also received remdesivir. No other AEs were reported for more than one subject in either treatment group.

CCB-CRISIS-02 in Non-Hospitalized Patients

The CRISIS-02 trial: A phase 2, randomized, double blind, placebo-controlled, multi-center study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in out-patient adults with SARS-CoV-2.

The CRISIS-02 trial studied outpatients (non-hospitalized patients) who had a positive SARS-CoV-2 RT-PCR test using a saliva sample and were symptomatic. Subjects were randomized to receive SOC + 5 days of brequinar or SOC + 5 days of placebo. The purpose of this study was to determine if the *in vitro* antiviral activity of brequinar translated to patients infected with SARS-CoV-2 by measuring the effect of treatment with brequinar on SARS-CoV-2 RNA levels (henceforth called “viral load”).

The study enrolled 115 subjects (56 in the SOC plus brequinar group and 59 in the SOC plus placebo group). All subjects received SOC for treatment of patients with COVID-19 infection. In addition to SOC, the subjects self-administered one capsule of brequinar or placebo once daily for 5 days. Subjects were randomly assigned in a 1:1 ratio to SOC plus brequinar or SOC plus placebo.

The median decrease in viral load was higher in the SOC plus brequinar group beginning at Day 12 (Days 12, 15, 22, and 29). None of the comparisons to placebo reached statistical significance. None of the other efficacy endpoints showed a difference between the SOC plus brequinar compared to the SOC plus placebo treatments. There was no effect in reducing the time to clinical symptom resolution, however the majority of patients had very mild disease making improvements difficult to assess.

Brequinar was safe and well-tolerated in this population. No subjects discontinued study drug treatment or discontinued from the study due to an AE. No subjects died. One subject in the brequinar plus SOC group (1.8%) experienced one non-study-drug-related SAE (admitted to hospital for COVID-19 pneumonia). A total of 23 subjects (52.2%) experienced a total of 28 TEAEs; 10/56 subjects (17.9%) reported 22 TEAEs in the SOC plus brequinar group; 13/59 (22.0%) reported 6 TEAEs in the SOC plus placebo group. AEs were experienced by one subject only with the exceptions of nausea and rash each of which were experienced by two subjects.

The majority of AEs were mild or moderate; there was one subject (1.8%) with a non-related Grade 3 AE in the SOC plus brequinar group (COVID-19 pneumonia) and 3 subjects with Grade 3 AEs in the SOC plus placebo group (chills, pain, injury and breast pain); all of the related AEs were considered Mild (Grade 1) by the investigators. There were no Grade 4 or higher AEs in either treatment group.

A total of 6 subjects had AEs considered possibly related to treatment, 3 in each group.

5.5 Adverse Reactions

Brequinar:

As discussed above, brequinar is an investigational drug that has been given to 71 patients with COVID-19. Adverse events related to brequinar were mild to moderate and infrequent, and no subjects discontinued brequinar treatment due to a related adverse event in either of the two COVID-19 studies.

Brequinar has also been given to more than 800 patients with various forms of cancer in more than 20 clinical trials and has also been tested in patients with psoriasis and those who have had a kidney or liver transplant. The most common side effects in cancer patients when given higher doses of brequinar have been:

- Thrombocytopenia, which may require replacement. Low platelet count can lead to bruising, nose bleeds, vomiting blood, bloody diarrhea, blood in the urine, bloody gums, coughing up blood, and taking longer to stop bleeding from cuts.
- Stomatitis/mucositis.
- Other risks associated with brequinar include:
  - Skin rash,
  - Nausea,
  - Vomiting,
  - Diarrhea,
  - Leukopenia,
  - Anemia,
  - Yellowing of the skin or whites of the eyes caused by high levels of the pigment bilirubin,
  - Abnormal liver tests,
  - Abnormal kidney function,
  - Cardiac complications, and
  - Fatigue

Some of these side effects were severe enough in patients treated with brequinar to require hospitalization or caused death. In most cases, these side effects went away within about 2 weeks after patients stopped taking brequinar.

Patients must be contact to study doctor/study staff if they experience any of the following:

- Discoloration/bruising of the skin or a rash of red/purple spots on your skin. These can be caused by bleeding in or under the skin,
- Nose bleed,
- Coughing up blood,

- Blood in urine,
- Bleeding gums,
- Prolonged bleeding time from needle sticks, abrasions or lacerations,
- Vomiting blood,
- Rectal bleeding,
- Blood in stool,
- Any other unusual bleeding

Dipyridamole:

Dipyridamole will be used in this study as a pyrimidine salvage inhibitor when co-administered with brequinar (see Rationale below). When used per the labeled indications of stroke prevention and inhibitor of blood clot formation, adverse reactions at therapeutic doses are usually minimal and transient. In combination with warfarin, the dipyridamole label reports dizziness (13.6%), abdominal distress (6.1%), headache (2.3%), and rash (2.3%). Reactions from uncontrolled studies include diarrhea, flushing, and pruritus. Angina pectoris has been reported rarely and there have been rare reports of liver dysfunction. In post-marketing reporting experience, there have been rare reports of hypersensitivity reactions (such as rash, urticaria, severe bronchospasm, and angioedema), larynx edema, fatigue, malaise, myalgia, arthritis, nausea, dyspepsia, paresthesia, hepatitis, thrombocytopenia, alopecia, cholelithiasis, hypotension, palpitation, and tachycardia. In the case of real or suspected overdose, symptoms may occur such as warm feeling, flushes, sweating, restlessness, and feeling of weakness and dizziness. There is an increased risk of thrombocytopenia when taking dipyridamole. There are no clinical data to suggest that dipyridamole is beneficial for treating COVID-19.

Co-Administration of Brequinar and Dipyridamole:

This combination has not previously been tested in the clinic. There is a potential for increased bleeding when taking either drug as well as the combination, and the risk compared to brequinar or dipyridamole when administered alone is unknown. To address any potential increased risk, careful attention will be paid to laboratory reports and any increased signs or symptoms of bleeding during this study.

5.6 Rationale

Rationale for the use of brequinar and dipyridamole in COVID-19 disease:

Brequinar is a potent DHODH inhibitor that blocks *de novo* pyrimidine synthesis in the host and has been previously studied in more than 1,000 cancer, psoriasis, and organ transplant patients.

Brequinar has potent *in vitro* antiviral activity against many RNA viruses including SARS-CoV-2. The *in vitro* antiviral activity of brequinar against SARS-CoV-2 is likely due to DHODH inhibition and shows nanomolar potency and a high selectivity index in inhibiting viral replication these studies. Brequinar has also been studied in two clinical trials in patients with confirmed SARS-CoV-2 infection. In these two studies, 25 were hospitalized (15 treated with brequinar) and 115 were non-hospitalized (56 treated with brequinar). Results in these 71 COVID-19 patients demonstrated that brequinar 100 mg x 5 days was safe and well-tolerated in these populations. Brequinar's antiviral activity was demonstrated in the out-patient study as shown by decreased viral load compared to placebo at days 12, 15, 22 and 29 and a shorter duration of viral shedding. The strong

safety data in 71 COVID-19 subjects treated with daily brequinar at 100 mg for 5 days provides strong support for the further investigation of brequinar in the treatment of COVID-19.

The antiviral effects of brequinar may be blunted *in vivo* by pyrimidine salvage. One approach to enhancing the antiviral effect of brequinar is to block the pyrimidine salvage pathway by combining brequinar with a pyrimidine salvage inhibitor. Dipyridamole has been shown *in vitro* to block pyrimidine salvage and may potentiate the antiviral activities of DHODH inhibition on RNA viruses (Liu et al., 2020). Blocking pyrimidine salvage via dipyridamole shows improved *in vitro* antiviral efficacy of *de novo* pyrimidine synthesis inhibition via DHODH inhibition and will be used in this study in combination with brequinar to enhance brequinar's antiviral activity.

Dipyridamole is a well-tolerated, FDA-approved medication that is a nucleoside transport inhibitor and PDE3 inhibitor that inhibits blood clot formation and causes vasodilation. Dipyridamole was first approved by the US FDA in 1961 for prevention of thromboembolism in patients who have had cardiac valve replacement. It has also been widely prescribed in combination with aspirin to prevent stroke. There is no clinical evidence that dipyridamole used alone is effective for treating SARS-CoV-2.

The CCB-CRISIS-04 trial will study subjects who have mild to moderate COVID-19 infection confirmed by a positive SARS-CoV-2 RT-PCR qualitative test / rapid antigen test and have mild/moderate signs and/or symptoms ongoing at study entry. The purpose of this study is to determine if the antiviral activity of brequinar can be improved by combining brequinar with dipyridamole in patients infected with SARS-CoV-2.

5.7 Hypothesis

Treatment with brequinar combined with dipyridamole in patients with SARS-CoV-2 viral infection will reduce viral load, decrease time to resolution of COVID-19-related clinical signs and/or symptoms and improve clinical outcomes compared with current standard care.

6.0 STUDY OBJECTIVE

Primary Objective:

- To characterize the safety and tolerability of the brequinar-dipyridamole combination in COVID-19 subjects as measured by frequencies of grade 3 and 4 toxicities and serious adverse events (SAEs) considered by the investigator to be related to the combination.

Secondary Objectives:

For subjects treated with the brequinar-dipyridamole combination compared to subjects treated with brequinar and to subjects treated with placebo through Day 29, to determine:

- Reduction of qPCR SARS-CoV-2 levels through Day 29 and at days 4, 8, 12, 15, 22, and 29;
- Reduction in time to symptom improvement;
- Reduction in percentage of subjects requiring hospital admission/re-admission as an in-patient for >24 hours;

- Reduction in percentage of subjects requiring medical attended visits, e.g., hospitalization, emergency room visits, Urgent Care/Family Doctor visits;
- Reduction in percentage of subjects requiring supplemental support such as oxygen.

Exploratory Objectives:

- To determine brequinar-dipyridamole combination and brequinar's pharmacokinetic profile in a subset of subjects agreeing to participate in the PK aspect of the study.

7.0 STUDY ENDPOINTS

Primary Endpoints:

- Frequencies of grade 3 and 4 toxicities and serious adverse events (SAEs) considered by the investigator to be related to the combination, brequinar alone or placebo alone.

