CCB-CRISIS-01

THE CRISIS STUDY: A RANDOMIZED OPEN-LABEL STUDY ASSESSING THE SAFETY AND ANTI-CORONAVIRUS RESPONSE OF SUPPRESSION OF HOST NUCLEOTIDE SYNTHESIS IN HOSPITALIZED ADULTS WITH CORONAVIRUS-19 (COVID-19)

NCT04425252

STATISTICAL ANALYSIS PLAN DATE: 17-DEC-2020

Statistical Analysis Plan

Sponsor:	Clear Creek Bio, Inc
Protocol No:	CCB-CRISIS-01
Protocol Title:	A randomized open-label study assessing the safety and anti-coronavirus response of suppression of host nucleotide synthesis in hospitalized adults with coronavirus-19 (COVID-19)
Document Date:	17-Dec-2020
Document Revision	1.0

APPROVAL SIGNATURES

Prosoft Personnel

Title	Printed Name	Signature	Date
Manager, Statistics	Daisy Chen	DocuSigned by: Daisy Chen Signer Name: Daisy Chen Signing Reason: I have reviewed this document Signing Time: 17-Dec-2020 | 1:30:14 PM PST 2B3FFE9315C431EB126300C7C7DAC74	17-Dec-2020
Associate Vice President, Statistics	Diane Tipping	DocuSigned by: Signer Name: Diane Tipping Signing Reason: I approve this document Signing Time: 17-Dec-2020 | 4:32:51 PM EST 92A2CD2F77564D0E959E82FB02359B17	17-Dec-2020

CCB Personnel

Title	Printed Name	Signature	Date
Vice President, Clinical Operations	Barbara Powers, PhD	DocuSigned by: Barbara Powers Signer Name: Barbara Powers Signing Reason: I approve this document Signing Time: 17-Dec-2020 | 1:39:56 PM PST 57DEAAD17C2240FEA72C57ABA124E827	17-Dec-2020

DOCUMENT HISTORY

Rev No	Date	Description
1.0	17-Dec-2020	Original document

TABLE OF CONTENTS

List of Abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
DHO	Dihydroorotate
DHODH	Dihydroorotate Dehydrogenase
DSMB	Data Safety Monitoring Board
EHR	Electronic Health Record
ICU	Intensive Care Unit
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
mITT	Modified Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NEWS2	National Early Warning System 2
Q1	First Quartile
Q3	Third Quartile
RNA	Ribonucleic Acid
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SE	Standard Error
SOC	Standard of Care
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHODrug	World Health Organization Drug Dictionary

1. INTRODUCTION

1.1 Background

Beginning in December 2019, Chinese scientists isolated a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from patients with virus-infected pneumonia which was later designated as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO). Approximately 14% of those affected with this virus will develop severe disease requiring hospitalization and oxygen support; 5% will require admission to the intensive care unit (ICU). Coronaviruses, like other Ribonucleic acid (RNA) based viruses, do not have the machinery to synthesize their own nucleotides and thus depend upon the host intracellular pool of nucleotides for viral replication. In essence, viruses steal the host RNA building blocks, and without these building blocks they are unable to replicate.

Dihydroorotate dehydrogenase (DHODH) is a clear therapeutic target for the inhibition of host pyrimidine synthesis. Brequinar is an orally available and potent inhibitor of DHODH. Brequinar is one of more than 300 quinoline-carboxylic acid derivatives prepared in an analog synthesis program in the 1980s, which was started after it was found that a compound of this class had antitumor activity.

The CRISIS trial will study standard of care (SOC) and SOC with 5 days of DHODH inhibition. Clear Creek Bio hypothesizes that a defined 5-day course of brequinar will inhibit the enzyme DHODH to a degree sufficient to result in the transient depletion of host pyrimidine nucleotides, thereby inhibiting viral replication.

1.2 Trial Design

This will be a phase 1a randomized, open label, multi-center study with approximately 24 subjects. All subjects will receive SOC per institutional guidelines for treatment of patients with COVID-19 infection. In addition to SOC, the brequinar group will receive brequinar 100 mg once daily for 5 days.

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

1.2.1 Number of Subjects and Randomization

Subjects who meet all the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 24 subjects have completed the study. Subjects will be randomized to either SOC or SOC plus brequinar or in a 1:2: ratio (approximately 8 subjects assigned to SOC alone and approximately 16 subjects on SOC plus brequinar).

1.3 Trial Objectives

1.3.1 Primary Objectives

The primary objective of this study is to determine the safety and tolerability of SOC and SOC plus brequinar in hospitalized COVID-19 subjects.

1.3.2 Secondary Objectives

The secondary objectives of this study are

- To determine the changes in clinical status measures through Day 15
  - hospitalization status
  - duration of hospitalization
  - NEWS2 Score
- To determine survival status through Day 29

1.3.3 Exploratory Objectives

- To determine the change in SARS-CoV-2 nasopharyngeal viral load through Day 15
- To determine the change in inflammatory markers through Day 15
- To determine the change in DHO levels through Day 15
- To determine the change in brequinar concentration levels through Day 7

2. STATISTICAL METHODOLOGY

2.1 General Principles

In general, continuous parameters will be summarized by number of non-missing observations (N), mean, standard error (SE), median, quartiles, minimum, and maximum. Categorical parameters will be summarized by count and percentage of the non-missing observations, and

95% confidence interval (CI), when appropriate. All statistical analyses will be performed using SAS® Version 9.4. Adverse events (AEs), procedures and medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0. Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODrug) Enhanced March 2020. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 will be utilized for adverse event and laboratory reporting.

All study data collected will be presented in listings.

2.2 Sample Size Determination

Formal sample size calculations are not applicable for this phase 1a, open label study. Up to 24 subjects are planned to be entered in this trial. Additional subjects may be enrolled following data review.

2.3 Trial Populations

The modified Intent to Treat (mITT) population will include all randomized subjects who had at least one post-randomization assessment, and who received at least one dose of study medication if randomized to SOC + Brequinar group. All analyses will be based on the mITT population.

2.4 Subject Accounting and Baseline Characteristics

Demographics and baseline characteristics (including NEWS2 score and ICU level of care at randomization) will be summarized by treatment. Prior and concomitant medications/procedures will be summarized by treatment. A medication/procedure may be classified as both prior and concomitant. Medical history will be summarized by treatment.

2.5 Efficacy Analyses

2.5.1 Primary Efficacy Analyses

None

2.5.2 Secondary Efficacy Analyses

Hospitalization Status and Duration

Hospitalization status (died, hospitalized in ICU, hospitalized not in ICU, discharged for initial hospitalization and re-hospitalization) will be summarized on Study Day 3, 5, 7 and 15. Kaplan

Meier estimates and plots will be provided to assess the duration of hospitalization (Study Day at time of initial discharge). Subjects who were not discharged by the Day 15 visit will be censored at the Day 15 visit. Subjects who did not complete the trial while still hospitalized will be censored at the date of last contact.

NEWS2 Score

Changes from baseline to Day 3, 5, 7, and 15 in NEWS2 scores will be summarized by treatment. In addition, the NEWS2 scores will be summarized by category (0-4, 5-6, 7 or above). The NEWS2 parameters will be summarized at each visit, including changes from baseline for continuous parameters. (See Section 3.2 for derivation of NEWS2 score).

Mortality

Mortality will be summarized through Day 29 by treatment group. Kaplan Meier estimates and plots will be provided to assess the time to death (date of death minus date of randomization). Subjects who are alive at the Day 29 contact will be censored at the Day 29 contact. Subjects whose Day 29 survival is unknown will be censored at the date of last contact.

