Statistical Analysis Plan

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

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CCB-CRISIS-02

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Glossary of Abbreviations

Abbreviation	Term
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
COVID-19	Coronavirus-19 infection
CRF	Case report form
DMC	Data Monitoring Committee
eCRF	Electronic case report form
ITT	Intent-to-treat
LLOQ	Lower limit of quantification
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
MES	Microbiology Evaluable Set
MMRM	Mixed model for repeated measures
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis System
SD	Standard Deviation
SI	International System of Units
SOC	Standard of care
SOC	System Organ Class
SpO_2	Peripheral capillary oxygen saturation
TFLs	Tables, Figures and Listings
WHO	World Health Organization

STATISTICAL ANALYSIS PLAN AMENDMENT 1

This section is not required at this time, but will be populated in a future approved version of this document.

1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	01-Oct-2020	4.0
CRF	21-Oct-2020	PROD 2.00

2. Protocol Details

2.1 Study Objectives

Primary Objective:

To demonstrate a change from baseline in quantitative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load for brequinar-treated subjects compared to placebo-treated subjects through Day 29.

Secondary Objectives:

Through Day 29:

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

Exploratory Objectives:

Through Day 29:

- To determine time to viral clearance (two consecutive undetectable tests);
- To determine time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline;
- To determine time to clinical improvement as measured by a favorable shift in the WHO Ordinal Scale score for the subset of subjects with baseline WHO Ordinal Scale of 2 or 3 for brequinar subjects compared to subjects who received placebo.

2.2 Overall Study Design

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

Subjects will have a Screening Visit followed as soon as possible with Study Day 1. Study procedures are presented in detail in the Schedule of Events (Table 1). Study visits (virtual or in person) will take place at Screening and on Study Days 1 - 8, 12, 15, 22, and 29. The visits that include bloodwork must be conducted at the study site or arrangements made for sample collection at the subject's home or other appropriate location. Other visits/visit activities for that visit may be conducted remotely using telephone, telemedicine or other remote technique. Subjects are to self-collect a viral load sample, obtain their respiratory rate, heart rate, body temperature and peripheral capillary oxygen saturation (SpO_2), and complete a symptom assessment checklist with the site via telemedicine on Days 1, 4, 8, 12, 15, 22, and 29. The site will also have a telephone call with the subject on Study Days 2, 3, 5, 6, and 7 for changes in concomitant medications and assessment of adverse events, especially those that may indicate thrombocytopenia and mucositis. A home health nurse will visit the subject at Screening and on study Days 1, 8, 15, and 29. Telemedicine only visits will be conducted by site staff on study Days 4, 12, and 22.

Table 1 CCB-CRISIS-02 Schedule of Events

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

[a]Do not repeat if within 48h of Day 1 visit. Send to Covance Central Laboratory Services (CCLS) for analysis.
[b]Vital signs include heart rate, respiratory rate, body temperature, and SpO_2. Subject will be provided with a thermometer and pulse oximeter with heart rate monitoring capability. Training will be provided during the first visit by the home health nurse. Vital signs parameters will be observed and recorded by study staff via telemedicine or during a visit by the home health nurse.
[c]Symptom Assessment will use a checklist provided to the subject with symptoms such as sore throat, cough, GI symptoms (vomiting, diarrhea), anosmia, dysgeusia, other (specify), etc. Severity None, Mild, Moderate, or Severe will be collected.
[d] RT-PCR at Screening may be performed by the site if the subject cannot provide documentation of a positive SARS-CoV-2 result. Samples collected after Screening will be saliva samples sent for viral load analysis. Day 1 sample must be obtained prior to dosing. Viral load specimens after Screening will be saliva samples self-collected by the subject using an Omnigene® collection system or similar. The home health nurse will train the subject and observe sample collection on Day 1. These samples are to be sent to CCLS for analysis. The viral load sample may also be used to perform viral cultures (sample can be split by the central laboratory, no additional sample required).
[e]Subject will self-administer study drug once daily Days 1 – 5 and record doses in a medication diary. Note that any visits/visit activities may be conducted via telephone, telemedicine, or digital media other than serum pregnancy test and chemistry/hematology sample collection. These labs may be collected at the clinical site or another designated out-patient facility/laboratory or collected via home visit. Arrangements for shipping viral load samples will be made by the study team.
[f]HH = Home Health in-person visit; TC = Telephone Call with site and subject; TM = Telemedicine with site and subject.