Secondary Endpoints:

- qPCR SARS-CoV-2 levels through Day 29 and at days 4, 8, 12, 15, 22, and 29;
- Time to symptom improvement through Day 29;
- Percentage of subjects requiring hospital admission/re-admission as an in-patient for >24 hours through Day 29;
- Percentage of subjects requiring medical attended visits, e.g., hospitalization, emergency room visits, Urgent Care/Family Doctor visits through Day 29;
- Percentage of subjects requiring supplemental support such as oxygen through Day 29.

Exploratory Endpoints (PK):

- Analysis of brequinar's pharmacokinetic profile in a subset of patients that have received brequinar as a part of therapy and have consented to provide PK samples.

Clinical improvement will be defined as a 2-point or greater improvement on an 8-point WHO ordinal scale in every subject measured on each designated day, from the date of randomization through day 29. This scale has been used in the current COVID-19 outbreak.

Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitaion of activities	1
	Limitation of activities	2
Hospitalized	Hospitalized, no oxygen therapy	3

Mild disease	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

8.0 SELECTION AND WITHDRAWAL OF PATIENTS

Subjects will be selected on the basis of the following inclusion and exclusion criteria.

8.1 Inclusion Criteria

Subjects will be eligible if they meet all of the following 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. Subjects between ≥18 and ≤65 years of age.
3. Subjects found positive for SARS-CoV-2 either by rapid antigen test or by reverse transcription polymerase chain reaction (RT-PCR) using ICMR-validated kit.
   Note: Test need not be repeated in those with possession of confirmed positive report but positive result test date must be ≤5 days of first dose of study drug.
4. Mild or Moderate COVID-19 as per latest updated version of CLINICAL MANAGEMENT PROTOCOL for COVID-19 (in Adults) released by Government of India Ministry of Health and Family Welfare Directorate General of Health Services (EMR Division).
5. The effects of brequinar on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men and women treated or enrolled on this protocol must also agree to use adequate contraception for the duration of study participation, and for 90 days after completion of brequinar administration.
6. Male subjects must agree to refrain from sperm donation and female subjects must agree to refrain from ovum donation from initial study drug administration until 90 days after the last dose of brequinar.
7. At least one non-respiratory COVID-19 symptom characterized as moderate to severe by the Investigator including but not limited to fatigue, chills, fever, body aches, nasal congestion, nausea, vomiting, or other sign or symptom commonly associated with COVID-19 in the opinion of the investigator. Symptom onset must be ≤5 days prior to first dose. Subject must have one or more signs/symptoms present at first dose.
8. Willing to participate in the PK subset if at one of the identified sites.
9. Able to swallow capsules.

8.2 Exclusion Criteria

Subjects will not be eligible for this study if any of the following in present at the time of study inclusion:

1. Have an oxygen saturation of <90% while breathing ambient air.
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 subject.
3. Nursing women or women of childbearing potential (WOCBP) with a positive pregnancy test.
4. Treatment with another DHODH inhibitor (e.g., leflunomide, teriflunomide) or other agents known to cause bone marrow suppression leading to thrombocytopenia.
5. Ongoing treatment with aspirin and or dipyridamole, famotidine or cimetidine. Remdesivir and ivermectin are prohibited through Study Day 8. Steroids are permitted per the guidelines.
6. Platelets ≤125,000 cell/mm^3.
7. Hemoglobin <10 gm/dL.
8. Absolute neutrophil count <1000 cells/mm^3.
9. Renal dysfunction, i.e., creatinine clearance <30 mL/min.
10. AST or ALT >3 x ULN, or total bilirubin >ULN. Gilbert's Syndrome is allowed.
11. Bleeding disorders or blood loss requiring transfusion in the six weeks preceding enrollment.
12. Ongoing gastrointestinal ulcer, or gastrointestinal bleeding within 6 weeks of first dose.
13. HIV, Chronic hepatitis B infection, active hepatitis C infection, active liver disease and/or cirrhosis per subject report.
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).

8.3 Withdrawal Criteria

Subjects may voluntarily withdraw from the study at any time without assigning any reason thereof by withdrawing their consent. They may be considered withdrawn if they state an intention to withdraw, or fail to return for visits, or become lost to follow up for any other reason.

If premature withdrawal occurs for any reason, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information in the CRF. For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, other means of communication even though patient is unwilling to attend further visits etc.

If study participation is discontinued, the final evaluation will be performed as completely as possible. Any comments (spontaneous or elicited) or complaints made by the patient and the reason for termination, date of stopping the study medication and the total amount of study medication must be recorded in the source documents or CRFs.

Criteria for a withdrawal of patients from clinical study:

The subject may be withdrawn from the trial at the discretion of the investigator or the sponsor, if judged non-compliant with trial procedures or due to safety concern.

A subject must in addition be withdrawn from treatment with IMP if the following applies:

- AE requiring permanent discontinuation of study drug.
- The subject suffers from significant intercurrent illness or undergoes surgery requiring study discontinuation during the course of the study.
- Any subject who requires the use of an unacceptable concomitant medicine.
- If the Investigator believes it is not in the subject's best interest to continue.
- The subject wishes to withdraw his/her consent.
- Any other justifiable reason, which should be adequately documented.
- Any subject whose condition worsens, requiring treatment with immunomodulators including but not limited to tocilizumab and / or antiviral drugs including but not limited to remdesivir as per the best judgement of the Investigator.
- Non-compliance: The participant may be withdrawn from the trial at the discretion of the Investigator if it is judged that participant is non-compliant to study assessment and schedule leading to safety concerns.
- Positive pregnancy test: A female participant with a positive pregnancy test will be withdrawn from the trial.

The sponsor or its representative may be contacted for clarification as required on a case-by case basis.

Handling of Withdrawals:

In the case of premature discontinuation of study subject, the investigator should schedule a study discontinuation visit to complete all assessment according to End of Study / Early Termination visit requirements. All reasons for ending participation must be recorded in the source documents or in the CRF.

If the subject discontinues because of an adverse event (serious or non-serious), the investigator must follow up patient's recovery until resolution or stabilization of AEs or up to 30 days after administration of last dose of IMP, whichever is earlier.

This visit should be documented in the appropriate section of the Case Report Form (CRF). The investigator will record the reason for study discontinuation, provide or arrange for appropriate follow-up for such subjects, and document the course of the subject's condition. In addition, the investigator will report the subject's withdrawal to the responsible study monitor immediately.

Subjects withdrawn from investigational product treatment will be treated as routine subjects. The investigator will discuss the appropriate therapy with each subject who withdraws early from this study. Determination of the appropriate follow-on therapy will be left to the discretion of the investigator and investigator could treat such subjects as per his/her routine practice.

9.0 STUDY PROCEDURE

9.1 Study Design

The first part of the study will be a phase II, randomized, assessor-blind, multicenter, multi-dose, placebo-controlled study in approximately 64 subjects with mild to moderate COVID-19 infection confirmed by a positive SARS-CoV-2 RT-PCR qualitative test /rapid antigen test and who have at least mild to moderate signs and/or symptoms ongoing at study entry.

Approximately 32 subjects (50% of subjects per arm per cohort) at selected sites will be invited to participate in the "PK" arm of the study until approximately 8 subjects in each cohort have been recruited after providing written informed consent for the same. PK includes brequinar and dipyridamole plasma concentrations.

If a particular cohort meets study stopping criteria (as defined in section "Stopping Criteria") or is found to be unsafe by DSMB members, then the study will not proceed with enrollment of subsequent cohorts.

An expansion cohort of approximately 48 subjects will be added to the cohort with the highest brequinar dose that meets safety criteria.

Safety data of cohort 1 to cohort 4 (or highest dose cohort evaluated) will be submitted to the regulators and their approval will be obtained prior to commencing recruitment in the expansion cohort.

All subjects will receive SOC as per relevant guidelines for treatment of patients with mild to moderate COVID-19 infection.

Subjects will be randomized to one of the following cohorts in Part 1:

Cohort 1:

- Arm 1: 5 days of standard of care (SOC) + brequinar 50 mg OD + dipyridamole 75 mg TID (N = 8)
- Arm 2: 5 days of SOC + brequinar 50 mg OD (N = 4).
- Arm 3: 5 days of SOC + brequinar placebo 50 mg OD (N = 4).

Cohort 2:

If the 50 mg brequinar OD + dipyridamole 75 mg TID meets safety criteria as pre-defined in the protocol the brequinar dose will be escalated to 100 mg.

- Arm 1: 5 days of standard of care (SOC) + brequinar 100 mg OD + dipyridamole 75 mg TID (N = 8)
- Arm 2: 5 days of SOC + brequinar 100 mg OD (N = 4).
- Arm 3: 5 days of SOC + brequinar placebo 100 mg OD (N = 4).

Cohort 3:

If the 100 mg brequinar OD + dipyridamole 75 mg TID meets safety criteria as pre-defined in the protocol the brequinar dose will be escalated to 150 mg:

- Arm 1: 5 days of standard of care (SOC) + brequinar 150 mg (100 mg + 50 mg) OD + dipyridamole 75 mg TID (N = 8)
- Arm 2: 5 days of SOC + brequinar 150 mg (100 mg + 50 mg) OD (N = 4)
- Arm 3: 5 days of SOC + brequinar placebo 150 mg (100 mg + 50 mg) OD (N = 4).

Cohort 4:

If the 150 mg brequinar OD + dipyridamole 75 mg TID meets safety criteria as pre-defined in the protocol the brequinar dose will be escalated to 200 mg:

- Arm 1: 5 days of standard of care (SOC) + brequinar 200 mg (100 mg +100 mg) OD + dipyridamole 75 mg TID (N = 8)
- Arm 2: 5 days of SOC + brequinar 200 mg (100 mg +100 mg) OD (N = 4)
- Arm 3: 5 days of SOC + brequinar placebo (100 mg + 100 mg) OD (N = 4).

Expansion Cohort:

Approximately forty-eight (48) subjects will be added to the cohort with the highest brequinar dose that meets safety criteria in a 2 : 1 ratio of active treatment (approximately 32 in SOC + brequinar + dipyridamole treated and 16 in SOC + brequinar monotherapy group). Additional sites may be added if required to meet enrollment of the expansion cohort in an efficient manner.

9.2 Study Procedure

To be eligible for screening, subjects must have a documented positive SARS-CoV-2 test result within 5 days of first dose of study drug and have at least one ongoing symptom consistent with SARS-CoV-2 infection rated as at least mild to moderate in the opinion of the investigator. The subject's earliest symptom must have an onset date within 5 days of first dose of study drug.