2.5.3 Exploratory Efficacy Analyses

Changes from baseline will be summarized by treatment:

- Viral load (nasopharyngeal) (Days 3, 5, 7, and 15)
- Inflammatory markers (Days 3, 5, 7, and 15)
- DHO levels (Days 3, 5, 7, and 15)
- Brequinar concentration levels (Days 3, 5 and 7)

For inflammatory markers (including pro-inflammatory cytokines), results from both local and central laboratories will be combined, where the local test result will be normalized where necessary. (See Section 3.2 for normalization method).

Viral culture results will be provided in data listings only.

2.6 Safety Analyses

Adverse Events

An overall summary of treatment-emergent adverse events (TEAEs) will be presented by treatment and total, including the total number of events, frequency counts and percentages for:

- Any TEAE
- Treatment-related TEAEs
- CTCAE Grade 3 or above TEAEs
- TEAEs leading to drug withdrawn
- TEAEs leading to study discontinuation
- Serious TEAEs
- Fatal TEAEs
- TEAEs of interest

The incidence of TEAEs by treatment and total will be tabulated by MedDRA system organ class and preferred term for:

- All TEAEs
- Treatment-related TEAEs
- TEAEs by severity
- TEAEs leading to study discontinuation
- Serious TEAEs
- TEAEs of interest

AEs will be considered treatment-emergent if the onset date is on or after the day of randomization. “Drug related” will include ‘Definite’, ‘Probable’ and ‘Possible’ relationship to drug as determined by the Investigator.

Safety Laboratory Assessments

Safety laboratory tests (Chemistry and Hematology) will be performed throughout the study. Laboratory parameters of interest (AST, ALT, ALP, Total Bilirubin, Creatinine, Hemoglobin, WBC, Absolute Neutrophils, Absolute Lymphocytes and Platelets) will be summarized for changes from baseline.

NCI CTCAE grades will be derived for the lab parameters included in Appendix 1 and presented in data listings. Separate listings of Grade 3 or 4 values will also be provided.

2.7 Interim Analyses

No interim analysis is planned for this trial. A Data Safety Monitoring Board (DSMB) will meet periodically to review the safety and scientific conduct of the study. At a minimum, the DSMB is to review adverse events and safety laboratory assessments after the first six subjects complete Day 5 of treatment, and again after the first 12 subjects complete Day 5 of treatment.

3. DATA HANDLING

3.1 Baseline and Study Visits

Study Day 1 will be the day of randomization.

The summary of hospitalization status will be based on the Study Day (derived relative to the day of randomization).

For the summary of inflammatory markers, Baseline will be the last assessment prior to dosing (SOC plus brequinar group) or last assessment on or prior to Study Day 1 (SOC group). .Post-baseline timepoints will be based on the Study Day (derived relative to the day of randomization), where Day 15 includes a 4-day window (Study Day 11-19). If there are multiple results on the same day, the earliest result will be used.

For all other summaries, post-baseline timepoints will use the visit as recorded on the case report form, and Baseline will be the last non-missing value prior to randomization, including unscheduled assessments. Otherwise, unscheduled data will not be used in the analyses, but will be presented in the listings.

3.2 Derived Data

Prior and Concomitant Medication/Procedure

A prior medication/procedure is any medication/procedure that started prior to date of randomization. A concomitant medication/procedure is any medication/procedure that either has a start date on or after date of randomization, or is ongoing on the date of randomization.

Hospitalization Status

If a subject experiences multiple hospitalization status types on the given day, the worst status will be summarized on the day of interest.

NEWS2 Score

Chart 1: The NEWS scoring system

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

Use Chart 1 NEW2 scoring system to derive NEW2 score of each physiological parameter collected from case report forms. If hypercapnic respiratory failure, use SpO2 Scale 2; otherwise use SpO2 Scale 1. The total possible score ranges from 0 to 20. If any one of the NEWS2 parameters is not available on the study visit, the NEWS2 score will not be derived.

Normalization

In order to summarize inflammatory marker results across the laboratories which have different normal ranges, normalization will be performed. The scale model will be applied for data transformation using the scale normalization formula:

$$S = X \times \frac{ULNs}{ULNx}$$

where X represents an assay value from the local laboratory, ULN_x is the ULN from the laboratory, and ULN_s is the upper limit of normal (ULN) from Site 02. Markers that are performed only at the central laboratory will not be normalized.

3.3 Missing Data and Data Conventions

No imputation is planned for missing data.

The follow conventions will be used for data handling:

- If SARS-Cov-2 is “not detected” in specimen, the test result will be set to 0 for analysis.
- For DHO and brequinar concentration levels, samples below the lower limit of quantitation (LLOQ) will be set to half of the LLOQ value for the summary tables (LLOQ of DHO is 5 ng/mL, LLOQ of concentration level is 5 mcg/mL).
- If a laboratory test result is reported as “< xxx” or “> xxx”, the value of “xxx” will be used for analysis.
- If a medication or procedure has an incomplete start date, it is assumed to have started prior to randomization, unless the month and year are after randomization.
- If a medication or procedure is not checked as ongoing and has an incomplete stop date, it is assumed to have stopped after randomization, unless the month and year are prior to randomization.

4. CHANGES FROM THE PROTOCOL

Plasma viral load was listed in the protocol (Section 11.3) but will not be collected.

Nasopharyngeal viral culture was not listed in the protocol but was added to the central laboratory assessments.

The mITT population was not included in the protocol, but will be used for all analyses instead of the ITT population.

APPENDIX 1 CTCAE V4.03 GRADING FOR LABORATORY VALUES

Lab Test	Lab Unit	Grade 1	Grade 2	Grade 3	Grade 4
Albumin	G/DL	3 to <LLN	2 to <3	<2	Clinical Review Needed: Life-threatening consequences; urgent intervention indicated
Alkaline Phosphatase	U/L	>ULN to 2.5xULN	>2.5xULN to 5xULN	>5xULN to 20xULN	>20xULN
Alanine Amino Transferase	U/L	>ULN to 3xULN	>3xULN to 5xULN	>5xULN to 20xULN	>20xULN
Aspartate Amino Transferase	U/L	>ULN to 2.5xULN	>2.5xULN to 5xULN	>5xULN to 20xULN	>20xULN
Bilirubin Total	MG/DL	>ULN to 1.5xULN	>1.5xULN to 3xULN	>3xULN to 10xULN	>10xULN
Calcium	MG/DL	>ULN to 11.5	>11.5 to 12.5	>12.5 to 13.5	>13.5
Calcium	MG/DL	8 to <LLN	7 to <8	6 to <7	<6
Creatinine	MG/DL	>ULN to 1.5xULN	>1.5xULN to 3xULN	>3xULN to 6xULN	>6xULN
Glucose	MG/DL	>ULN to 160	>160 to 250	>250 to 500	>500
Glucose	MG/DL	55 to <LLN	40 to <55	30 to <40	<30
Potassium	MMOL/L	>ULN to 5.5	>5.5 to 6	>6 to 7	>7

