Montreal Health Innovations Coordinating Center
A Division of the Montreal Heart Institute

MHICC

STATISTICAL ANALYSIS PLAN

Protocol number: DAL-401

A Double-blind, Placebo-controlled, Phase 2a Proof-of-concept Trial of Dalcetrapib in Patients with Confirmed Mild to Moderate COVID-19

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Revision History

Version	Date (DD-MMM-YYYY)	Author	Summary of Changes
Final	30-APR-2021	Anna Nozza	Initial version
Amendment 1	01-JUN-2021	Anna Nozza	Section 3: Sentence saying that populations of analysis will be confirmed by the sponsor added, details on the per-protocol population added and formula for number of days on study medication corrected to add 1 day. Section 6.2.2.1: Maximum clinical outcome scale for imputation corrected to be 7 (maximum severity if alive) or 8 (maximum severity if dead). Imputation method for non-numeric viral load results added. Section 6.4.2.1: Classification of day of assessment into visit identifiers added. Section 6.4.2.2: Details on the calculation of the area under the curve added. Section 6.4.3.4: Classification of day of assessment into visit identifiers added. Section 6.5.1: Formula for duration of exposure corrected to add 1 day. Section 7: Numbering of tables corrected. Appendix 2 with the algorithm to classify day of assessment added. Clarifications throughout the text that Day 1 corresponds to date of first dose and other minor corrections regarding visit names added. References to figures and listings corrected throughout the text.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the curve
BUN	Blood Urea Nitrogen
CI	Confidence Interval
eCRF	Electronic Case Report Form
ECMO	Extracorporeal Membrane Oxygenation
ePRO	Electronic Patient Reported Outcome
GFR	Glomerular Filtration Rate
GGT	Gamma Glutamyl Transferase
ITT	Intent To Treat
LDH	Lactate Dehydrogenase
LOCF	Last Observation Carried Forward
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MHICC	Montreal Health Innovations Coordinating Center
PCR	Polymerase Chain Reaction
PP	Per Protocol
PT	Preferred Term
RBC	Red blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus 2
SOC	System Organ Class (MedDRA classification)
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
WBC	White Blood Cell
WHO	World Health Organization

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to present the statistical methodology that will be used for the final analysis of DalCor Pharmaceuticals DAL-401. This plan also provides a description of the tables, figures and listings that will be included in the final statistical report. It is based on the protocol dated 22-OCT-2020 and on the annotated case report form (CRF) version 1.0. In case of differences in terms of descriptions or explanations between the SAP and the clinical protocol, the SAP will supersede the protocol. Any deviation to this SAP would be reported in the statistical report.

Since the protocol was developed and discussed with the regulatory authorities, a greater understanding of COVID-19 and clinical trials in COVID-19 has emerged. New variants have also been observed and their clinical course needs to be taken into consideration. Based on this emerging knowledge, a higher emphasis will be placed on viral load analyses when interpreting the data and deciding on POC in this study. Less emphasis will therefore be placed on the current primary endpoint of Patient Reported Outcomes and endpoints that look at changes in symptoms of COVID-19. Certain symptoms such as loss of taste and loss of smell as well as cough are chronic symptoms which may not resolve over the course of a 28-day study. In view of this the endpoints evaluating symptoms will not include taste, smell or cough in some analyses.

2 STUDY DESCRIPTION

2.1 Study Design

This is a randomized, double-blind, multicenter Phase 2a proof-of-concept study in outpatients with confirmed, mild to moderate, symptomatic COVID-19. Electronic informed consent must be obtained from all patients or their legally authorized representative during screening before any study-related procedures are performed. The Screening/Baseline assessments may be performed at the study site or as a home visit.

A total of 208 patients will be randomized to receive 900, 1800, or 3600 mg of dalcetrapib or placebo once daily (52 patients to each of 900 mg, 1800 mg, 3600 mg and placebo) for 10 days. Patients will be randomized and receive first dose of study drug within 72 hours of receiving a positive PCR or Point-of-care test for SARS-CoV-2. Patients need to have at least two of the 14 common COVID-19-related symptoms described in the inclusion criteria rated as mild or moderate, as evaluated by ePRO assessment or eCRF. Symptoms will be assessed at each study visit daily for the first 10 days, then at Day 14 and Day 28, and as clinically indicated. Symptoms will be evaluated as absent, mild, moderate, or severe depending on their impact on activities of daily living. SARS-CoV-2 viral loads will be obtained by both saliva (Oragene) collection and mid-turbinate nasal swab self-collection under supervision of a healthcare professional (virtual or home visit) at Screening/Baseline, Day 1, Day 3, Day 5, Day 7, Day 10, and Day 28. Patients who require hospitalization after initiation of study treatment will be followed for safety assessment through Day 28.