Subjects will undergo screening (day -4 to 0) for confirming eligibility for participation in the study. Study Day 1 includes randomization visit.

Subjects will be randomized to a cohort as described above.

Screening activities as well as randomization can take place on the same day as a combined Screening/Day 1 visit, if the site team is able to obtain Screening lab results on the same day. Otherwise, Day 1 is to take place as soon as Screening lab results are available.

Study Day 1 and first dose of study drug must take place ≤5 days from onset of first symptom.

Subjects may be hospitalized as many as 9 days in the study (day 0 to 8) or more for the PK sample as per Investigator discretion.

For subjects participating in the PK subset,

Blood samples for estimating brequinar concentrations will be drawn (PK):

- Day 1: Pre-dose (within 1 hour prior to study drug administration) and post dose at 1h, 2h, 4h, and 8h; note that the 8h sample is to be obtained prior to the next dose of dipyridamole;
- Days 2 – 5 pre-dose and Day 8.

Aliquots of the NP/OP swab samples are to be stored at the testing laboratory for possible additional virological testing.

Screening visit and study visits on Days 1, 8, 15, 22 and 29 will be either in person or a combination of in-person and virtual visit (telemedicine or other remote technique) or by visit to patient's home by site team.

Study visits on Day 4 and 12 may be virtual visits (telemedicine or other remote technique) or in person.

On Days 2, 3, 5, 6 and 7, the site will have a telephone call / or in-person communication with the subject for changes in concomitant medications and assessment of adverse events (same will also be captured by the subject using a patient diary card or these visits will be conducted in person).

Note:

- Study procedures are presented in detail in the Schedule of Events.
- Days 1, 8, 15 and 29 require sample collection for performing laboratory tests and will be conducted at the site or via home visit.
- Any in-person visit may also have telemedicine or telephone components if all study activities cannot be completed in person.
- The visits that include bloodwork must be conducted at the study site or arrangements made for sample collection at the subject's home or other appropriate location.
- Site staff (in case of an in-person visit) or subjects (in case of a remote visit) will assess respiratory rate, heart rate, body temperature and SpO_2 (a thermometer and pulse oximeter are to be provided to subjects who are home quarantined, leave the hospital or are unable to return for study visits).
- Subjects will record details of concomitant medications, adverse events in the patient diary card (PDC).
- Subjects will complete a symptom assessment form on designated days daily during the study period (days 1 – 8, 12, 15, 22, and 29).
- In case the subject is hospitalized during the course of study, the activities specified in scheduled visits / time points will be carried out within the hospital facility.
- Study completion or the reason for study discontinuation will be recorded in the source document and the eCRF.

DSMB Meeting:

A Data Safety Monitoring Board (DSMB) will meet to review the safety and scientific conduct of the study. At a minimum, the DSMB will review the protocol and study design prior to study start, after the end of the first part of the study prior to the expansion phase, and at the end of the study.

At each interim meeting the DSMB members will determine whether to stop the study, amend the protocol, or continue the study per protocol. The study enrollment will not be suspended for routine DSMB meetings.

The DSMB will be convened and enrollment suspended if Cohort-Level Stopping Criteria are met. The DSMB may allow the enrollment to resume following their review if safety criteria are met.

9.3 Hospitalization

Subjects may be hospitalized for approximately 9 days (day 0 to 8) in the study as per Investigator discretion for the PK blood sample draws. Subjects may leave after this period (if medically discharged) after the Day 8 blood work has been drawn. Extended stays beyond study Day 8 are permitted if the facility is a dedicated COVID-19 unit or other relevant hospital type or if per the Investigator the extended stay facilitates study procedures; this continuation will not be considered as an SAE. However, prolongation of hospitalization due to increase in disease severity or any other safety concerns related to the subjects will be considered as an SAE.

Hospitalization for the purpose of PK sample collection may be done at Investigator's discretion, in this case hospitalization may be for selected few days and may not be for entire 8 days duration. Appropriate documentation of the same will be done in source file.

9.4 Unscheduled Visits and Early Discontinuation Visit

An Unscheduled Visit is allowed at any time, for any reason, if in the Investigator's opinion it is warranted. If the Unscheduled Visit is due to an AE, the Investigator will determine whether additional visits are needed.

If a subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit and all procedures scheduled for End of Study visit will be performed.

If the Unscheduled Visit is not an Early Discontinuation Visit (i.e., the subject will continue to take part in the study), then the reason for unscheduled visit is documented and required procedures at the discretion of investigator considering the reason for visit will be performed.

If the Investigator determines that the subject's condition has worsened to the degree that it is unsafe for the subject to continue in the study, the subject may be discontinued from the study as treatment failure and a standard of care treatment may be advised at the Investigator's discretion.

In case of ongoing AEs, telephonic safety follow up will be continued until resolution or stabilization of AEs or up to 30 days after administration of last dose of IMP, whichever is earlier.

9.5 Sample Collection Procedure

Blood collection for PK analysis:

PK blood samples will be collected through an indwelling intravenous cannula (Venflon or similar) placed in the forearm vein of the subjects for up to 24 hours or may also be collected through a fresh vein puncture at each time point. A 10 mL of blood per sample will be obtained using syringe/adaptor and transferred in to pre-

labelled vacutainers containing K_2EDTA as anticoagulant. Filled vacutainers will be placed on wet ice bath (below 10 ^{0}C) during sample collection activity and until storage of plasma.

Time of collection of each blood sample (as displayed in the calibrated digital clock) will be recorded in 24-hour clock format (hh:mm) on the PK blood sample collection log and same will be transcribed to eCRFs.

If an intravenous indwelling cannula is placed, maintain this as long as possible by injecting 0.5 mL of 5 IU/mL of heparin in normal saline solution or per hospital's usual practice to maintain the cannula patentcy. When sampling through the cannula, collect study blood samples after discarding the first 0.5 mL of heparinised blood from the cannula. If insertion of cannula is not possible, alternatively blood samples may be drawn by a fresh venipuncture or in case of blockade in an existing cannula, extra heparinised saline will be injected to stimulate the cannula and later blood samples will be collected after discarding the heparinised blood or central line. If the time window does not allow, it is recommended to directly use a disposable syringe for extraction, and appropriately dispose of the retained needle after blood collection.

The blood samples will be withdrawn using syringe or adaptor and transferred into pre-chilled (maintained at temperature below 10 °C), pre-labelled (mentioning Site number, Protocol number, Subject number, Period number, Sampling time point and Sample ID) sample collection tubes containing K_2EDTA as an anticoagulant kept on wet ice bath (below 10 ^{0}C) until centrifugation. Immediately following blood collection, the vacutainers are to be gently inverted 5 - 7 times to mix the anticoagulant.

It is recommended that collected blood samples be placed on wet ice bath (below 10 ^{0}C) from the point of collection until storage of plasma.

NP/OP Sample Collection for qPCR

The Laboratory Manual will provide details regarding collection, processing, storage and shipment for qPCR samples.

9.6 Sample Size

No statistical powering has been performed for this study. The number of subjects is designed to provide information on the safety, tolerability, and efficacy of the IMP tested in this study. In Part 1, approximately 64 subjects will be randomized to up to 4 cohorts of 5 consecutive days of one of the following regimens in addition to SOC in 2:1:1 ratio as shown below:

Treatment Arm[a]	Day 1	Day 2	Day 3	Day 4	Day 5
Brequinar + Dipyridamole (N=8)	BRQ XX mg OD DPY 75 mg TID	BRQ XX mg OD DPY 75 mg TID	BRQ XX mg OD DPY 75 mg TID	BRQ XX mg OD DPY 75 mg TID	BRQ XX mg OD DPY 75 mg TID
Brequinar (N=4)	BRQ XX mg OD	BRQ XX mg OD	BRQ XX mg OD	BRQ XX mg OD	BRQ XX mg OD
Placebo (N=4)	PBO XX mg OD	PBO XX mg OD	PBO XX mg OD	PBO XX mg OD	PBO XX mg OD

[a]All subjects will also received standard of care (SOC).

The brequinar dose will start at 50 mg and may be escalated to 100 mg, 150 mg, and 200 mg if safety criteria are met for each cohort (see Safety Criteria below).

The hospital pharmacist is to be unblinded. Bulk supplies of investigational medicinal product (IMP) of brequinar 50 mg, brequinar 100 mg, dipyridamole 75 mg, brequinar placebo 50 mg and brequinar placebo 100 mg will be supplied to the unblinded hospital pharmacist.

The unblinded hospital pharmacist is to prepare the assigned IMP for each individual subject at that institution and create an appropriately labeled bottle/zip lock bag of study medication sufficient for a 5-day treatment course. The randomization assignment will be provided via an IWRS.

Alternatively, the hospital pharmacist and study team may decide to distribute IMP on a daily basis for 5 days for brequinar and dipyridamole while the subject is hospitalized, depending on the most convenient method.

9.7 Patient identification and Randomisation

Randomization will be carried out using SAS® (SAS Institute Inc., USA) version 9.4 or higher. Randomization will be done in blocks using PROC PLAN such that the design is unstructured. The treatment allocation will be determined according to the randomization schedule and randomization schedule will be done per cohort.

Screening and Randomization Numbering

Each subject will be assigned a unique number that will serve to identify laboratory specimens and all documents, and if randomized throughout the study. If a subject fails to qualify for allocation to the study i.e. is a screen failure, the subject's unique number will not be used for another subject.

Screening number will be a combination of center number, project number and subject number. The center number will be assigned by Veeda to the investigative site (e.g. A, B, C, D) and subsequent sites are assigned consecutive alphabet numbers. Upon signing the informed consent form, the subject will be assigned a screening number by the Investigator. At each site the first subject consented is assigned screening number e.g. A-21-0372-001, and subsequent subjects are assigned consecutive numbers (e.g., the second subject consented is assigned screening number A-21-0372-002, the third subject is assigned screening number A-21-0372-003). Once a screening number is assigned to a subject, that number will not be reused.

If the subject is deemed eligible for enrollment into the study and will commence dosing, then a randomization number will be assigned via IWRS as defined in the randomization plan. Subjects will be randomized with the next qualifying subject given the next available randomization number.