Lab Test	Lab Unit	Grade 1	Grade 2	Grade 3	Grade 4
Potassium	MMOL/L	Clinical Review Needed: Check Grade 2 and reassign if not symptomatic and no intervention indicated	3 to <LLN	2.5 to <3	<2.5
Sodium	MMOL/L	>ULN to 150	>150 to 155	>155 to 160	>160
Sodium	MMOL/L	130 to <LLN	-	120 to <130	<120
Lymphocytes, Absolute	10^3/UL	-	>4 to 20	>20	-
Lymphocytes, Absolute	10^3/UL	0.8 to <LLN	0.5 to <0.8	0.2 to <0.5	<0.2
Neutrophils, Absolute	10^3/UL	-	-	<1	Clinical Review Needed: Life-threatening consequences; urgent intervention indicated
Neutrophils, Absolute	10^3/UL	1.5 to <LLN	1 to <1.5	0.5 to <1	<0.5
Hemoglobin	G/DL	>0 to 2	>2 to 4	>4	
Hemoglobin	G/DL	>ULN to ULN+2	>ULN+2 to ULN+4	>ULN+4	
Hemoglobin	G/DL	10 to <LLN	8 to <10	<8	Clinical Review Needed: Life-threatening consequences; urgent intervention indicated
Platelet Count	10^3/UL	75 to <LLN	50 to <75	25 to <50	<25

Lab Test	Lab Unit	Grade 1	Grade 2	Grade 3	Grade 4
White Blood Cell	10^3/UL	-	-	>100	Clinical Review Needed: Clinical manifestations of leucostasis; urgent intervention indicated
White Blood Cell	10^3/UL	3 to <LLN	2 to <3	1 to <2	<1

Note: For these laboratory tests, Grade 0 is assigned if result does not meet above ranges.

CLEAR CREEK BIO. INC.
PROPOSED TABLES and LISTINGS
PROTOCOL CCB-CRISIS-01

Version 1.0
17-Dec-2020

CLEAR CREEK BIO. INC.
PROPOSED TABLES and LISTINGS
PROTOCOL CCB-CRISIS-01

Version 1.0
17-Dec-2020

Signature Page

The proposed tables and listings have been reviewed and approved by the following personnel:

Prosoft Personnel

Title	Printed Name	Signature	Date
Manager, Statistics	Daisy Chen	DocuSigned by: Daisy Chen Signer Name: Daisy Chen Signing Reason: I have reviewed this document Signing Time: 17-Dec-2020 | 1:30:59 PM PST 2B3FFE95115C431EB126300C7C7DAC74	17-Dec-2020
Associate Vice President, Statistics	Diane Tipping	DocuSigned by: Diane Tipping Signer Name: Diane Tipping Signing Reason: I approve this document Signing Time: 17-Dec-2020 | 4:33:16 PM EST 92A2CD2F77564D0E959E82FB02359B17	17-Dec-2020

CCB Personnel

Title	Printed Name	Signature	Date
Vice President, Clinical Operations	Barbara Powers, PhD	DocuSigned by: Barbara Powers Signer Name: Barbara Powers Signing Reason: I approve this document Signing Time: 17-Dec-2020 | 1:40:07 PM PST 57DEAAD17C2240FEA72C57ABA124E827	17-Dec-2020

CLEAR CREEK BIO. INC.
PROPOSED TABLES and LISTINGS
PROTOCOL CCB-CRISIS-01

TABLES

BOLD = SAMPLE IS PROVIDED.

LISTINGS

Conventions:

- For categorical data:
  - Percents are displayed with one decimal
  - When displaying counts and percents, the percent is contained within parentheses and does not include the "%" symbol
  - If the count is zero, no percent is displayed
  - If missing data occurs, a "Missing" row will be added to the summary table. The count of missing will be presented (no percent). The percentages for remaining rows will be based on the number of non-missing responses (i.e., the denominator does not include the missing counts)
- For continuous data, rounding will be based on the following conventions unless otherwise specified
  - Min and Max displayed to the same number of decimals as the original data
  - Mean, Median, and other percentiles displayed to 1 more decimal than the original data
  - SE and CIs displayed to 2 more decimals than the original data

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Table 14.1.1

Summary of Populations by Site and Treatment

	SOC + Brequinar n (%)	**SOC n (%)**
Overall		
Randomized	xx	xx
Modified Intent-to-Treat[a]	xx (xx.x)	xx (xx.x)
Site xx		
Randomized	xx	xx
Modified Intent-to-Treat[a]	xx (xx.x)	xx (xx.x)

a: Modified Intent-to-Treat (mITT) population includes all randomized subjects who had at least one post-randomization assessment, and who received at least one dose of study medication if randomized to SOC + Brequinar group.

Source: Listing 16.X.X.X

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Table 14.1.2

Summary of Subject Disposition by Site and Treatment

Modified Intent-to-Treat Population

	SOC + Brequinar (N=xx) n (%)	**SOC (N=xx) n (%)**
Overall		
Completed the study (through Day 15)	xx (xx.x)	xx (xx.x)
Discontinued	xx (xx.x)	xx (xx.x)
Physician Decision	xx (xx.x)	xx (xx.x)
Adverse Event	xx (xx.x)	xx (xx.x)
Withdrawal by Subject	xx (xx.x)	xx (xx.x)
Study Terminated by Sponsor	xx (xx.x)	xx (xx.x)
Protocol Violation	xx (xx.x)	xx (xx.x)
Lost to Follow-Up	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)
Site xx		
Completed the study (through Day 15)	xx (xx.x)	xx (xx.x)
Discontinued	xx (xx.x)	xx (xx.x)
Physician Decision	xx (xx.x)	xx (xx.x)
Adverse Event	xx (xx.x)	xx (xx.x)
Withdrawal by Subject	xx (xx.x)	xx (xx.x)
Study Terminated by Sponsor	xx (xx.x)	xx (xx.x)
Protocol Violation	xx (xx.x)	xx (xx.x)
Lost to Follow-Up	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)
Source: Listing 16.X.X.X		

Programming note: Sort in descending frequency based on the number of subjects in the SOC + Brequinar group, except for “Other” that shall stay at the last row. Sort alphabetically to break ties.

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Table 14.1.3

Summary of Demographics and Baseline Characteristics by Treatment

Modified Intent-to-Treat Population

Parameter	**SOC + Brequinar (N=xx)**	**SOC (N=xx)**
Age (years)		
n	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx
Sex, [n (%)]		
Male	xx (xx.x)	xx (xx.x)
Female	xx (xx.x)	xx (xx.x)
Ethnicity, [n (%)]		
Hispanic or Latino	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	xx (xx.x)	xx (xx.x)
Race, [n (%)]		
White	xx (xx.x)	xx (xx.x)
Black or African American	xx (xx.x)	xx (xx.x)
Asian	xx (xx.x)	xx (xx.x)
American Indian or Alaska Native	xx (xx.x)	xx (xx.x)
Native Hawaiian or Other Pacific Islander	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)
Height (cm)		
n	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx
Weight (kg)		
n	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx
BSA (m2)		
n	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx

Source: Listing 16.X.X.X

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Table 14.1.3

Summary of Demographics and Baseline Characteristics by Treatment

Intent-to-Treat Population

Parameter	**SOC + Brequinar (N=xx)**	**SOC (N=xx)**
NEWS2 Score		
n	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx
ICU Level of Care at Randomization, [n (%)]		
Yes	xx (xx.x)	xx (xx.x)
No	xx (xx.x)	xx (xx.x)
Source: Listing 16.X.X.X		

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Table 14.1.4

Summary of Medical History by Treatment

Modified Intent-to-Treat Population

System Organ Class **Preferred Term**	**SOC+ Brequinar** **(N=xx)** **n (%)**	**SOC** **(N=xx)** **n (%)**
Any Medical History Event		
Overall	xx (xx.x)	xx (xx.x)
SOC 1		
Overall	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)
SOC 2		
Overall	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)
etc.		