2.3 Sample Size and Power

Formal sample size calculations are not applicable for this proof-of-concept study. The sample size of approximately 100 subjects planned to be entered in this trial is expected to be adequate to provide safety and efficacy information to advise future study design. Subjects who meet all of the inclusion and none of the exclusion criteria will be enrolled in the study until approximately 100 subjects have completed the study.

2.4 Randomization

The trial will be conducted in double blinded, randomized manner with random assignment to standard of care plus brequinar or standard of care plus placebo in a 1:1 ratio at each site. The brequinar and placebo capsules will be provided to each participating institution in pre-numbered bottles intended for individual subjects to be dispensed by the institution's pharmacist or designated person. Randomization assignments will be provided by an independent statistician at Prosoft Clinical to the drug packaging company. The pharmacist/designated person will dispense the next number in sequence to the next patient who qualifies for the study at an individual site.

3. Efficacy and Safety Variables

3.1 Primary Efficacy Endpoint

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

3.2 Secondary Efficacy and Clinical Endpoints

Through Day 29:

- Duration of viral shedding;
- Percentage of subjects requiring admission as an inpatient for >24 hours;
- All-cause mortality.

3.3 Exploratory Efficacy and Clinical Endpoints

Through Day 29:

- Time to viral clearance (two consecutive undetectable tests);
- Viral culture through Day 29;
- Time to resolution of new onset COVID-19-related clinical symptoms and pre-existing non-COVID-19 symptoms returned to baseline;

- Time to clinical improvement measured by a favorable shift in WHO Ordinal Scale score for the subset of subjects with baseline WHO Ordinal Scale of 2 or 3.

3.4 Safety Variables

- Rates of AEs and SAEs;
- Laboratory assessments through Day 29;
- Vital signs through Day 29.

4. Pharmacokinetic/Pharmacodynamic variables

Not applicable.

5. Analysis populations

5.1 Screened

All subjects who consent to participate and who undergo screening will be included in the Screened population.

5.2 Safety Analysis Set

The Safety Analysis Set (Safety) will consist of all subjects who received at least one dose of study drug. Safety analysis subjects are analyzed according to their actual treatment received.

5.3 Intent-to-treat Set

The Intent-to-treat Set (ITT) will consist of all randomized subjects. ITT subjects are analyzed according to their randomized treatment.

5.4 Microbiology Evaluable Set

The Microbiology Evaluable Set (MES) will consist of all randomized subjects with detectable SARS-CoV-2 viral load at baseline and at least one non-missing post-baseline viral load assessment. Microbiology evaluable subjects are analyzed according to their randomized treatment.

5.5 Per Protocol Set

Not applicable.

6. Data Handling

6.1 Time points and Visit Windows

Day 1 is defined as the day of first dose of study drug. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

All data will be analyzed using nominal study visits as defined in the Study Schedule and eCRF. No visit windows will be applied for summary and analysis.

6.2 Handling of Dropouts, Missing Data, and Outliers

A subject may withdraw from the study at any time for any reason. The Sponsor or Investigator may also terminate a subject's study participation after discussion with the other party if it is believed it would be unsafe for the subject to continue in the study. All scheduled evaluations will be collected/conducted even for subjects who discontinue study medication prior to completing the treatment period unless consent is withdrawn.

Missing efficacy data will not be imputed except for the automatic imputation done by the statistical modeling. Viral load values of the form of "<x" (i.e. below the lower limit of quantification) will be imputed as "x" in the analysis of viral load changes but displayed as "<x" in the listing.

Missing safety data will generally not be imputed. However, laboratory values of the form of "<x" (i.e. below the lower limit of quantification) or ">x" (i.e. above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings. Additionally, AEs that have missing causality (after data querying) will be assumed to be related to study drug.

If start date of a prior/concomitant medication is partially missing, impute as follows:

- If both Month and Day are missing, then set to January 1
- If only Day is missing, then set to the first day of the month

If end date of a prior/concomitant medication is partially missing, impute as follows:

- If both Month and Day are missing, then set to December 31
- If only Day is missing, then set to last day of the month

If start date and/or end date of a prior/concomitant medication is completely missing, do not impute.

Listings will present the actual partial dates; imputed dates will not be shown.

No rules for outlier detection are planned.

7. Statistical Methods

7.1 General Principles

All data processing, summarization and analyses will be performed using Covance's SAS Environment / Version 9.3 (or later) of the SAS® statistical software package.