A source document maintained at the site will link the screening number to the randomization assignment number (once assigned) and the same will be reflected in screening and enrollment log of Investigator site file.

The assigned subject number will be recorded in the CRF of the subject.

The personnel involved in dispensing of study drug and verification of dispensed study drugs will be accountable for ensuring compliance to randomization schedule.

9.8 Blinding

Instructions provided in this section are a general description of operational procedures. Investigators are instructed to always refer to latest version of respective study plans/manuals for detailed and latest information.

The intent of blinding is to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of the clinical study. The essential aim of blinding, therefore, is to prevent identification of the treatments by the Investigator and others associated with the conduct of the study until all such opportunities for bias have passed.

Due to unavailability of a matching dipyridamole placebo, subjects in the brequinar-dipyridamole treatment arm will have a daily dose of one brequinar capsule of appropriate strength and three 75 mg dipyridamole tablets whereas subjects in the SOC + brequinar only arm will receive only brequinar capsule(s) daily at the appropriate strength. Subjects in the SOC + brequnar placebo arm will receive only brequinar placebo capsule(s) daily at the appropriate strength. No dipyridamole placebo tablets will be provided to the subjects assigned to the brequinar only or brequninar placebo treatment arms.

The Sponsor will provide investigational medicinal product (IMP) bulk drug supplies to the ThermoFisher depot. ThermoFisher will supply each site with bulk supplies of brequinar 50 mg and 100 mg capsules (50 count bottles) and dipyridamole (100 count bottles). An unblinded independent site staff member (e.g., hospital pharmacist) will dispense the IMP for each subject according to the assigned cohort and randomization schedule, and perform IMP accountability by collecting used and unused products. The unblinded pharmacist will not participate in the clinical trial assessments in order to minimize potential bias, and will be instructed not to discuss the IMP with assessors and other blinded study personnel.

The unblinded pharmacist should use an opaque bottle or envelope to ensure that the blinded study team is not able to see the IMP. The subjects will be instructed not to reveal the contents of the bottle(s)/envelope(s) to the blinded investigator or study staff.

The blinded investigational staff performing the assessments and data analysts (with the exception of the biostatistician who will undertake the generation of the randomisation scheme) will remain blinded to the identity of the treatment assignments for individual subjects from the time of randomization until database lock, using the following methods:

- Randomization data will be kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study.
- Only the unblinded pharmacist or designate will be involved in dispensing, administering and collecting the study medication.
- Unblinding of blinded study personnel will be permitted only in the case of patient in emergency condition and at the conclusion of the study.

Data that may potentially unblind the intervention assignment (i.e., study intervention preparation/accountability data, intervention allocation or other specific laboratory data) will be handled with special care to ensure that the integrity of the blinding is maintained and the potential for bias is minimized.

Site specific randomization schedule, drug dispensing logs, drug accountability forms and other papers identifying treatment allocation are kept in a separate binder in a locked cupboard to which the investigators does not have access. Trial staff is provided training in the importance of maintaining blinding, and trial medication delegates/trial coordinators are also helped to set up systems at the clinic.

Every effort must be made to limit the number of unblinded study personnel to ensure the integrity of this study.

In the event of a Quality Assurance audit after the study has been unblinded, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

9.8.1 Unblinding of treatment assignment

If necessary, the Investigator may be required to unblind a participant if an adverse event (AE) meets criteria in order to fulfill expedited regulatory reporting requirements. In this event, Investigator will inform the same to sponsor or its designee/study medical monitor if possible to discuss the particular situation, before breaking the blinding unless this could delay emergency treatment of the participant. Telephone contact with the medical monitor will be available 24 hours per day, 7 days per week. The Sponsor/CRO PV and/or safety review team will access the AE report and conclude whether unblinding is required. Once Sponsor/CRO PV and/or safety review team conclude that study participant requires the unblinding, Investigator will ask unblinded study personnel to provide the treatment sequence.

Investigators are instructed to always refer to latest version of respective unblinding procedure manuals for detailed and latest information.

9.8.2 Emergency unblinding of treatment assignment

Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. While the responsibility to break the intervention code in emergency situations resides solely with the evaluating investigator, it is recommended that the investigator contact the sponsor or its designee/study medical monitor if possible to discuss the particular situation, before breaking the blinding unless this could delay emergency treatment of the participant. Telephone contact with the medical monitor will be available 24 hours per day, 7 days per week. If a participant's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind.

The investigator will inform the participant how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number, study drug name if available, participant number, and instructions for contacting the sponsor (or any entity to which it has delegated responsibility for emergency

code breaks) to the participant in case emergency unblinding is required at a time when the investigator and backup are unavailable.

An assessment will be done by the appropriate site personnel and the Study Lead after an emergency unblinding to assess whether or not study drug should be discontinued for a given participant.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed.

9.9 Study Duration

Study duration will be approximately 34 days including a maximum screening period of 5 days.

9.10Treatment

All subjects will receive standard of care (SOC) including treatment for COVID-19 signs and/or symptoms as required. Study encounters may be conducted remotely or at the study site depending on visit requirements, site facilities and subject and study team preferences.

9.11Clinical Safety Measures

It is the responsibility of the investigator to ensure that adequate medical supervision and care is available for the study subjects during the study to ensure their utmost safety and well being.

- Demography (subject reported / measured height and weight, age, sex and race/ethnicity): At screening
- Medical history (relevant within 30 days or ongoing) / History of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection): At screening
- Physical Examination (subject self-reported / examiner evaluated): At screening
- Vital signs (body temperature, respiratory rate, heart rate, SpO_2) assessment: At screening, Day 4 (±8 hrs), Day 8 (±8 hrs), Day 12 (± 1 day), Day 15 (±1 day), Day 22 (±1 day), End of study [EoS; Day 29 (±2 day)].

  Note: If subject is hospitalized, Vital signs assessment will be done on daily basis by site team during hospitalization through Day 8 then following the Vital signs visits as listed above.
- Hematology, biochemistry and urine analysis: At screening, Day 1 unless same day as Screening visit, Day 8 (±8 hrs), Day 15 (±1 day), End of study [EoS; Day 29 (±2 day)].
- HCV, HbSAg, HIV Test: At screening
- Serum pregnancy test (Women of child bearing potential (WOCBP)): At screening.
- Urine pregnancy test (WOCBP): End of study [EoS; Day 29 (±2 day)].

  Note: WOCBP: A premenopausal female capable of becoming pregnant
- Rapid antigen test / SARS-CoV-2 RT-PCR Qualitative (in a clinically relevant specimen (Naso-Oro-

Pharyngeal as appropriate)): Screening

Note: Test need not be repeated in those with possession of confirmed positive report. Date of positive report must be ≤5 days prior to randomization.

- RT-PCR Quantitative Viral (in a clinically relevant specimen (Naso-Oro-Pharyngeal as appropriate)): Day 1 (Prior to dosing), Day 4 (±8 hrs), Day 8 (±8 hrs), Day 12 (±1 day), Day 15 (±1 day), Day 22 (±1 day) and End of study [EoS; Day 29 (±2 day)]
- Ordinal Scale Assessment: Screening, Day 8 (±8 hrs), Day 15 (±1 day), Day 22 (±1 day) and End of study [EoS; Day 29 (±2 day)]
- Adverse events/ Serious Adverse Events: Adverse events/ Serious Adverse Events will be recorded from the time of first study drug administration till end of study safety assessments. Other medical events not related to disease condition under study and occurring before IMP administration, but after signing the informed consent form will be recorded on the medical history/current medical conditions of case report form.
- In addition to protocol-specific laboratory tests and/or clinical examinations at scheduled time points, additional tests/clinical examination may be conducted to evaluate subject safety at any time during the study, at the discretion of the Investigator (can be done in local laboratory or nearby clinic/hospital/institution).
- Medication taken prior to first dosing: All prescription medications and over-the-counter drugs (including vitamins) taken within 30 days prior to screening must be recorded in the eCRF as Medication history.
- Concomitant medications: Medications taken from time of signing of Informed Consent form until study completion (i.e. End of study) will be captured as concomitant medications.
- Prohibited medications: Any other antiviral medications or medication with antiviral potential.

Note:

- It is recommended that general precautions need to be taken by the staff caring for COVID patients during the trial.
- In case the subject is hospitalized during the course of study, the activities specified in scheduled visits / time points will be carried out within the hospital facility.

9.12Discontinuation/ Termination of Study

Investigator reserves the right to discontinue the study for safety reasons at any time. Ethics Committee (EC) and/or Regulatory Authority may ask to terminate the study, if there are major violations of ethical considerations or due to any serious adverse event(s). Reasons for termination of study will be provided to subjects. In case sponsor/PI decides to terminate the study, reason for the same will be notified to Central Licensing Authority within thirty working days of such termination and/or notified to EC as applicable.

Note: In case of IMP termination, ongoing subjects will continue with standard treatment based on PI's discretion.

Discontinuation of the trial at one particular centre:

The sponsor may stop this trial at one particular centre for any of the following reasons or more:

- Serious and/or persistent non-compliance with the protocol
- False documentation in the source
- Inadequate co-operation with the sponsor, or its representatives
- Non-compliance with GCP and/or regulatory requirements
- The investigator requests discontinuation.

10.0 STUDY TREATMENT

10.1 Investigational Medicinal Product and Combination Product Dosage

1. Brequinar 50 mg capsules (used for the 50 mg and 150 mg doses)
2. Brequinar 100 mg capsules (used for the 100 mg, 150 mg and 200 mg doses)
3. Dipyridamole 75 mg tablets
4. Brequinar Placebo 50 mg and 100 mg capsules

Note:

- The subjects will take the study medication as directed on study days 1 – 5.
- Treatment assignment will be randomized, assessor-blind.
- IMP dispensing will be performed by an unblinded pharmacist.
- Study assessments will be performed by blinded Investigator or other designed blinded site personnel.
- Brequinar and brequinar placebo doses will be administered once daily.
- Dipyridamole doses will be given thrice daily.
- The 150 mg brequinar or brequinar placebo dose will be given as 1 capsule of 100 mg and 1 capsule of 50 mg; the 200 mg brequinar or brequinar placebo dose will be given as 2 capsules of brequinar or placebo 100 mg.

10.1.1 Assessment of Compliance

Compliance for dosing at home will be captured using a patient diary card.