Note: Subjects reporting multiple occurrences of the same preferred term are only counted once within a given cell.
Source: Listing 16.X.X.X

Programming note: Sort in descending frequency based on the number of subjects in the SOC+ Brequinar group. Sort alphabetically to break ties.

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Table 14.1.5.1

Summary of Prior Medications by Treatment

Modified Intent-to-Treat Population

Pharmacological Subgroup **Prior Medication**	**SOC+ Brequinar** **(N=xx)** **n (%)**	**SOC** **(N=xx)** **n (%)**
Any Prior Medication		
Overall	xx (xx.x)	xx (xx.x)
Subgroup 1		
Overall	xx (xx.x)	xx (xx.x)
Medication 1	xx (xx.x)	xx (xx.x)
Medication 2	xx (xx.x)	xx (xx.x)
Subgroup 2		
Overall	xx (xx.x)	xx (xx.x)
Medication 1	xx (xx.x)	xx (xx.x)
Medication 2	xx (xx.x)	xx (xx.x)
etc.		
Note: Subjects reporting multiple medications of the same coded term are only counted once within a given cell. Source: Listing 16.X.X.X		

Programming note: Sort medications in descending frequency based on the number of subjects in the SOC + Brequinar group. Sort alphabetically to break ties. Pharmacological Subgroup comes from ATC3. If ATC3 is not available, use ATC2

Change column header to “System Organ Class Preferred Term” for Procedure tables.

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Table 14.2.1

Summary of Hospitalization Status and Mortality Rate by Treatment and Visit

Modified Intent-to-Treat Population

Study Day **Hospitalization Status**	**SOC + Brequinar** **(N=xx)** **n (%)**	**SOC** **(N=xx)** **n (%)**
Study Day 3		
Died	xx (xx.x)	xx (xx.x)
Hospitalized in ICU	xx (xx.x)	xx (xx.x)
Initial Hospitalization	xx (xx.x)	xx (xx.x)
Re-Hospitalization	xx (xx.x)	xx (xx.x)
Hospitalized (not ICU)	xx (xx.x)	xx (xx.x)
Initial Hospitalization	xx (xx.x)	xx (xx.x)
Re-Hospitalization	xx (xx.x)	xx (xx.x)
Discharged	xx (xx.x)	xx (xx.x)
Initial Hospitalization	xx (xx.x)	xx (xx.x)
Re-Hospitalization	xx (xx.x)	xx (xx.x)
Missing	xx	xx
etc.		
Study Day 15		
Died	xx (xx.x)	xx (xx.x)
Hospitalized in ICU	xx (xx.x)	xx (xx.x)
Initial Hospitalization	xx (xx.x)	xx (xx.x)
Re-Hospitalization	xx (xx.x)	xx (xx.x)
Hospitalized (not ICU)	xx (xx.x)	xx (xx.x)
Initial Hospitalization	xx (xx.x)	xx (xx.x)
Re-Hospitalization	xx (xx.x)	xx (xx.x)
Discharged	xx (xx.x)	xx (xx.x)
Initial Hospitalization	xx (xx.x)	xx (xx.x)
Re-Hospitalization	xx (xx.x)	xx (xx.x)
Missing	xx	xx
Day 29 Contact		
Died	xx (xx.x)	xx (xx.x)
Alive	xx (xx.x)	xx (xx.x)
Missing	xx	xx
Source: Listing 16.x.x.x		

Programming notes: summarize hospitalization status and death on Study Day 3, 5, 7, 15; summarize only death on Day 29. Include missing rows to capture unknown status.

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Table 14.2.2.1

Summary of Kaplan Meier Estimates for Duration of Hospitalization by Treatment

Modified Intent-to-Treat Population

	SOC + Brequinar (N=xx)	**SOC (N=xx)**
Total Patients Discharged	xx	xx
Number of Censored[a]	xx	xx
Not Discharged by Day 15 Visit	xx	xx
Did Not Complete Study	xx	xx
Q1	xx	xx
Median	xx	xx
Q3	xx	xx

Note: Duration of hospitalization is defined as Study Day at time of initial discharge.

a: Subjects who were not discharged by the Day 15 visit will be censored at the Day 15 visit. Subjects who did not complete the trial while still hospitalized will be censored at the date of last contact.

Source: Listing 16.x.x.x

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01
Figure 14.2.2.2
Duration of Hospitalization by Treatment
Modified Intent-to-Treat Population

Note: Duration of hospitalization is defined as the Study Day at time of initial discharge. Subjects who were not discharged by the Day 15 visit will be censored at the Day 15 visit. Subjects who did not complete the trial while still hospitalized will be censored at the date of last contact.

Source: 16.x.x.x

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Table 14.2.3.1

Summary of Kaplan Meier Estimates for Time to Death by Treatment

Modified Intent-to-Treat Population

	SOC + Brequinar (N=xx)	**SOC (N=xx)**
Number of Deaths	xx	xx
Number of Censored[a]	xx	xx
Alive at Day 29 Contact	xx	xx
Unknown	xx	xx
Q1	xx	xx
Median	xx	xx
Q3	xx	xx

a: Subjects who are alive at the Day 29 contact will be censored at the Day 29 contact. Subjects whose Day 29 survival is unknown will be censored at the date of last contact.

Source: Listing 16.x.x.x

Clear Creek Bio., Inc.: Protocol CCB-CRISIS-01
Figure 14.2.3.2
Time to Death by Treatment
Intent-to-Treat Population

Note: Subjects who are alive at the Day 29 contact will be censored at the Day 29 contact. Subjects whose Day 29 survival is unknown will be censored at the date of last contact.
Source: 16.x.x.x

Clear Creek Bio., Inc.: Protocol CCB-CRISIS-01

Table 14.2.4.1

Summary of NEWS2 Scores by Treatment and Visit

Modified Intent-to-Treat Population

Visit	SOC + Brequinar (N=xx)		SOC (N=xx)	
	Visit	**Change from Baseline**	**Visit**	**Change from Baseline**
Baseline				
n	xx		xx	
Mean (SE)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Q1, Q3	xx.x, xx.x		xx.x, xx.x	
Min, Max	xx, xx		xx, xx	
0-4	xx (xx.x)		xx (xx.x)	
5-6	xx (xx.x)		xx (xx.x)	
7 or Higher	xx (xx.x)		xx (xx.x)	
Day 3				
n	xx	xx	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
0-4	xx (xx.x)		xx (xx.x)	
5-6	xx (xx.x)		xx (xx.x)	
7 or Higher	xx (xx.x)		xx (xx.x)	
etc.				
Source: Listing 16.x.x.x				

Programming note: Include Day 3, 5, 7, 15.

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Table 14.2.4.2

Summary of NEWS2 Parameters by Treatment and Visit

Modified Intent-to-Treat Population

	SOC + Brequinar (N=xx)		**SOC (N=xx)**	
Parameter **Visit**	**Visit**	**Change from Baseline**	**Visit**	**Change from Baseline**
Systolic Blood Pressure (mmHg) **Baseline**				
n	xx		xx	
Mean (SE)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Q1, Q3	xx.x, xx.x		xx.x, xx.x	
Min, Max	xx, xx		xx, xx	
Day 3				
n	xx	xx	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
…				
Supplemental Oxygen **Baseline**				
Subject with value	xx		xx	
Yes, [n (%)]	xx (xx.x)		xx (xx.x)	
No, [n (%)]	xx (xx.x)		xx (xx.x)	
…				
Hypercapnic Respiratory Failure **Baseline**				
Subject with value	xx		xx	
Yes, [n (%)]	xx (xx.x)		xx (xx.x)	
No, [n (%)]	xx (xx.x)		xx (xx.x)	
Unknown, [n (%)]	xx (xx.x)		xx (xx.x)	
etc.				