The following principles will be applied to all tables, figures, and listings (TFLs) unless otherwise stated:

Principle	Value
Significant tests	Two-sided and use a 5% significance.
Treatment group labels and order presented	SOC + Brequinar 100 mg SOC + Placebo
Tables	Data in summary tables presented by treatment group, assessment and visit (where applicable), unless otherwise specified.
Listings	All data collected presented by treatment group, site, subject, assessment and visit (where applicable), unless otherwise specified.
Descriptive summary statistics for continuous variables	Number of subjects/observations (N), mean, standard deviation (SD), median and range.
Descriptive summary statistics for categorical variables	Frequency counts and percentages [n (%)]
Denominator for percentages	Number of subjects in the analysis population, unless stated otherwise in table shell(s)
Include "Missing" as category	Yes, when the number missing is greater than zero for at least one treatment group.
Display for 0 percentages	Blank
Display to one more decimal place than collected value	Mean Standard Error Mean Difference Median
Display to two more decimal places than collected value	Standard Deviation Confidence Interval
Limit of precision for displays	3 decimal places
Date Format	DDMMMYYYY
Dictionary names and versions	The dictionary names and versions will be included in a footnote in all AE, medical history, prior and concomitant medication TFLs that present coded terms from the dictionaries.

Time to event or duration of event endpoints will be based on the actual date rather than Visit Day.

7.2 Subject Disposition and Data Sets Analyzed

Subject disposition will be listed and summarized by treatment group and overall and will include the number and percentage of subjects:

- screened;
- randomized;
- randomized and not treated;
- treated;
- included in each analysis population (ITT, MES, Safety).

In addition, the number and percentage of subjects who complete the study and who discontinue early, including a breakdown of the primary reasons for discontinuation, will be presented for ITT population.

A summary of subject enrollment by site will also be provided.

A summary of the reasons for screen failure as well as the number of subjects screened but not randomized will be produced. No other information for screen failures will be presented.

7.3 Protocol Deviations

Protocol deviation management process, including project specific protocol deviations list, deviation detection, management and escalation, and review of protocol deviations, is defined in the Protocol Deviation Management Plan. Protocol deviations will be identified before data are unblinded. All protocol deviations will be listed. Important protocol deviations will be summarized by treatment group for the ITT population.

7.4 Demographics and Other Baseline Characteristics

Demographics will be listed and summarized by treatment group and overall for the ITT population. Standard descriptive statistics will be presented for the continuous variables of:

- age (years) [calculated as (year of informed consent – year of birth) if age is not recorded on the eCRF];
- weight (kg);
- height (cm);
- body mass index (kg/m^2) [calculated as ($weight/height^2$) where weight is in kg and height is in m].

The total counts and percentages of subjects will be presented for the categorical variables of:

- age group (years) (grouped as <65, ≥65);
- gender;
- race;
- ethnicity.

In addition, baseline characteristics collected prior to the first dose of study drug will be listed and summarized by treatment group and overall for the ITT population. Standard descriptive statistics will be presented for the continuous variables of:

- temperature (^{0}C);
- oxygen saturation, SpO_2 (%);
- respiratory rate (breaths/min).

The total counts and percentages of subjects will be presented for the categorical variables of:

- SARS-CoV-2 viral load (detectable, undetectable);
- COVID-19 symptom type;
- WHO Ordinal Scale.

No formal tests of statistical significance will be performed on the demographic and baseline data.

Other baseline measurements, such as vital signs, laboratory results will be summarized by treatment group with the post-baseline measurements.

7.4.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 (or a later version if updated during the study). All medical history will be listed, and the number and percentage of subjects with any medical history will be summarized for the ITT population by system organ class (SOC) and preferred term (PT) for each treatment group and overall.

7.4.2 Previous and Concomitant Medications

Medications received prior to or concomitantly with study drug will be coded by Covance using the WHODrug Dictionary Version March 2019 Global Dictionary Version B3 (or a later version if updated during the study), Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

Prior medications are those taken prior to study drug with a stop date prior to the first dose of study drug.

Concomitant medications are those with a start date on or after the first dose date of study drug, or those with a start date before the first dose date of study drug and a stop date on or after the first dose date of study drug or ongoing end of study.

If a medication cannot be classified as "prior" or "concomitant" after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

Prior medications and concomitant medications will be listed together and summarized separately for the ITT population.

The number and percentage of subjects using each medication will be displayed together with the number and percentage of subjects using at least one medication within each therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and generic term.