10.2 Procurement, Storage and Accountability Procedures for Investigational Products

10.2.1 Receipt and storage of investigational products

Adequate supplies of investigational medicinal products for dosing will be distributed to the sites in bulk from the chosen depot. Investigational medicinal products will be stored per the storage condition supplied by sponsor. Certificates of analysis (COA) containing required product information will be received from sponsor.

The hospital pharmacist will receive bulk supplies of IMP (brequinar 50 mg, brequinar 100 mg, dipyridamole 75 mg and brequinar placebo 50 mg and 100 mg) and will be unblinded to treatment. For each individual subject, the hospital pharmacist will use the IWRS to assign the randomization subject numbers. Hospital pharmacist will create an opaque, labeled zip lock bag or bottle for IMPs as assigned for individual subjects either per day or for all 5 days in the requisite packaging.

10.2.2 Accountability of investigational products

Sites will maintain accountability of IMPs received, stored, administered and returned to CRO/ destroyed at site. Only subjects enrolled in the study should be administered IMP per this protocol. Investigator/ designee supervising the dosing will be responsible for compliance to randomization schedule at site. Overall responsibility of IMP accountability at the site lies with the Investigator.

10.2.3 Handling of Unused Investigational products

Unused IMPs will be returned to the CRO or destroyed locally (per IMP plan).

10.2.4 Maintenance of Dispensing Record

A copy of site-specific dispensing record will be maintained in the Site Investigator File as well as in Central Investigator File.

10.2.5 Concomitant medication

Any allowable concomitant medication being taken by the subject should be continued on same dose during the study. Any change in the dose needs to be documented and subjects can continue in the study if the investigator deems proper. Administration of the following medications is not permitted after screening until after the end of each subject's study participation.

Prohibited Medications:

The following concomitant medications, products or procedures will not be allowed while enrolled in the study:

- Hydroxychloroquine
- Ivermectin
- Immunomodulators such as tocilizumab
- Antiviral drugs or drugs with antiviral potential including but not limited to remdesivir

The use of any of the above mentioned medications/procedure will result in withdrawal of the subject from the study.

Note: This list of drug is not exhaustive. However, any drug which is not mentioned above and having a possible on study drug *efficacy and safety, should be confirmed with Medical Monitor/Medical Expert.*

Permissible Medications: Other than those prohibited.

Standard treatment [(Standard Of Care (SOC)] provided in all the arms will be per the latest updated version of CLINICAL MANAGEMENT PROTOCOL for COVID-19 (in adults) released by Government of India Ministry of Health and Family Welfare Directorate General of Health Services (EMR Division).

If drug therapy other than that specified in the protocol is required prior to or during the study period, decisions shall be taken by the investigator to continue or discontinue the subject based on the following:

- The pharmacology and pharmacokinetic of the non-study medication.
- The likelihood of a drug–drug interaction.
- The time and duration of administration of the non-study medicine.

The start and stop date of concomitant medication use during the study should be recorded in source data. All such instances will be recorded and reported in the final report with details of start date, stop date and reason for medication use.

11.0 EFFICACY ASSESSMENT

Efficacy will primarily be assessed by reduction in SARS-CoV-2 RNA levels as measured by the quantitative RTPCR test for SARS COV2 in brequinar-dipyridamole treated subjects compared to brequinar-only and placebo-treated subjects through Day 29.

Symptom improvement will be defined in the SAP. Clinical improvement for the ordinal scale will be defined as defined as a 2-point or greater improvement on an 8-point WHO ordinal scale in every subject measured on each designated day (i.e Screening, Days 1, 4, 8, 12, 15, 22, 29), until Day 29 from the date of randomization. This scale has been used in the current COVID-19 outbreak.

Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitaion of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4

Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

12.0 SAFETY ASSESSMENT

The study will include the following evaluations of safety and tolerability according to the time points provided in the 3.2 Schedule of Activities.

12.1 Demographic Characteristics

Demographic data (subject reported / measured height and weight, age, sex and race/ethnicity) will be captured as specified in the 3.2 Schedule of Activities.

12.2 Medical and Medication History

The Investigator or his/her designee will obtain a detailed medical history and medication history as specified in the 3.2 Schedule of Activities.

Medical history includes clinically significant diseases within 30 days or ongoing and history of current illness (date of symptom onset or change in baseline co-morbidity thought to be due to COVID-19 infection).

Information on all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 30 days prior to baseline visit will be recorded on the CRF.

Concomitant medications administered from screening to randomization will be recorded as a medication history on the CRF.

12.3 Physical Examination

This evaluation will include an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system evaluation. Information about the physical examination must be present in the source documentation at the study site. If any abnormalities are noted during the study, the participant may be referred to another doctor. The investigator should use his or her clinical judgment for appropriate treatment and/or medical referral.

Clinically significant findings/abnormalities prior to the signing of ICF must be included in the relevant medical history/current medical conditions section of the CRF. Significant findings after the start of the IMPs that meet the definition of an AE must be recorded in the Adverse Event section of the CRF. Physical examination should

be done at specified in the 3.2 Schedule of Activities. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event CRF.

12.4 Vital Signs

Vital signs will include measurements of body temperature, respiratory rate, heart rate and SpO_2 taken with the participant in a seated position after resting for 5 minutes. Vital signs will be measured at specified in the 3.2 Schedule of Activities. If the subject needs to be assessed remotely due to COVID-19 restrictions or for other reasons, the subject is to be provided with a pulse oximeter and digital thermometer.

12.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia)
- Is clinically significant in the investigator's judgment
- Requires a change in concomitant therapy (i.e. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event CRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event CRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

12.6 Clinical Safety Laboratory Assessments

Clinical laboratory tests will be performed at specified in the 3.2 Schedule of Activities. (Refer to section 26.0: for the list of clinical laboratory tests).

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during the study or within 30 days after the last dose of study intervention should be documented as AE. The abnormal test should be repeated until the values return to normal or baseline or are no longer considered clinically significant.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

12.7 Other safety evaluations as appropriate and as indicated in the schedule of activities

- Pregnancy test (Serum and Urine): At specified in the 3.2 Schedule of Activities.

12.8 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia)
- Is clinically significant in the investigator's judgment
- Requiring a change in concomitant therapy (i.e. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

It is the responsibility of the investigator to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the adverse event CRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the adverse event CRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium").

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the adverse event CRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

For each laboratory abnormality reported as an AE, the following laboratory values should be reported in the laboratory section of the CRF: the value indicative of the onset of each toxicity grade; the most abnormal value observed during the AE, and the value supporting recovery to Grade ≤1 or to baseline values. The CTCAE version 5 scale will be used to grade AEs including laboratory AEs.

12.9 Handling and Reporting of Adverse Events

An adverse event is any untoward medical occurrence (including a symptom or disease or an abnormal laboratory finding) during treatment with an investigational drug or a pharmaceutical product in a subject that does not necessarily have a relationship with the treatment being given.

*Abnormalities based on laboratory parameters, vital signs, and 12-Lead ECG will be called AE, if they are associated with at least one of the following:

- Interruption or stoppage of the study medication
- Associated with signs or symptoms
- Requiring treatment
- Considered clinically significant by the investigator

Safety Criteria:

An independent, unblinded study physician (from CRO) will assess each cohort for safety. A cohort will be declared safe are as soon as all results are available for the Day 15 visit if the following conditions are met:

- No toxic deaths (deaths judged by the investigator to be related to either study drug);
- Not more than 1 toxic SAE (SAEs judged by the investigator to be related to either study drug);
- No Grade 3 or higher toxicities (including laboratory AEs as per CTCAE version 5.0 or higher) (AEs judged by the investigator to be related to either study drug);
- <4 subjects with any grade toxicity (AEs judged by the investigator to be related to either study drug).

In addition to the cohort-level safety, the independent study physician (from CRO) will determine if any subjects meet Individual Stopping Criteria:

- Subjects who develop a Grade 3 toxicity that is assessed by the investigator to be related to the study drug are to be permanently discontinued from study treatment but will continue in the study for safety assessments.
- Subjects who develop a Grade 4 toxicity, regardless of relatedness to study drug, are to be permanently discontinued from study treatment but will continue in the study for safety assessments.

In addition to the individual subject-level safety, the independent study physician (from CRO) will determine if a cohort meets Cohort-level Stopping Criteria prior to completing the 16 subjects, in which case no additional subjects will be enrolled into that cohort and no higher brequinar doses will be assessed:

- ≥3 brequinar-treated or combination-treated subjects meet the individual stopping criteria.
- ≥5 brequinar-treated or combination-treated subjects develop a Grade 3 or higher AE regardless of relationship to study drug.

Adverse Drug Reaction is a noxious and unintended response to a medicinal product related to any dose. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

An **Unexpected Adverse Drug Reaction (UADR)** is an adverse reaction, the nature or severity of which is not consistent with the applicable product information [e.g., investigator's brochure for an unapproved investigational medicinal product or company core data sheet or package insert for marketed product].

Subjects will be monitored throughout the study period for adverse events. Subjects will be instructed to bring to the notice of study personnel any adverse event that may occur during the entire study period.

The following information is to be recorded for each adverse event individually in Adverse Event Reporting Form.

- Type of adverse event*
- Is it serious or non-serious?
- Date of onset/reporting
- Date of onset and resolution
- Severity (as per section 12.12)
- Association with the study medication (as per section 12.13)
- Action taken
- Outcome of adverse event (as per section 12.14)
- Further details of the AE, if any.

*The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

For the recording of signs and symptoms, the subject will be required to report spontaneously any AEs as well as the intensity of these events. In addition, each subject will be asked by the investigator for AEs during vital

signs and physical examination. All AEs including both observed and volunteered ones will be recorded in the Adverse Event Reporting Form, irrespective of its association with study medications. All findings considered clinically relevant and reportable as AE by investigator will be reported on the "Adverse event" page in the CRF and in the subject's medical records.

Each AE will be evaluated for duration, severity and action taken, outcome and association with study medication.

Adverse events/ Serious Adverse Events will be recorded from signing informed consent form through the end of the study safety assessments. Other medical events not related to study screening occurring before first dose administration, but after signing the informed consent form will be recorded on the medical history/current medical conditions of case report form.

12.10 Serious Adverse Events (SAEs)

A serious adverse event is any untoward medical occurrence during a study which satisfies one or more of the following conditions:

- resulting in death or
- permanent disability, or
- hospitalisation of the trial subject, or
- prolongation of hospitalisation, or
- significant disability, or
- incapacity, congenital anomaly, birth defect ,or
- life threatening event.