Note: Percentages of Supplemental Oxygen, Hypercapnic Respiratory Failure and Level of Consciousness Alert are based on the Subject with value.

Source: Listing 16.x.x.x

Programming notes: summarize all NEWS2 parameters on Day 3, 5, 7, 15. CFB for Oxygen, Hypercapnic and Alert won't be provided.

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Table 14.2.5

Summary of Change from Baseline in SARS-CoV-2 Viral Load (copies/mL) by Treatment and Visit

Modified Intent-to-Treat Population

Visit	SOC + Brequinar (N=xx)		SOC (N=xx)	
	Visit	**Change from Baseline**	**Visit**	**Change from Baseline**
Baseline				
n	xx		xx	
Mean (SE)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Q1, Q3	xx.x, xx.x		xx.x, xx.x	
Min, Max	xx, xx		xx, xx	
Day 3				
n	xx	xx	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Day 5				
n	xx	xx	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
etc.				
Source: Listing 16.2.x				

Programming note: Include Day 3,5,7,15.

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Table 14.2.6

Summary of Change from Baseline in Inflammatory Markers by Treatment and Visit

Modified Intent-to-Treat Population

	SOC + Brequinar (N=xx)		**SOC (N=xx)**	
Parameter **Visit**	**Visit**	**Change from Baseline**	**Visit**	**Change from Baseline**
Parameter 1 (unit), Normal Range=xx-xx **Baseline**				
n	xx		xx	
Mean (SE)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Q1, Q3	xx.x, xx.x		xx.x, xx.x	
Min, Max	xx, xx		xx, xx	
Day 3				
n	xx	xx	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Day 5				
n	xx	xx	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
etc.				
Parameter 2 (unit), Normal Range=xx-xx **Baseline**				
Source: Listing 16.x.x.x				

Programming note: Include all parameters from local and central labs on Day 3, 5, 7, 15.

Clear Creek Bio., Inc.: Protocol CCB-CRISIS-01

Table 14.2.7

Summary of Change from Baseline in DHO Level (ng/mL) by Treatment and Visit

Intent-to-Treat Population

Visit	SOC + Brequinar (N=xx)		SOC (N=xx)	
	Visit	**Change from Baseline**	**Visit**	**Change from Baseline**
Baseline				
n	xx		xx	
Mean (SE)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Q1, Q3	xx.x, xx.x		xx.x, xx.x	
Min, Max	xx, xx		xx, xx	
Day 3				
n	xx	xx	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Day 5				
n	xx	xx	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
etc.				
Source: Listing 16.x.x.x				

Programming note: Include Day 3, 5, 7, 15.

Clear Creek Bio., Inc.: Protocol CCB-CRISIS-01

Table 14.2.8

Summary of Change from Baseline in Brequinar Concentration Level (mcg/mL)
by Treatment and Visit

Intent-to-Treat Population

Visit	SOC + Brequinar (N=xx)		SOC (N=xx)	
	Visit	**Change from Baseline**	**Visit**	**Change from Baseline**
Baseline				
n	xx		xx	
Mean (SE)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Q1, Q3	xx.x, xx.x		xx.x, xx.x	
Min, Max	xx, xx		xx, xx	
Day 3				
n	xx	xx	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Day 5				
n	xx	xx	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Day 7				
n	xx	xx	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Source: Listing 16.x.x.x				

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Table 14.3.1.1

Overall Summary of Treatment-Emergent Adverse Events by Treatment

Modified Intent-to-Treat Population

	SOC + Brequinar (N=xx) n (%)	**SOC (N=xx) n (%)**	**Total (N=xx) n (%)**
Subjects with 1 or more TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with 1 or more treatment-related[a] TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with 1 or more Grade 3 or above TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with 1 or more TEAE leading to drug withdrawn	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with 1 or more TEAE leading to study discontinuation	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with 1 or more serious TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with fatal TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with TEAE of interest	xx (xx.x)	xx (xx.x)	xx (xx.x)
Total number of TEAEs	xx	xx	xx
Total number of study drug-related[a] TEAEs	xx	xx	xx
Total number of Grade 3 or above TEAEs	xx	xx	xx
Total number of TEAEs leading to drug withdrawn	xx	xx	xx
Total number of TEAEs leading to study discontinuation	xx	xx	xx
Total number of serious TEAEs	xx	xx	xx
Total number of TEAEs of interest	xx	xx	xx

a: Includes possible, probable and definite.
Source: Listing 16.X.X.X

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Table 14.3.1.2

Summary of Treatment-Emergent Adverse Events by Treatment

Modified Intent-to-Treat Population

System Organ Class Preferred Term	SOC + Brequinar (N=xx)		SOC (N=xx)		Total (N=xx)	
	Subjects[a] n (%)	Events n	Subjects[a] n (%)	Events n	Subjects[a] n (%)	Events n
Any Adverse Event						
Overall	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SOC 1						
Overall	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term 3	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
SOC 1						
Overall	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term 1	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term 2	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
Preferred Term 3	xx (xx.x)	xx	xx (xx.x)	xx	xx (xx.x)	xx
etc.						

a: Subjects experiencing one or more TEAEs are counted only once for each adverse event term.
Source: Listing 16.X.X.X

Programming note: Sort SOCs in descending frequency using total number of subjects in the SOC + Brequinar group, then sort preferred terms in descending frequency. Sort alphabetically to break ties.

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Table 14.3.1.7

Summary of Treatment-Emergent Adverse Events by Severity and Treatment

Modified Intent-to-Treat Population

System Organ Class Preferred Term	SOC + Brequinar (N=xx)						SOC (N=xx)					
	Subjects[a] n (%)	Grade 1[b] n	Grade 2[b] n	Grade 3[b] n	Grade 4[b] n	Grade 5[b] n	Subjects[a] n (%)	Grade 1[b] n	Grade 2[b] n	Grade 3[b] n	Grade 4[b] n	Grade 5[b] n
Overall												
Overall	xx (xx.x)	xx	xx	xx	xx	xx	xx (xx.x)	xx	xx	xx	xx	xx
SOC1												
Preferred Term 1	xx (xx.x)	xx	xx	xx	xx	xx	xx (xx.x)	xx	xx	xx	xx	xx
Preferred Term 2	xx (xx.x)	xx	xx	xx	xx	xx	xx (xx.x)	xx	xx	xx	xx	xx
Preferred Term 3	xx (xx.x)	xx	xx	xx	xx	xx	xx (xx.x)	xx	xx	xx	xx	xx

a: Subjects experiencing one or more TEAEs are counted only once for each adverse event term.
b: Subjects experiencing one or more TEAEs are counted only once for each adverse event term and counted only by the maximum severity.
Source: Listing 16.X.X.X

Programming note: Sort SOCs in descending frequency using total number of subjects in the SOC + Brequinar group, then sort preferred terms in descending frequency. Sort alphabetically to break ties.