7.5 Measurements of Study Drug Compliance

Percentage compliance is calculated as:

100 * actual number of capsules taken/expected number of capsules taken, where expected capsules taken is specified to be 5.

Percentage compliance will be summarized descriptively by treatment group for the Safety population.

The number and percentage of compliant subjects will be presented for the Safety population, where compliant is defined as percentage compliance between 80.0% and 100.0% inclusive. The number and percentage of subjects with compliance <80.0% as well as number and percentage of subjects who received more than one capsule in a calendar day will also be presented.

7.6 Efficacy

7.6.1 Primary Efficacy Analysis

SARS-CoV-2 Viral load will be reported as below.

- # of copies/mL;
- <# of copies/mL, if detected but under the lower limit of quantification (LLOQ);
- no SARS CoV-2 detected, if not detected.

SARS-CoV-2 Viral load (log_{10} copies/mL) and change from baseline will be summarized by visit using standard descriptive statistics for the MES population. The baseline value is defined as last scheduled or unscheduled viral load collected prior to the first dose of study drug. For post-baseline, only data from scheduled visits will be included in the summary tables. For the analysis purpose, viral load below the

LLOQ will be considered equal to the LLOQ. Number of subjects with undetectable SARS-CoV-2 viral load at each visit will be presented as well.

Changes from baseline in SARS-CoV-2 viral load data (log_{10} copies/mL) will be statistically analyzed using a mixed model for repeated measures (MMRM) in the MES population. The model will contain baseline as a covariate, treatment, day and treatment-by-day interaction as fixed effects. The unstructured covariance matrix will be selected initially; if this analysis fails to converge another covariance structure will be selected based on AIC and BIC values. The least square (LS) means and treatment difference at Days 4, 8, 12, 15, 22 and 29 will be calculated and presented with their corresponding 95% confidence intervals (CIs). All available data will be used in the analysis.

7.6.2 Secondary Efficacy Analysis

The duration of viral shedding is defined as the time (in days) from Day 1 to the first time where no SARS-CoV-2 is detected. When deriving viral shedding, any missing viral load data will be considered detectable. Subjects will be censored at the last SARS-CoV-2 viral load test if SARS-CoV-2 is detected at all tests.

Kaplan-Meier curves will be used to estimate the distribution of duration of viral shedding in the MES population. The 50th percentile of Kaplan-Meier estimates will be used to estimate the median duration of viral shedding. A two-sided 95% CI will be provided for this estimate. The 25th and 75th percentiles, and the range (minimum, maximum) will be presented as well. The range will be determined including censored observations. Duration of viral shedding will be compared between treatment groups using a unstratified log rank test. The two-sided p-value for the log rank test will be presented.

7.6.3 Exploratory Efficacy Analysis

7.6.3.1 Time to Viral Clearance

The time to viral clearance is defined as the time (in days) from Day 1 to the first time where no SARS-CoV-2 is detected for subjects with two consecutive tests of undetectable SARS-CoV-2. When deriving viral clearance, any missing viral load data will be considered detectable. Subjects without two consecutive tests of undetectable SARS-CoV-2 will be censored at the last SARS-CoV-2 viral load test.

Time to viral clearance will be analyzed using the same method as specified in section 7.6.2 for the secondary efficacy endpoint in the MES population.

7.6.3.2 Viral Culture

Viral culture will be listed and summarized by treatment group and visit.

Viral culture data and changes from baseline in viral culture will be summarized by visit using standard descriptive statistics for the MES population. The baseline value

is defined as last scheduled or unscheduled value collected prior to the first dose of study drug. For post-baseline, only data from scheduled visits will be included in the summary table.

7.6.4 Secondary Clinical Analysis

7.6.4.1 Hospital Admission

Subjects requiring hospital admission as an inpatient for >24 hours will be analyzed in the ITT population. Number and proportion of subjects requiring hospital admission along with 95% exact binomial CI (Clopper-Pearson) will be presented for each treatment group. Two-sided 95% CI will also be presented for the difference in percent of subjects requiring hospital admission between treatment groups with an approximate normal distribution. The Fisher's exact test will be used to compare the proportion of subjects requiring hospital admission. The two-sided p-value for the Fisher's exact test will be presented.

7.6.4.2 Death

Number of subjects who died and the cause of death will be presented for each treatment group for the ITT population. The proportion of subjects who died along with 95% exact binomial CI (Clopper-Pearson) will be presented for each treatment group. Two-sided 95% CI will also be presented for the difference in percent of subjects who died between treatment groups with an approximate normal distribution. The Fisher's exact test will be used to compare the proportion of subjects who died. The two-sided p-value for the Fisher's exact test will be presented.