The term 'Life threatening' refers to an event in which the subject was at immediate risk of death at the time of event. It does not refer to an event which may have caused death if it was more severe.

The Investigator will be responsible to report all SAE to the central regulatory (e.g. DCGI-Central Licensing Authority), Sponsor's representative and respective Ethics Committee within 24 hours of SAE occurrence/knowledge of occurrence if required. Investigator will be responsible for reporting the detailed report to the local regulatory (e.g. DCGI), chairman of the Ethics Committee and the head of the institution where the trial has been conducted within 14 days of SAE occurrence if required. Each AE will be evaluated for duration, severity, action taken, outcome and association with Investigational Medicinal Product. The study may be suspended or terminated depending upon the seriousness of SAEs.

12.11 Reporting and Follow-up

The investigator must complete SAE form, verify the accuracy of the information recorded in corresponding source documents, and send a copy (by fax /mail) to sponsor/representative/CRO.

Investigator:

The investigator shall report all serious adverse events (SAE) to the central licensing authority (DCGI), the Sponsor/CRO and chairperson of ethics committee within 24 hour of SAE occurrence, if required.

The investigator shall report all SAE after due analysis to the central licensing authority (DCGI), chairperson of ethics committee and head of the institution where the trial has been conducted within fourteen days of SAE occurrence, if required. Subsequent follow-up information shall be reported to all stakeholders as mentioned above.

In case, Investigator fails to report any SAE within stipulated period, the investigator shall have to furnish the reason for the delay to the satisfaction of central licensing authority along with the report of SAE.

Sponsor or Sponsor's Representative:

In case of SAE the Sponsor and/or CRO will be responsible for reporting the due analysis report of SAE to chairman of the Ethics Committee, the central licensing authority and the head of the institution where the trial has been conducted within 14 days of SAE occurrence, if required.

Note: In case if SAE occurrence time and reporting time by subject to investigator is not same, investigator may fail to report such serious adverse event within the stipulated period. In such case Investigator shall have to furnish the reason for the delay to the satisfaction of the central licensing authority along with the report of the serious adverse event.

Name of the sponsor representative:

Barbara Powers, MSN, Ph.D.

E-mail: bpowers@clearcreekbio.com

Sponsor Medical Monitor:

John Pottage, MD

E-mail: John.pottagemd@gmail.com

CRO contact details:

Veeda Clinical Research Ltd.

E-mail: safety@veedacr.com

Fax: +91-79-3001 3010

Follow-up of Adverse Events:

All AEs (serious or not) will be followed to resolution (the subject's health has returned to his/her baseline status or all variables have returned to normal or clinically acceptable level), an outcome is reached, stabilization (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained regardless of whether the subject is still participating in the study. Where appropriate, medical tests and examinations will be performed to document resolution of event(s).

The Investigator should institute any supplemental investigations of SAE based on their clinical judgment of likely causative factors.

If required, a follow-up report including all relevant new or reassessed information (e.g., concomitant treatment, medical history) obtained on the SAE will be prepared and same will be marked “Follow-up report”. Follow up reports are to be sequentially numbered to allow tracking. These reports will be sent to the sponsor/CRO.

Adverse events occurring between informed consent and the last visit

The investigator should follow up on all AEs which occurred from signature of study-specific informed consent until the last visit of the subject, at which point the outcome assessment is documented in the CRF.

Ongoing serious adverse events at the time of last visit

For any SAEs still ongoing at the time of last visit considered to be related to IMP, the investigator should continue to follow-up until the SAE has resolved or has stabilized / is judged permanent for SAEs, and for up to 30 days after the last visit of subject for non-related SAEs. Where appropriate, medical tests and examinations will be performed to document resolution of event(s). The investigator should send SAE follow-up reports including all relevant new or reassessed information (e.g., concomitant treatment, medical history) obtained on the SAE /pregnancy to the sponsor/CRO.

If a subject dies during participation in the study and an autopsy is performed, a copy of the report must be submitted.

Serious adverse events occurring after the last visit

Any SAEs experienced after the last visit should only be reported to sponsor if the investigator suspects a causal relationship to study treatment. The investigator must report the SADR to recipients as per the ‘SAE Reporting’ section 12.10.

Pregnancy Reporting:

Pregnancy recorded for any trial participant after study drug administration should be reported immediately to the sponsor/representative. The subject will be withdrawn from the trial and every effort will be made to gather information regarding the pregnancy outcome until 8 weeks post-partum/termination of pregnancy. It will be the responsibility of the Investigator to obtain this information. Pregnancy recorded after screening but before randomization will be reported and subject will be withdrawn from the study and further follow up will not be done. In case of pregnancy, separate pregnancy form should be filled. Cases of pregnancy exposure associated with SAE and/or abnormal pregnancy outcome should be reported as per SAE reporting timelines. If any congenital anomaly is observed in offspring then the follow up should be conducted till six months after birth, if applicable.

Ethics Committee Timelines for Reporting of SAE:

In case of SAE, the Ethics Committee shall forward its report along with its opinion on the financial compensation (if any) to the licensing authority within 30 days of the occurrence of the SAE, if required.

12.12 Classification of Severity of Adverse Event

Adverse event will be assessed for onset time, occurrence (single or repeat) and intensity. In terms of grade,

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care ADL**.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

*Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

12.13 Causality Assessment/Association with the Study Medication

Every effort will be made to obtain all the required information to determine whether the Adverse Event is related or unrelated to the study procedure or Investigational Medicinal Product (causal relationship).

In terms of relationship

Causality term	Assessment criteria
Definite*	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Re-challenge satisfactory, if necessary
Probable*	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Re-challenge not required
Possible*	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely#	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Not Related#	• The AE is clearly NOT related to the study treatment

Note: #Unlikely and Not Related will be considered as Not Related.

*Definite, Probable and Possible will be considered as Related.

12.14 Outcome Categories

The outcome of adverse event will be categorized as following:

- Recovered/ Resolved
- Recovering/ Resolving
- Recovered with sequelae/ Resolved with sequelae
- Not recovered/ Not Resolved
- Fatal
- Unknown

13.0 SAMPLE PROCESSING AND TRANSFER PROCEDURES

Clinical Laboratory Samples:

All clinical laboratory blood and urine samples will be transferred to the central laboratory in controlled temperature and in pre validated laboratory kits which will be supplied to all the sites by the central laboratory. In case of emergency, samples can be sent to local laboratory for safety assessment at the discretion of the investigator.

Pharmacokinetic (PK) samples:

After collection of PK blood samples from all subjects at each time point, they will be centrifuged at 4000 RPM for 10 minutes at 5 ± 3 °C to separate plasma. For precaution purpose, the blood samples will be kept on wet ice bath (below 10 ^{0}C) both before centrifugation and after separation.

The separated plasma will be transferred to pre-labeled polypropylene tubes in 2 aliquots:

For Brequinar and Dipyridamol PK:

Aliquot 1: Approximately 1.7 mL of plasma

Aliquot 2: Approximately 1.2 mL of plasma

Aliquot will be stored upright in a box containing dry ice or in a freezer at a temperature –15 °C or colder for interim storage at different investigator sites until shipment to Veeda Clinical Research Ltd., Ahmedabad, for analysis.

Note: Entire activity from blood sample collection to storage in a freezer should be completed within 60 minutes time.

During shipment the samples will be packed in thermocol boxes containing adequate amount of dry ice. The temperature will be monitored using calibrated data logger during shipment. Samples will then be stored at -78 ± 8 °C until completion of analysis at Veeda Clinical Research Ltd., Ahmedabad.

Shipment for each aliquot will be carried out separately.

A designated person from bioanalytical department will receive the samples at Veeda Clinical Research Ltd., Ahmedabad or designate on arrival. The condition of the samples will be examined on arrival at Veeda Clinical Research Ltd., Ahmedabad and if any of the samples are not in a frozen condition, clinical facility and\or Sponsor will be informed for the same. After receiving the samples at Veeda Clinical Research Ltd., Ahmedabad, the samples will be stored at –78 ± 8 °C until completion of analysis.

Note: Samples of patients enrolled in Arm 3 (SOC + Placebo) of each cohort will not be analysed.

qPCR Samples

The qPCR samples are to be collected, processed, stored, and shipped as per the instructions in the Laboratory Manual.

14.0 BIOANALYTICAL PROCEDURES

The Bioanalytical procedures will be performed at Bioanalytical facility of Veeda Clinical Research Ltd. Validated analytical method will be used for the PK analysis of the plasma samples.

14.1 Method Validation

Bioanalytical method will be validated at Veeda clinical research Ltd., which is in accordance with the regulatory guidelines on validation of bioanalytical methods.

Method validations of Brequinar and Dipyridamol will be carried out by using analytical method developed at Veeda Clinical Research Ltd. This analytical methods will be validated for the sensitivity, specificity, matrix effect, linearity, ruggedness, accuracy and precision (repeatability and reproducibility), percent recovery and stability of samples (bench-top stability, autosampler stability, short-term, long-term stability of stock solution and internal standard) and effect of concomitant medications, if any.

14.2 Assay of Samples

The Brequinar and Dipyridamol will be quantified using a validated method. All available plasma samples of all subjects in the study will be analyzed as per approved protocol irrespective of withdrawn or dropped out from the study.

The analysis of subject’s samples will be done using calibration curve with quality control samples, distributed throughout each batch. The details for the preparation of the calibration curve and quality control samples and the analytical batch acceptance criteria will be discussed in the respective in-house procedure. The analyst will not have access to the randomization schedule until analysis is completed.

Note: Samples of patients enrolled in Arm 3 (SOC + Placebo) of each cohort will not be analysed.

14.3 Incurred Study Sample Re-analysis

Incurred Study Sample Re-analysis will be performed to ensure method reproducibility as per SOP (VIN-BRD-092).

15.0 STATISTICAL ANALYSIS

15.1 Statistical Analysis Plan

A statistical analysis plan (SAP) will be prepared and finalized prior to the database lock. Detailed description of the statistical methodology, population and handling of missing data will be described in this document. Mock tables and listings will be provided with the SAP.

15.2 Sample Size Estimation

There is no prospective powering in this study. The sample size was chosen to provide an adequate number of subjects to provide reasonable safety and efficacy data for this type of study.