The study will be overseen by an independent Data Monitoring Committee (DMC). The DMC will review the safety data throughout the study. The DMC and Sponsor will review efficacy data at the interim analysis and at the end of the study. A DMC Charter, which includes detailed processes, will be prepared. One interim analysis will be conducted once 120 patients have a follow-up time of 28 days.

All patients will be closely monitored for adverse events (AEs) from informed consent for at least 18 days after the final dose of study treatment (until Day 28±2). Patients who withdraw early from the

study treatment will have follow-up phone calls to collect safety data until End of Study on Day 28±2. On days of laboratory assessments and PK sample collection, outpatient subjects may have a home visit.

2.2 Study Objectives

The primary efficacy objective of the study is:

- To evaluate the time to sustained clinical resolution of symptoms (excluding cough, sense of smell and taste) in patients with confirmed, mild to moderate, symptomatic COVID-19 treated with dalcetrapib.

The key secondary efficacy objectives of the study are:

- To evaluate change from baseline in log10 viral load
- To evaluate the time to sustained clinical resolution of symptoms in patients with confirmed, mild to moderate, symptomatic COVID-19 treated with dalcetrapib.

Other secondary efficacy objectives of the study are:

- To evaluate the time to viral clearance using SARS-CoV-2 polymerase chain reaction (PCR)
- To evaluate time to complete clinical resolution of symptoms (excluding cough, sense of smell and taste), defined in the same way as the primary endpoint, but considering that all symptoms must resolve to a score of 0 for 72 hours
- To evaluate time to complete clinical resolution of symptoms considering that all symptoms must resolve to a score of 0 for 72 hours
- To evaluate the change from baseline in COVID-19 total symptom score at all collected time points
- To evaluate the WHO Clinical Outcome Scale (9-point scale) at Day 3, Day 5, Day 10, Day 14 and Day 28
- To evaluate the rate of hospitalization through Day 28
- To evaluate the rate of progression to oxygen therapy through Day 28
- To evaluate the duration of hospitalization
- To evaluate the mortality rate by Day 28

The safety objective of the study is:

- To assess the safety and tolerability of dalcetrapib active doses compared to placebo in patients with COVID-19

The pharmacokinetics (PK) objective of the study is:

- To evaluate the PK of dalcetrapib in patients with COVID-19. The methodology for PK analysis will not be documented in this SAP but in a separate PK plan.

3 DATASETS ANALYZED

Subjects who were not eligible for randomization but who have been erroneously randomized into the study will be excluded from all datasets analyzed, if they did not receive study product.

The populations of analysis will be reviewed and confirmed by the sponsor prior to database lock.

3.1 Intent-To-Treat (ITT) Population

The Intent-To-Treat Population will include all participants who were randomized [a randomization number is provided in the eCRF Form "Randomization"] and received at least 1 dose of study drug [as confirmed in the eCRF Form "Study Drug Administration"] and not reported as a screen failure [in the eCRF Form "Disposition-Study Completion"]. Participant data will be summarized by treatment assigned.

3.2 Per-Protocol Population

The Per Protocol (PP) Population will include all participants from the ITT population who have no important study protocol deviations during the study. Because the number of days on study medication is likely to impact the efficacy endpoints, patients who will deviate from the protocol by not taking study medication at least 5 days (as assessed by the difference between date of study treatment last dose – date of study treatment first dose + 1 day) will be excluded. These patients shall be excluded from the PP population prior to database lock.

3.3 Safety Population

The Safety Population will include all participants who received at least 1 dose of study drug. Participant data will be summarized by actual treatment received.

4 EFFICACY ENDPOINTS

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is:

- Time to sustained clinical resolution of symptoms (excluding cough, sense of smell and taste)

Sustained clinical resolution is defined as occurring when no key COVID-19 related symptom (excluding cough, sense of smell and taste) has a score higher than 1 over a 72-hour period (as documented using an electronic patient-reported outcome [ePRO] instrument or in the eCRF),. The time to resolution will be taken as the time from randomization until the first day of the last 72-hour period where the patient meets the definition of resolution within 28 days. Patients who do not meet the definition of resolution 28 days after randomization will be considered not resolved.