7.6.5 Exploratory Clinical Analysis

7.6.5.1 Time to Resolution of Symptoms

Symptom assessment will use a checklist provided to the subject with symptoms such as sore throat, cough, gastrointestinal symptoms (vomiting, diarrhea), anosmia, dysgeusia, other (specify), etc. Symptoms start date, end date (or ongoing), severity "None", "Mild", "Moderate", or "Severe" and symptoms status "Resolved", "Ongoing", or "Returned to Baseline" will be collected.

Resolution of symptoms is defined as new COVID-19 symptoms are completely resolved (i.e. status of "Resolved") and pre-existing non-COVID-19 symptoms return to baseline (i.e. status of "Returned to Baseline") reported on the eCRF of "COVID-19 Symptom Assessment". The time to resolution of symptoms is defined as the time (in days) from Day 1 to the first date where symptoms have been resolved. Subjects didn't achieve resolution of symptoms will be censored at the date of last assessment of symptoms. The median (95% CI) time to resolution of symptoms will be presented by treatment groups using the Kaplan-Meier method for the ITT population.

7.6.5.2 Time to Clinical Improvement

Clinical progression will be assessed using the WHO Ordinal Scale (Table 2). Baseline is defined as last non-missing assessment prior to the first dose of study drug. Frequency counts and percentages will be presented by visit for WHO Ordinal Scale.

Table 2 Who Ordinal Scale

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

Clinical improvement is defined as at least 1-point decrease from baseline in WHO Ordinal Scale. Time to clinical improvement will be analyzed in the subset of ITT subjects with baseline WHO Ordinal Scale of 2 or 3. The time to clinical improvement is defined as the time (in days) from Day 1 to the first date of clinical improvement. Subjects didn't achieve clinical improvement will be censored at the date of last assessment of WHO Ordinal Scale. The median (95% CI) time to clinical improvement will be presented by treatment groups using the Kaplan-Meier method.

7.7 Safety

7.7.1 Extent of Exposure

Not applicable.

7.7.2 Adverse Events

AEs will be collected from the time of first dose of study drug through Day 29. After Day 29, only SAEs which are assessed by the Investigator or designated person to be related to study drug and have an onset within 14 days of study completion (Day 29 or earlier if discontinue prior to Day 29) will be collected/recorded. All AEs recorded on the eCRF will be coded using the MedDRA dictionary Version 23.1 (or a later version if updated during the study).

All AE data will be listed by treatment group. In addition, corresponding listings of study drug-related AEs and SAEs will be produced.

The relationship between an AE and study drug is assessed as definite, probable, possible, unlikely, or unrelated. A study drug-related AE is an AE considered by the investigator as definitely, possibly, or probably related to study drug or with missing relationship to study drug.

An overview table will summarize the number and percentage of subjects with at least one of the following AEs, where subjects with more than one AE in a particular category are counted only once in that category:

- any AE;
- AE by maximum severity grade;
- study drug-related AE;
- AE leading to study drug discontinuation;
- study drug-related AE leading to study drug discontinuation;
- severity grade 3 or higher study drug-related AE;
- SAE;
- study drug-related SAE;
- SAE leading to study drug discontinuation;
- AE leading to death;
- study drug-related AE leading to death.

The number and percentage of subjects reporting each AE will be summarized for each treatment group and overall, by System Organ Class (SOC) (sorted alphabetically) and Preferred Term (PT) (sorted by descending overall total) for the Safety population. The following summaries will be produced:

- AEs, by SOC and PT;
- AEs by PT;
- study drug-related AEs, by SOC and PT;
- study drug-related AEs, by PT;
- AEs by relationship to study drug, by SOC and PT;

- AEs by severity grade, by SOC and PT;
- study drug-related AEs by severity grade, by SOC and PT;
- AEs leading to discontinuation of study drug, by SOC and PT;
- study drug-related AEs leading to discontinuation of study drug, by SOC and PT;
- severity grade 3 or higher AEs, by SOC and PT;
- severity grade 3 or higher study-drug related AEs, by SOC and PT;
- SAEs, by SOC and PT;
- study drug-related SAEs, by SOC and PT;
- SAEs leading to discontinuation of study drug, by SOC and PT;
- AEs leading to death, by SOC and PT;
- study drug-related AEs leading to death, by SOC and PT.