Clear Creek Bio., Inc.: Protocol CCB-CRISIS-01

Table 14.3.2

Summary of Change from Baseline in Laboratory Parameters of Special Interest by Treatment and Visit

Modified Intent-to-Treat Population

	SOC + Brequinar (N=xx)		**SOC (N=xx)**	
Parameter **Visit**	**Visit**	**Change from Baseline**	**Visit**	**Change from Baseline**
Parameter 1 (unit) **Baseline**				
n	xx		xx	
Mean (SE)	xx.x (xx.xx)		xx.x (xx.xx)	
Median	xx.x		xx.x	
Q1, Q3	xx.x, xx.x		xx.x, xx.x	
Min, Max	xx, xx		xx, xx	
Day 2				
n	xx	xx	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
Day 3				
n	xx	xx	xx	xx
Mean (SE)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
etc.				
Parameter 2 (unit) **Baseline**				
Source: Listing 16.x.x.x				

Programming note: Include selected lab parameters: AST, ALT, ALP, Total Bilirubin, Creatinine, Hemoglobin, WBC, Absolute Neutrophils, Absolute

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Listing 16.2.1

Listing of End of Study Status by Treatment

Site-Subject	Date of Last Contact	Did the patient complete the study?	Primary Reason Did Not Complete	Comments
SOC + Brequinar				
xx-xxxx	9999-99-99	Yes		
xx-xxxx	9999-99-99	Yes		xxxxxxxxxxxxxx
SOC				
xx-xxxx	9999-99-99	No	xxxxxxxxxxxxxx	xxxxxxxxxxxxxx
xx-xxxx	9999-99-99	Yes		

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Listing 16.2.2

Listing of Inclusion/Exclusion Criteria and Randomization

Site-Subject	Does the subject meet all the Inclusion/Exclusion criteria?	Criterion Not Met	Comment / Explain Reason for Ineligibility	Date of Randomization	Time of Randomization	Treatment Assignment	ICU Level of Care at Randomization
xx-xxxx	Yes			9999-99-99	99:99	SOC	No
xx-xxxx	No	Exclusion 2 Inclusion 1	xxxxxxxxxxx xxxxxxxxxxx				Yes
xx-xxxx	Yes			9999-99-99	99:99	SOC + Brequinar	No
xx-xxxx	No	Inclusion 3	xxxxxxxxxxx				No
xx-xxxx	Yes			9999-99-99	99:99	SOC + Brequinar	Yes
xx-xxxx	Yes			9999-99-99	99:99	SOC	No

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Listing 16.2.3

Listing of Informed Consent and Study Populations by Treatment

Site-Subject	Date of Informed Consent	Time of Informed Consent	Modified Intent-to-Treat Population[a]
SOC + Brequinar			
xx-xxxx	9999-99-99	99:99	Yes
xx-xxxx	9999-99-99	99:99	Yes
xx-xxxx	9999-99-99	99:99	Yes
SOC			
xx-xxxx	9999-99-99	99:99	xxx
xx-xxxx	9999-99-99	99:99	xxx
xx-xxxx	9999-99-99	99:99	xxx

a: Modified Intent-to-Treat (mITT) population includes all randomized subjects who had at least one post-randomization assessment, and who received at least one dose of study medication if randomized to SOC + Brequinar group.

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Listing 16.2.4.1

Listing of Subject Demographics by Treatment

Site-Subject	Date of Birth	Age (years)	Sex	Ethnicity	Race	Height (unit)	Weight (unit)	BSA (m2)
SOC + Brequinar								
xx-xxxx	9999-99-99	xx	Male	xxxxxxxxxxxxx	xxxxxxxxxxxxx	xxx (in)	xxx (lb)	x.x
xx-xxxx	9999-99-99	xx	Female	xxxxxxxxxxxxx	xxxxxxxxxxxxx	xxx (cm)	Not Done	
xx-xxxx	9999-99-99	xx	Male	xxxxxxxxxxxxx	Other: xxxxxxxxxxxxx	Not Done	xxx (kg)	
SOC								
xx-xxxx	9999-99-99	xx	xxxxx	xxxxxxxxxxxxx	xxxxxxxxxxxxx	xxxx	xxxx	x.x
xx-xxxx	9999-99-99	xx	xxxxx	xxxxxxxxxxxxx	xxxxxxxxxxxxx	xxxx	xxxx	x.x
xx-xxxx	9999-99-99	xx	xxxxx	xxxxxxxxxxxxx	Other: xxxxxxxxxxxxx	xxxx	xxxx	x.x

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Listing 16.2.4.2

Listing of Medical History by Treatment

Site-Subject	Diagnosis and/or Procedure	System Organ Class / Preferred Term	Onset Date	Resolution Date (Ongoing)
SOC + Brequinar				
xx-xxxx	COVD-19	xxxxxxxxxxx / xxxxxxxxxxx	9999-99-99	Ongoing
	xxxxxxxxxxx	xxxxxxxxxxx / xxxxxxxxxxx	9999-99-99	9999-99-99
xx-xxxx	COVD-19			
SOC				
xx-xxxx	COVD-19	xxxxxxxxxxx / xxxxxxxxxxx	9999-99-99	Ongoing
	xxxxxxxxxxx	xxxxxxxxxxx / xxxxxxxxxxx	9999-99-99	9999-99-99
	xxxxxxxxxxx	xxxxxxxxxxx / xxxxxxxxxxx	9999-99-99	9999-99-99
xx-xxxx	COVD-19	xxxxxxxxxxx / xxxxxxxxxxx	9999-99-99	Ongoing

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Listing 16.2.4.3

Listing of Prior and Concomitant Medications by Treatment

Site-Subject	M: Medication or Treatment[a] P: Pharmacological Subgroup C: Coded Term	Indication	Start Date	Stop Date (Ongoing)	Dose	Unit	Route	Prior/ Con[a]
SOC + Brequinar								
xx-xxxx	M: xxxxxxxxxxx P: xxxxxxxxxxx C: xxxxxxxxxxx	xxxxxxx	9999-99-99	9999-99-99	xxx	xxx	xxxxx	P
xx-xxxx	M: xxxxxxxxxxx* P: xxxxxxxxxxx C: xxxxxxxxxxx	xxxxxxx	9999-99-99	Ongoing	xxx	xxx	Other: xxxxx	P, C
	M: xxxxxxxxxxx P: xxxxxxxxxxx C: xxxxxxxxxxx	xxxxxxx	9999-99-99	9999-99-99	xxx	xxx	xxxxx	C
SOC								
xx-xxxx	None							
xx-xxxx	M: xxxxxxxxxxx* P: xxxxxxxxxxx C: xxxxxxxxxxx	xxxxxxx	9999-99-99	Ongoing	xxx	Other: xxx	xxxxx	C

a: P=Prior medication, C=Concomitant medication. A prior medication is any medication that started prior to date of randomization. A concomitant medication is any medication that either has a start date on or after date of randomization, or is ongoing on the date of randomization.

Programming Note: Pharmacological Subgroup comes from ATC3. If ATC3 is not available, use ATC2.

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Listing 16.2.4.4

Listing of Prior and Concomitant Procedures by Treatment

Site-Subject	P: Procedure S: System Organ Class T: Preferred Term	Indication	Start Date	Stop Date (Ongoing)	Dose	Unit	Route	Prior/ Con[a]
SOC + Brequinar								
xx-xxxx	P: xxxxxxxxxxx S: xxxxxxxxxxx T: xxxxxxxxxxx	xxxxxxx	9999-99-99	9999-99-99	xxx	xxx	xxxxx	P
xx-xxxx	P: xxxxxxxxxxx S: xxxxxxxxxxx T: xxxxxxxxxxx	xxxxxxx	9999-99-99	Ongoing	xxx	xxx	Other: xxxxx	P, C
	P: xxxxxxxxxxx S: xxxxxxxxxxx T: xxxxxxxxxxx	xxxxxxx	9999-99-99	9999-99-99	xxx	xxx	xxxxx	C
SOC								
xx-xxxx	None							
xx-xxxx	P: xxxxxxxxxxx S: xxxxxxxxxxx T: xxxxxxxxxxx	xxxxxxx	9999-99-99	Ongoing	xxx	Other: xxx	xxxxx	C

a: P=Prior procedure, C=Concomitant procedure. A prior procedure is any procedure that started prior to date of randomization. A concomitant procedure is any procedure that either has a start date on or after date of randomization, or is ongoing on the date of randomization.