15.3 Study Population for Analysis

- Intent-to-treat population:

Intent-to-treat (ITT) analysis set will include all the subjects who undergo randomization.

- Safety Population:

The safety population will include all randomized subjects who receive at least one dose of the study product.

15.4 Analysis of Efficacy Data

All statistical analysis will be done using SAS® Version 9.4 or higher (SAS Institute Inc., USA).

For continuous variables, the summary statistics will be the number of observations, mean, standard deviation, median, minimum and maximum values. Categorical values will be summarized using frequencies and percentages.

Primary Endpoints:

- Frequencies of grade 3 and 4 toxicities and serious adverse events (SAEs) considered by the investigator to be related to the combination, brequinar alone or placebo alone.

  Because the primary study endpoint is a safety parameter no formal statistical testing will be performed for this parameter.

Secondary Endpoints:

For subjects treated with the brequinar-dipyridamole combination compared to subjects treated with the brequinar and to subjects treated with the placebo combination through Day 29, to determine:

- SARS-CoV-2 levels through Day 29 and at days 4, 8, 12, 15, 22, and 29 will be analyzed using analysis of covariance (ANCOVA) test;
- Time to symptom improvement through Day 29 will be analyzed using Kaplan-Meier time-to-event analysis;
- Percentage of subjects requiring hospital admission/re-admission as an in-patient for >24 hours through Day 29 will be analyzed using Fisher exact / chi square test;
- Percentage of subjects requiring medical attended visits, e.g., hospitalization, emergency room visits, Urgent Care/Family Doctor visits through Day 29 will be analyzed using Fisher exact / chi square test ;
- Percentage of subjects requiring supplemental support such as oxygen through Day 29 will be analyzed using Fisher exact / chi square test.

Exploratory Endpoints:

- Brequinar's pharmacokinetic profile in a subset of patients that have received brequinar as a part of therapy and have consented to provide PK samples will be analyzed descriptively.

15.5 Safety Analysis

All safety analysis will be conducted using the safety population set.

Frequency distribution or summary statistics of all demographics variable and baseline characteristics will be generated by treatment arm.

The evaluation of the drug safety will be based on clinical AEs, vital signs, physical examination, concomitant medications and laboratory abnormalities reported during the study and incidence of adverse events and treatment emergent adverse events in each arm during the study. All safety presentations will include subjects who receive at least one dose of the study medication and will group subjects by treatment received. Frequency distributions and individual listings of all adverse events will be generated. Changes in clinical laboratory test results from baseline will be listed.

A treatment emergent adverse event is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terms using the version that is current at the time the first subjects is enrolled and will be summarized by system organ class (SOC) and preferred term within SOC. The Common Terminology Criteria for Adverse Events CTCAE 5.0 will be used to grade the severity of adverse events.

Adverse Events will be summarized by treatment and overall. AE summary tables will include counts of subjects and the number of events. If a subject experiences more than one episode of a particular AE, that subject will be conducted only once for that event. If a subject has more than one AE that coded to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than one AE within a SOC, the subject will be counted only once in that SOC.

16.0 AMENDMENT TO THE PROTOCOL

Any significant change in the study procedure or study design will only be effected upon mutual agreement between the Sponsor, CRO and Investigator and after obtaining a favorable opinion from the Ethics Committee and regulatory authority(ies). All such changes will be documented in the amended version of the protocol and a list of changes with reference to the previous version will be generated and submitted to the IEC and regulatory authorities as soon as possible. In cases where there is an immediate safety hazard to the subjects, the amended protocol will be effective immediately and approval of the IEC will be obtained as soon as possible.

17.0 SOURCE DATA ACCESSIBILITY

Quality Assurance (QA) auditors and study monitors of Veeda Clinical Research Ltd. as well as sponsor's monitors, IEC and Regulatory agency(ies) will have access to raw data during inspection and audits.

18.0 STUDY MONITORING

Monitoring procedures developed by Veeda will be followed in order to comply with GCP guidelines and to ensure acceptability of the study data for national registration purposes. During the course of the study, a monitor from Veeda will perform site visits to review protocol compliance, compare CRFs to individual subject's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. CRF entries will be verified with source documentation.

The Sponsor or its representative may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study.

This clinical trial is to be conducted at Investigator sites and the Investigators should permit the different stakeholders for monitoring/ auditing/ inspections at their site.

19.0 QUALITY CONTROL AND QUALITY ASSURANCE AUDITS

Auditing procedures developed by Veeda will be followed in order to comply with GCP guidelines and to ensure accuracy, completeness and authenticity of the data generated, recorded and reported and acceptability of the study data for international registration purposes.

The raw data generated during the course of the study as well as reports will undergo a random quality assurance process for conformance to this protocol and all the governing SOPs by the Monitors and the auditors of Veeda Clinical Research Ltd, respectively. The final report will contain a statement of quality assurance duly signed

by the Head, Quality Assurance department.

20.0 ETHICS

20.1 Ethics Committee

This protocol and corresponding informed consent Document (ICD) (containing information about the study to be given to subjects) to be used to obtain written informed consent of study subjects will be reviewed by IEC and subjects will not be enrolled into the study until IEC approves the protocol and ICD.

The study will be conducted according to the current version of the IEC approved protocol, Relevant SOPs, [New Drugs & Clinical Trial Rules, 2019 of CDSCO (Central Drugs Standard Control Organization), Ministry of health and family welfare, Government of India], [Ethical guidelines for biomedical research on human participants, ICMR (Indian Council of Medical Research (2006)], [ICH (The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) E6 (R2) 'Guideline for Good Clinical Practice' 2016], Declaration of Helsinki – Brazil, October 2013].

20.2 Written Informed Consent

Investigator or designated study personnel before initiation of any study related procedure will inform the subject (in a language best understood by the subject) through an oral presentation regarding the purpose, procedures to be carried out, information on the investigational medicinal products, potential hazards, benefits and rights of the study subjects with maintaining adequate social distancing. Subjects will be encouraged to ask questions and clarify their doubts regarding any aspect of the study and the same would be documented in the source notes with sign and date. The ample time after completion of ICF discussion will be given to the subjects to think and take an informed and voluntary decision. Investigator will ensure that the entire process of informed consent is followed as per local regulatory requirement for each subject at the respective site maintaining the confidentiality of subject's personal information and all relevant records will be maintained in source file. The responsibility for taking informed consent must remain with that of a medically qualified person and cannot be delegated to a non-medically qualified person.

Subject (or legally acceptable representative) should be present during the entire informed consent process and will also append his/her signatures on the informed consent form. If subject or subject's legally acceptable representative is unable to read/write, an impartial witness should be present during the entire informed consent process, and will append his/her signatures on the informed consent form. In both the above cases, subjects will be required to give a thumb impression on the informed consent form. Only those subjects who are able to understand the ICF and able to communicate with the study personnel will be enrolled in the study.

The subjects will give their written consent for participation in the trial by signing or by putting a thumb impression on the informed consent form, which will also be signed by the Investigator or his/her designate.

If any new information becomes available during the course of the study that may be relevant to the subject's willingness to continue participating in the trial, the Investigator must inform the subject in a timely manner,

and a revised written informed consent must be obtained.

Investigator will ensure that all the subject are handed over a signed and dated copy of the informed consent form immediately once the informed consent process is completed.

21.0 DATA HANDLING AND RECORD KEEPING

All clinical data generated during the conduct of the study will be entered in the source notes and will be transcribed in the respective CRF. All raw data and transcribed data forms compiled by the study personnel assisting in the study will be checked for completeness. All data related to the project will be in the custody of the Investigator or Project Manager until transferred to archives.

All raw data generated during the conduct of the project compiled by the study personnel assisting in the study will be checked for completeness. Biostatistics department after receipt of the raw data will perform a statistical analysis and statistical data will be generated which will be further sent for compilation of the final clinical study report of the study.

22.0 STUDY REPORTS AND SUPPLEMENTARY DOCUMENTS

The final report will be compiled and sent as per eCTD (Module 5) format. All copies of supplementary documents such as approved final version of Protocol along with all appendices, IEC approval letter, List of IEC members, CVs of Investigators, all subject CRFs, adverse event form (if any), Investigational Product Accountability records, Randomization list, Summary report of statistical analysis, protocol deviations, demographics and baseline characteristics and safety data will be submitted to sponsor with the final study report.

23.0 ARCHIVING

All data generated in connection with this study, together with the copy of this protocol and the audited final report will be archived according to the ICH guideline for good clinical practice and regulatory requirement and the TMF plan agreed with the Sponsor. Subject files, original source notes with Signed informed consent form and Patient Information Sheet (PIS), CRFs (If paper CRF has been used) and the Site Investigator File will be retained at individual study site as per applicable regulatory guidelines.

All other data generated will be retained at Veeda as mentioned in Research Service Agreement. The sponsor will then arrange for the maintenance of these documents.

24.0 INSURANCE POLICY

The sponsor has a clinical trial insurance policy to cover the risks to subjects and/or any other eventualities pertaining to study.

25.0 CONFIDENTIALITY OF DATA

The data identifying each subject by name will be kept confidential and will be accessible to the study personnel and if necessary, to the QA auditors, IEC, Sponsor representative and Regulatory agency(ies).

Information related to COVID-19 infection may be highly sensitive in nature with a lot of scope for stigmatization, discrimination, violence etc. Maintaining confidentiality of research related data and its publication is important to protect the privacy of individuals and avoid any discrimination against them.

26.0 PUBLICATION POLICY

The results of the study including all data obtained will be the property of sponsor of this study. For any publication pertaining to the data or results of the study, a written approval of the sponsor will be obtained prior to communicating for publication and the manuscript will be sent for sponsor's approval, if the sponsor asks to do so.

27.0 REFERENCES

1. CLINICAL MANAGEMENT PROTOCOL: COVID-19 released by Government of India Ministry of Health and Family Welfare Directorate General of Health Services (EMR Division). Version 6. Released on: 24.05.21
2. WHO R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis. February 18, 2020, Geneva, Switzerland
3. Declaration of Helsinki, Fortaleza, Brazil, October 2013.
4. International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use- Good Clinical Practice (ICH-GCP) E6 (R2).
5. Ethical Guidelines for Biomedical Research On Human Participants, Indian Council of Medical Research, 2017.
6. Investigational Brochure Brequinar for COVID-19 Version: 5.0 Date: 23 September 2021.
7. Prescribing Information of dipyridamole USP 25 mg, 50 mg, and 75 mg tablets.