In the above summaries, subjects with more than one AE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one AE within a particular PT are counted only once for that PT. For summaries by relationship to study drug, subjects with multiple AEs within a particular SOC or PT will be counted under the strongest relationship within that SOC or PT. For summaries by severity grade, subjects with multiple AEs within a particular SOC or PT will be counted under the maximum severity grade within that SOC or PT.

No statistical comparisons of AEs between treatment groups will be performed.

7.7.3 Laboratory Evaluations

Data for the following hematology and chemistry received from central laboratory will be listed and summarized by treatment group and visit. If data for any additional analytes are also recorded, then these will be listed only.

Hematology	Chemistry
Hemoglobin	Albumin
Hematocrit	Alkaline Phosphatase
Platelets	Alanine Amino Transferase
Neutrophils Absolute	Aspartate Amino Transferase
Lymphocytes Absolute	Total Bilirubin
Monocytes Absolute	Calcium
Eosinophils Absolute	Chloride
Basophils Absolute	Creatinine
Neutrophils %	Glucose
Lymphocytes %	Potassium
Monocytes %	Sodium
Eosinophils %	Total Protein
Basophils %	Lactate Dehydrogenase
White Blood Cell Count	Blood Urea Nitrogen
Red Blood Cell Count (RBC)	Carbon Dioxide/Bicarbonate
RBC Morphology and Mean Corpuscular Volume	C-Reactive Protein

All laboratory data will be reported in International System of Units (SI) units. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings for all laboratory parameters except C-reactive protein.

For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Laboratory data will be summarized by visit using standard descriptive statistics for the Safety population. Changes from baseline will also be summarized.

For hematology and chemistry parameters, number and percentage of subjects with abnormal results (not clinically significant, clinically significant) at each visit will be provided for each treatment group.

For each laboratory analyte, the baseline value is defined as last scheduled or unscheduled value collected prior to the first dose of study drug. Assessments carried out on day of first study drug administration are considered to have taken place before the study drug administration, if the corresponding times have not been recorded. For post-baseline, only data from scheduled visits will be included in the summary tables.

7.7.4 Vital Signs

The following vital signs will be listed and summarized by treatment group and visit.

- heart rate (bpm);
- respiration rate (breaths/min);
- body temperature (°C);
- oxygen saturation, SpO_2 (%).

Vital signs data and changes from baseline in vital signs will be summarized by visit using standard descriptive statistics for the Safety population. The baseline value is defined as last scheduled or unscheduled value collected prior to the first dose of study drug. For post-baseline, only data from scheduled visits will be included in the summary table.

7.7.5 Electrocardiograms

Not applicable.

7.7.6 Physical Examination

Abnormalities identified from physical examination are recorded in the eCRF as Medical History as appropriate and will be listed and summarized as such [See Sections 7.4.1 (Medical History)].

7.7.7 Other Safety Variables

Pregnancy test data will be presented in the subject data listing.

7.8 Interim Analysis

A Data Monitoring Committee (DMC) will be established to provide independent oversight to this trial. The primary responsibility of the DMC will be to review the progress and conduct of the trial in order to maintain scientific rigor and to ensure the wellbeing of subjects participating in the trial. The specific responsibilities of the DMC will be detailed in a separate DMC charter. The DMC will perform periodic data review to assess whether there are clinically significant differences between treatment groups that could affect participant safety. The DMC will review AEs and safety laboratory assessments after the first 20 subjects complete the Day 8 visit, and again after the first 40 subjects complete the Day 8 visit. Following such a review, the DMC Chair will advise the Sponsor that the study be stopped, the design changed, or that the study may continue per protocol.

8. Changes in Planned Analysis

This section is not required at this time, but will be populated in a future approved version of this document.

9. Data Issues

This section is not required at this time, but will be populated in a future approved version of this document

10. References

1 ICH. *Statistical Principles for Clinical Trials*, Guideline E9, 1998. Available at http://www.emea.eu.int/pdfs/human/ich/036396en.pdf

2 Phillips A and Haudiquet V. *ICH E9 guideline "Statistical principles for clinical trials": a case study*. Statistics in Medicine 2003; 22:1-11

3 Brown D J. *ICH E9 guideline "Statistical principles for clinical trials": a case study. Response to A. Phillips and V. Haudiquet.* Statistics in Medicine 2003; 22:13-17

4 ICH. *ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers*, 2012. Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf

11. Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary/Reason for Changes
Version 1, Final, 04 November 2020	Not applicable; the first version