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Listing 16.2.5.1

Listing of Dosing Information (SOC + Brequinar Only)

Site-Subject	Day 1		Day 2		Day 3		Day 4		Day 5	
	Date of Dosing	Time of Dosing	Date of Dosing	Time of Dosing	Date of Dosing	Time of Dosing	Date of Dosing	Time of Dosing	Date of Dosing	Time of Dosing
xx-xxxx	9999-99-99	99:99	Not Done		9999-99-99	99:99	9999-99-99	99:99	9999-99-99	99:99
xx-xxxx	9999-99-99	99:99	9999-99-99	99:99	9999-99-99	99:99	9999-99-99	99:99	9999-99-99	99:99
xx-xxxx	9999-99-99	99:99	9999-99-99	99:99	9999-99-99	99:99	9999-99-99	99:99	Not Done	
xx-xxxx	Not Done		9999-99-99	99:99	9999-99-99	99:99	9999-99-99	99:99	9999-99-99	99:99

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Listing 16.2.5.2

Listing of PK/DHO Results by Treatment

Site-Subject	Visit	Not Done	Date Collected	Time Collected	PK Result (mcg/mL)[a]	DHO Result (ng/mL)[a]
SOC + Brequinar						
xx-xxxx	Day 1		9999-99-99	99:99	xxx	xxxx
	Day 3		9999-99-99	99:99	xxx	xxxx
	Day 5	Not Done				
	Day 7		9999-99-99	99:99	xxx	xxxx
	Day 15		9999-99-99	99:99	xxx	xxxx
SOC						
xx-xxxx	Day 1		9999-99-99	99:99	BLOQ (<5)	xxxx
	Day 3		9999-99-99	99:99	xxx	xxxx
	Day 5		9999-99-99	99:99	xxx	xxxx
	Day 7		9999-99-99	99:99	xxx	BLOQ (<5)
	Day 15		9999-99-99	99:99	xxx	xxxx

a: BLOQ = Below Limit of Quantification (limit of quantification in parentheses)

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Listing 16.2.6.1

Listing of NEWS2 Assessments by Treatment

Site-Subject	Visit	Date and Time Collected	SBP[a] (mmHg)	DBP[a] (mmHg)	Pulse (Beats/Min.)	Respiration (Breath/ Min.)	SpO_2 / SaO_2 (%)	Temp. (Celsius)	Supplemental Oxygen?	Hypercapnic respiratory failure?	Alert?	NEWS 2 Score
SOC + Brequinar												
xx-xxxx	Day 1	9999-99-99T99:99	xxx	xxx	ND	xxx	xxx	xx.x	Yes	Yes	Yes	xx
	Day 3	9999-99-99T99:99	xxx	xxx	xxx	xxx	xxx	xx.x	Yes	No	No	xx
	Day 5	9999-99-99T99:99	xxx	xxx	xxx	xxx	ND	xx.x	No	Yes	No	xx
	Day 7	Not Done										
	Day 15	9999-99-99T99:99	xxx	xxx	xxx	xxx	xxx	xx.x	No	Unknown	Yes	xx
SOC												
xx-xxxx	Day 1	9999-99-99T99:99	xxx	xxx	xxx	ND	xxx	xx.x	xxx	xxx	xxx	xx
	Day 3	9999-99-99T99:99	xxx	xxx	xxx	xxx	xxx	ND	xxx	xxx	xxx	xx
	Unscheduled											
	Day 5	9999-99-99T99:99	xxx	xxx	xxx	xxx	xxx	xx.x	xxx	xxx	xxx	xx
	Day 7	9999-99-99T99:99	ND	ND	xxx	xxx	xxx	xx.x	xxx	xxx	xxx	xx
	Day 15	9999-99-99T99:99	xxx	xxx	xxx			xx.x	xxx	xxx	xxx	xx

Note: ND=Not Done

a: SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure.

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Listing 16.2.6.2

Listing of Inflammatory Markers by Treatment

Parameter	Visit	Not Done	Laboratory	Date and Time Collected	Result	Abnormal?	Reference Range
SOC + Brequinar **Site-Subject= xx-xxxx**							
Parameter 1 (unit)	Day 1		Local	9999-99-99T99:99	xx.x	High	
	Day 3		Local	9999-99-99T99:99	xx.x	High	
	Day 5		Central	9999-99-99T99:99	xx.x		
	Day 7	Not Done					
	Day 15		Local	9999-99-99T99:99	xx.x		
Parameter 2 (unit)	Day 1		Local	9999-99-99T99:99	xx.x	Abnormal	
	Day 3		Local	9999-99-99T99:99	xx.x		
	Unscheduled		Local	9999-99-99T99:99	xx.x		
	Day 5		Local	9999-99-99T99:99	xx.x		
	Day 7	Not Done					
	Day 15		Local	9999-99-99T99:99	xx.x		
SOC **Site-Subject= xx-xxxx**							
Parameter 1 (unit)	Day 1		Central	9999-99-99T99:99	xx.x		
	Day 3		Central	9999-99-99T99:99	xx.x		
	Day 5		Central	9999-99-99T99:99	xx.x		
	Day 7		Central	9999-99-99T99:99	xx.x		
	Day 15		Central	9999-99-99T99:99	xx.x		

Programming note: Include all data collected in local and central labs, including the tests done in both labs or done multiple times.

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01
Listing 16.2.6.3
Listing of SARS-CoV-2 Viral Load and Viral Cultureunit by Treatment

Site-Subject	Visit	Not Done	Date Collected	Time Collected	Viral Load (copies/mL)	Viral Culture (unit)
SOC + Brequinar						
xx-xxxx	Day 1		9999-99-99	99:99		
	Day 3		9999-99-99	99:99		
	Day 5	Not Done				
	Day 7		9999-99-99	99:99		
	Day 15		9999-99-99	99:99		
SOC						
xx-xxxx	Day 1		9999-99-99	99:99		
	Day 3		9999-99-99	99:99		
	Day 5		9999-99-99	99:99		
	Day 7		9999-99-99	99:99		
	Day 15		9999-99-99	99:99		

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Listing 16.2.6.4

Listing of Hospitalization Log by Treatment

Site-Subject	Event Type	Event Date
SOC + Brequinar		
xx-xxxx	xxxxxxxxxxxx	9999-99-99
xx-xxxx	xxxxxxxxxxxx	9999-99-99
	Other: xxxxxxxxxxxx	9999-99-99
	xxxxxxxxxxxx	
SOC		
xx-xxxx	None	
xx-xxxx	Other: xxxxxxxxxxxx	9999-99-99
	xxxxxxxxxxxx	

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Listing 16.2.6.5

Listing of Survival Status by Treatment

Site-Subject	Visit	Date of Contact	Survival Status	Date of Death	Not Done, Comment
SOC + Brequinar					
xx-xxxx	Day 1 – Day 15		Alive		
	Day 29 Contact	9999-99-99	Alive		
xx-xxxx	Day 1 – Day 15		Patient Died	9999-99-99	
xx-xxxx	Day 1 – Day 15		Alive		
	Day 29 Contact				Not Done: xxxxxxxxxxxxxxx
SOC					
xx-xxxx	Day 1 – Day 15		Alive		
	Day 29 Contact	9999-99-99	Patient Died	9999-99-99	
xx-xxxx	Day 1 – Day 15		Alive		
	Day 29 Contact	9999-99-99	Alive		