28.0 CLINICAL LABORATORY TESTS

HEMATOLOGY		
Hemoglobin		
Absolute WBC Counts (Neutrophils, Lymphocyte, Eosinophils, Monocyte, Basophils)		
Complete Blood Counts, hematocrit, RBC count and indices		
White blood cell (WBC) count, Differential Leucocyte count, Platelet count		
BIOCHEMICAL PARAMETERS		
SGOT (AST)	Alkaline Phosphatase	Serum Magnesium
SGPT (ALT)	Random Blood Glucose	Serum Potassium
Total Bilirubin	Serum Cholesterol	Total Protein
Direct Bilirubin	Serum Triglyceride	
Indirect Bilirubin	Serum Creatinine	
Blood urea nitrogen (BUN)	Creatinine clearance	
Pregnancy test by β-hCG Method (for all females of child bearing potential)	Urea	
SEROLOGY		
HIV	HbsAg (Hepatitis B surface antigen)	HCV antibodies
URINE ANALYSIS		
Color	Glucose	WBC
Odor	Bilirubin	Epithelial Cells
Clarity	Blood	Casts
Specific gravity	Ketones	Crystals
pH	Urobilinogen	Bacteria
Protein	Nitrite	

- Any laboratory test, if required for adverse event management, may be performed at a local clinical laboratory at the discretion of Investigator.

29.0 LIST OF CHANGES IN THE PROTOCOL FROM VERSION 02 TO VERSION 2.1

Sr. No.	Section	Protocol (Version 02 Dated 30 Sep 2021)	Changes in Protocol (Version 2.1 Dated 28 Dec 2021)	Reason
1	Section 3.1 Synopsis (Study Design) & Section 9.1 Study Design	An expansion cohort of approximately 48 subjects will be added to the cohort with the highest brequinar dose that meets safety criteria. All subjects will receive SOC as per relevant guidelines for treatment of patients with mild to moderate COVID-19 infection.	An expansion cohort of approximately 48 subjects will be added to the cohort with the highest brequinar dose that meets safety criteria. **Safety data of cohort 1 to cohort 4 (or highest dose cohort evaluated) will be submitted to the regulators and their approval will be obtained prior to commencing recruitment in the expansion cohort.** All subjects will receive SOC as per relevant guidelines for treatment of patients with mild to moderate COVID-19 infection.	Updated for better clarification
2	Section 5.3 Safety of Dipyridamole	---	**Introduction:** **Dipyridamole was first approved for use in 1961 as an adjunct to coumarin anticoagulants in the prevention of postoperative thromboembolic complications of cardiac valve replacement. The primary therapeutic actions of dipyridamole relate to its activity in (1) inhibiting platelet function and aggregation and (2) vasodilatation.** **Dipyridamole inhibits the uptake of adenosine into platelets, endothelial cells and**	Additional dipyridamole information added

			erythrocytes in vitro and in vivo; the inhibition occurs in a dose-dependent manner at therapeutic concentrations (0.5−1.9 µg/mL). This inhibition results in an increase in local concentrations of adenosine which acts on the platelet A2-receptor thereby stimulating platelet adenylate cyclase and increasing platelet cyclic-3',5'-adenosine monophosphate (cAMP) levels. Via this mechanism, platelet aggregation is inhibited in response to various stimuli such as platelet activating factor (PAF), collagen and adenosine diphosphate (ADP). **Dipyridamole also inhibits phosphodiesterase (PDE) in various tissues. While the inhibition of cAMP-PDE is weak, therapeutic levels of dipyridamole inhibit cyclic-3',5'-guanosine monophosphate-PDE (cGMP-PDE), thereby augmenting the increase in cGMP produced by EDRF (endothelium-derived relaxing factor, now identified as nitric oxide).** **Preclinical study data:** **In addition to the effects upon platelet function, dipyridamole can cause vasodilatation.** **Hemodynamics:**	

			In dogs intraduodenal doses of dipyridamole of 0.5 to 4.0 mg/kg produced dose-related decreases in systemic and coronary vascular resistance leading to decreases in systemic blood pressure and increases in coronary blood flow. Onset of action was in about 24 minutes and effects persisted for about 3 hours. **Similar effects were observed following intravenous dipyridamole in doses ranging from 0.025 to 2.0 mg/kg.** **In man the same qualitative hemodynamic effects have been observed. However, acute intravenous administration of dipyridamole may worsen regional myocardial perfusion distal to partial occlusion of coronary arteries.**	
3	Section 5.5 Adverse Reactions	---	**Brequinar:** **As discussed above, brequinar is an investigational drug that has been given to 71 patients with COVID-19. Adverse events related to brequinar were mild to moderate and infrequent, and no subjects discontinued brequinar treatment due to a related adverse event in either of the two COVID-19 studies.** **Brequinar has also been given to more than 800 patients with various forms of cancer in more than 20 clinical trials**	Additional dipyridamole information added

			and has also been tested in patients with psoriasis and those who have had a kidney or liver transplant. The most common side effects in cancer patients when given higher doses of brequinar have been:
			• **Thrombocytopenia, which may require replacement. Low platelet count can lead to bruising, nose bleeds, vomiting blood, bloody diarrhea, blood in the urine, bloody gums, coughing up blood, and taking longer to stop bleeding from cuts.**
			• **Stomatitis/mucositis.**
			• **Other risks associated with brequinar include:**
			  ○ **Skin rash,**
			  ○ **Nausea,**
			  ○ **Vomiting,**
			  ○ **Diarrhea,**
			  ○ **Leukopenia,**
			  ○ **Anemia,**
			  ○ **Yellowing of the skin or whites of the eyes caused by high levels of the pigment bilirubin,**
			  ○ **Abnormal liver tests,**
			  ○ **Abnormal kidney function,**
			  ○ **Cardiac complications, and**
			  ○ **Fatigue**
			Some of these side effects were severe enough in patients treated with brequinar to require hospitalization or	

			caused death. In most cases, these side effects went away within about 2 weeks after patients stopped taking brequinar. **Patients must be contact to study doctor/study staff if they experience any of the following:** • **Discoloration/bruising of the skin or a rash of red/purple spots on your skin. These can be caused by bleeding in or under the skin,** • **Nose bleed,** • **Coughing up blood,** • **Blood in urine,** • **Bleeding gums,** • **Prolonged bleeding time from needle sticks, abrasions or lacerations,** • **Vomiting blood,** • **Rectal bleeding,** • **Blood in stool,** • **Any other unusual bleeding** **Dipyridamole:** **Dipyridamole will be used in this study as a pyrimidine salvage inhibitor when co-administered with brequinar (see Rationale below). When used per the labeled indications of stroke prevention and inhibitor of blood clot formation, adverse reactions at therapeutic doses are usually minimal and**	

			transient. In combination with warfarin, the dipyridamole label reports dizziness (13.6%), abdominal distress (6.1%), headache (2.3%), and rash (2.3%). Reactions from uncontrolled studies include diarrhea, flushing, and pruritus. Angina pectoris has been reported rarely and there have been rare reports of liver dysfunction. In post-marketing reporting experience, there have been rare reports of hypersensitivity reactions (such as rash, urticaria, severe bronchospasm, and angioedema), larynx edema, fatigue, malaise, myalgia, arthritis, nausea, dyspepsia, paresthesia, hepatitis, thrombocytopenia, alopecia, cholelithiasis, hypotension, palpitation, and tachycardia. In the case of real or suspected overdose, symptoms may occur such as warm feeling, flushes, sweating, restlessness, and feeling of weakness and dizziness. There is an increased risk of thrombocytopenia when taking dipyridamole. There are no clinical data to suggest that dipyridamole is beneficial for treating COVID-19. **Co-Administration of Brequinar and Dipyridamole:** **This combination has not previously been tested in the**	

			clinic. There is a potential for increased bleeding when taking either drug as well as the combination, and the risk compared to brequinar or dipyridamole when administered alone is unknown. To address any potential increased risk, careful attention will be paid to laboratory reports and any increased signs or symptoms of bleeding during this study.	
4	Section 5.6 Rational	(…) It has also been widely prescribed in combination with aspirin to prevent stroke. (…)	(…) It has also been widely prescribed in combination with aspirin to prevent stroke. **There is no clinical evidence that dipyridamole used alone is effective for treating SARS-CoV-2.** (…)	Additional dipyridamole information added
5	Section 3.1 Synopsis (Exclusion Criteria) & Section 8.2 Exclusion Criteria	(…) 13. Chronic hepatitis B infection, active hepatitis C infection, active liver disease and/or cirrhosis per subject report. (…)	(…) 13. **HIV,** Chronic hepatitis B infection, active hepatitis C infection, active liver disease and/or cirrhosis per subject report. (…)	To rectify the error
6	Section 27 References	(…) ---	(…) **6. Investigational Brochure Brequinar for COVID-19 Version: 5.0 Date: 23 September 2021.** **7. Prescribing Information of dipyridamole USP 25 mg, 50 mg, and 75 mg tablets.**	Updation

SIGNATURE(S) OF INVESTIGATOR(S)

I, the undersigned, have read and understood this protocol, entitled

"The CRISIS-04 Study: A phase II, randomized, assessor-blind, multicenter, multi-dose, placebo-controlled study assessing the safety and anti-coronavirus response of brequinar combined with dipyridamole in patients with mild to moderate SARS-CoV-2 infection."

and hereby agree to conduct the study in accordance with this protocol and to comply with all the requirements regarding the obligations of Investigators and all other pertinent requirements of the Ethical guidelines for biomedical research on human participants (ICMR) 2017 guidelines, New Drugs and Clinical Trial Rules (2019) of India, ICH (Step 5) 'Guidance on Good Clinical Practice' ICH Guidance E6 (R2), Declaration of Helsinki (Brazil, 2013) and with procedures oriented to Good Laboratory Practice and applicable regulatory guidelines.

I agree to comply with all relevant SOPs required for the conduct of this study. I further agree to ensure that all associates assisting in the conduct of this study are informed regarding their obligations.

_____ Date: _____
Investigator

Name:

Address: _____

_____

_____

_____

Tel. No.: _____

Fax: _____

E-mail: _____