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Listing 16.2.7.1

Listing of Adverse Events by Treatment

Site-Subject	Adverse Event Term/ System Organ Class/ Preferred Term	Onset Date and Time/ Resolution Date and Time	Continuing?	Outcome[a]	Severity	Causality	Action Taken with Study Treatment	Action Taken	Serious?
SOC + Brequinar									
xx-xxxx	xxxxxxx/ xxxxxxx / xxxxxxx*	9999-99-99T99:99/ 9999-99-99T99:99	Continuous	RG	Grade 2	Definite	Drug Interrupted	None	No
xx-xxxx	xxxxxxx/ xxxxxxx / xxxxxxx	9999-99-99T99:99/ 9999-99-99T99:99	Intermittent	RD	Grade 4	Probable	Drug Withdrawn	Treatment Prescribed	No
	xxxxxxx/ xxxxxxx / xxxxxxx	9999-99-99T99:99/ 9999-99-99T99:99	Continuous	RS	Grade 1	Possible	Unknown	Discontinued Study	No
SOC									
xx-xxxx	xxxxxxx/ xxxxxxx / xxxxxxx	9999-99-99T99:99/ 9999-99-99T99:99	Intermittent	NR	Grade 5	Unlikely	Not Applicable	Treatment Prescribed, Discontinued Study	Yes
	xxxxxxx/ xxxxxxx / xxxxxxx	9999-99-99T99:99/ 9999-99-99T99:99	Continuous	UN	Grade 3	Unrelated	Dose Not Changed	None	No
xx-xxxx	None								

* Not Treatment-Emergent (onset date is prior to the day of randomization

a: FA=Fatal, NR=Not Recovered/Not Resolved, RD=Recovered/Resolved, RS=Recovered/Resolved with Sequelae, RG=Recovering/Resolving, UN=Unknown.

Clear Creek Bio, Inc.: Protocol CCB-CRISIS-01

Listing 16.2.8.1.1

Listing of Chemistry Laboratory Tests by Treatment

Parameter	Visit	Not Done	Date and Time Collected	Lab Name	Result	Abnormal?	CTCAE Grade[a]	Reference Range
SOC + Brequinar **Site-Subject= xx-xxxx**								
Parameter 1 (unit)	Day 1		9999-99-99T99:99	xxx	xx.x	High	2	xx.x-xx.x
	Day 2		9999-99-99T99:99	xxx	xx.x	High	2	xx.x-xx.x
	Day 3		9999-99-99T99:99	xxx	xx.x	High	2	xx.x-xx.x
	Day 4		9999-99-99T99:99	xxx	xx.x		0	xx.x-xx.x
	Day 5		9999-99-99T99:99	xxx	xx.x		0	xx.x-xx.x
	Day 6		9999-99-99T99:99	xxx	xx.x		0	xx.x-xx.x
	Day 7		9999-99-99T99:99	Other: xxx	xx.x		0	xx.x-xx.x
	Day 15		9999-99-99T99:99	Other: xxx	xx.x		0	xx.x-xx.x
Parameter 2 (unit)	Day 1		9999-99-99T99:99	xxx	xx.x	Abnormal		xx.x-xx.x
	Day …		9999-99-99T99:99	xxx	xx.x			xx.x-xx.x
SOC **Site-Subject= xx-xxxx**								
Parameter 1 (unit)	Day 1		9999-99-99T99:99	xxx	xx.x		0	xx.x-xx.x
	Day 2		9999-99-99T99:99	xxx	xx.x		0	xx.x-xx.x
	Day 3		9999-99-99T99:99	xxx	xx.x		0	xx.x-xx.x
	Day 4		9999-99-99T99:99	xxx	xx.x		0	xx.x-xx.x
	Day 5	Not Done					0	
	Day 6		9999-99-99T99:99	xxx	xx.x		0	xx.x-xx.x
	Day 7		9999-99-99T99:99	xxx	xx.x	Low	1	xx.x-xx.x
	Day 15		9999-99-99T99:99	Other: xxx	xx.x	Low	1	xx.x-xx.x

a: Grades were derived using CTCAE criteria where applicable. Grade 0 was assigned for values that did not meet a CTCAE criteria.

Certificate Of Completion

Envelope Id: EF97B78FA0BD4089A86DE8A58A8ED301 Status: Completed

Subject: Please DocuSign: CCB-CRISIS-01 SAP v1.0 2020-12-17.docx, CCB-CRISIS-01 Mocks v1.0 2020-12-17.docx

Source Envelope:

Document Pages: 60 Signatures: 6 Envelope Originator:

Certificate Pages: 5 Initials: 0 Diane Tipping

AutoNav: Enabled 996 Old Eagle School Rd

EnvelopeId Stamping: Disabled Suite 1106

Time Zone: (UTC-05:00) Eastern Time (US & Canada) Wayne, PA 19087

d.tipping@prosoftclinical.com

IP Address: 100.19.112.47

Record Tracking

Status: Original Holder: Diane Tipping Location: DocuSign

12/17/2020 4:25:00 PM d.tipping@prosoftclinical.com

Signer Events	Signature	Timestamp
Daisy Chen D.Chen@prosoftclinical.com Manager, Biostatistics Qiuxu (Daisy) Chen Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 2B3FFE95-115C-431E-B126-300C7C7DAC74 Using IP Address: 69.136.93.119 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I have reviewed this document I have reviewed this document	Sent: 12/17/2020 4:28:47 PM Viewed: 12/17/2020 4:29:53 PM Signed: 12/17/2020 4:31:12 PM
Electronic Record and Signature Disclosure: Accepted: 5/22/2020 3:01:14 PM ID: edc55d18-a3ea-4040-9c52-2ba801cd124a		
Diane Tipping d.tipping@prosoftclinical.com VP Biostatistics Prosoft Clinical Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 92A2CD2F-7756-4D0E-959E-82FB02359B17 Using IP Address: 100.19.112.47 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document I approve this document	Sent: 12/17/2020 4:31:15 PM Viewed: 12/17/2020 4:32:21 PM Signed: 12/17/2020 4:34:09 PM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
Barbara Powers bpowers@clearcreekbio.com Security Level: Email, Account Authentication (Required)	Barbara Powers Signature Adoption: Pre-selected Style Signature ID: 57DEAAD1-7C22-40FE-A72C-57ABA124E827 Using IP Address: 173.44.85.49 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document I approve this document	Sent: 12/17/2020 4:34:13 PM Viewed: 12/17/2020 4:39:43 PM Signed: 12/17/2020 4:40:11 PM
Electronic Record and Signature Disclosure: Accepted: 12/17/2020 4:39:43 PM ID: 602703f1-c8af-4241-a59c-3ddd3fb840e0		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	12/17/2020 4:28:47 PM
Certified Delivered	Security Checked	12/17/2020 4:39:43 PM
Signing Complete	Security Checked	12/17/2020 4:40:11 PM
Completed	Security Checked	12/17/2020 4:40:11 PM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, Prosoft Clinical (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact Prosoft Clinical:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: t.sammartino@prosoftclinical.com

To advise Prosoft Clinical of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at t.sammartino@prosoftclinical.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from Prosoft Clinical

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to t.sammartino@prosoftclinical.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with Prosoft Clinical

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to t.sammartino@prosoftclinical.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify Prosoft Clinical as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by Prosoft Clinical during the course of your relationship with Prosoft Clinical.