The classification of sustained clinical resolution of symptoms (excluding cough, sense of smell and taste) follows similar steps as the algorithm presented in Appendix 1.

4.2 Secondary Efficacy Endpoints

The key secondary efficacy endpoints are:

- Change from baseline in log10 viral load, as measured using saliva and as measured using nasal swab. Changes will be calculated as value at follow-up visits – value at baseline.

- Time to sustained clinical resolution of symptoms.

  Sustained clinical resolution is defined as occurring when no key COVID-19 related symptom has a score higher than 1 over a 72-hour period (as documented using an electronic patient-reported outcome [ePRO] instrument or in the eCRF), except for sense of smell and taste (items 13 and 14) where the score should be 0 over a 72-hour period. The time to resolution will be taken as the time from randomization until the first day of the last 72-hour period where the patient meets the definition of resolution within 28 days. Patients who do not meet the definition of resolution 28 days after randomization will be considered not resolved.

  Refer to the algorithm in Appendix 1 for the derivation of this endpoint.

Other secondary efficacy endpoints are:

- Time to viral clearance based on PCR test for SARS-CoV-2, as measured using saliva and as measured using nasal swab

- Time to complete clinical resolution of symptoms (excluding cough, sense of smell and taste)

  Clinical resolution is defined in the same way as the primary endpoint, but considering that all symptoms (excluding cough, sense of smell and taste) must resolve to a score of 0 for 72 hours.

- Time to complete clinical resolution of symptoms

  Clinical resolution is defined as occurring when all key COVID-19 related symptom must resolve to a score of 0 for 72 hours.

  The derivation of this endpoint follows similar steps as the algorithm presented in Appendix 1.

- Change from baseline in COVID-19 total symptom score

Total symptom score is defined as the sum [range 0-42] of the scores of all 14 common COVID-19 symptoms.

- Score on the WHO Clinical Outcome Scale (9-point scale) [as collected on eCRF Form "WHO COVID-19 Clinical Improvement Score"]
- Rate of hospitalization [hospitalization will be identified in the eCRF Form "Adverse Event" if adverse event is serious and serious category is Hospitalization or prolonged hospitalization]
- Rate of progression to oxygen therapy [progression to oxygen therapy will be identified in the eCRF Form "Adverse Event" if event requires supplemental oxygenation or mechanical ventilation or extracorporeal membrane oxygenation]
- Duration of hospitalization [duration will be identified in the eCRF Form "Adverse Event" as the difference between date of discharge and date of admission]
- Mortality rate [death will be identified in the eCRF Form "Adverse Event" if outcome of adverse event is fatal]

5 SAFETY PARAMETERS

Safety variables include incidence of AEs (or TEAEs), laboratory test results and vital signs.

5.1 Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. This includes the following:

- Any clinically significant worsening of a pre-existing condition.
- Note: Emergence of a new pathogen associated with a clinical event during therapy at a site other than the initial site of infection will be considered to be an AE.
- Any recurrence of a pre-existing condition.
- An AE occurring from overdose of a Sponsor study drug whether accidental or intentional (i.e., a dose higher than that prescribed by a health care professional for clinical reasons).
- An AE occurring from abuse of a Sponsor study drug (i.e., use for nonclinical reasons).
- An AE that has been associated with the discontinuation of the use of a Sponsor study drug.

Note: A procedure is not an AE, but the reason for a procedure may be an AE.

A pre-existing condition is a clinical condition (including a condition being treated) that is diagnosed before the patient signs the ICF and that is documented as part of the patient's medical history.

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is a treatment-emergent AE. An AE is considered to be treatment-emergent if (1) it is not present when the active phase of the study begins and is not a chronic condition that is part of the patient's medical history, or (2) it is present at the start of the active phase of the study or as part of the patient's medical history, but the severity or frequency increases during the active phase. The active phase of the study begins at the time of the first dose of the study drug. The active phase of the study ends at the Follow-up/EOS.

Treatment-emergent AEs will be identified in the eCRF Form "Adverse Event" if the answer to the question "Did the AE start after the patient took the first dose?" is answered as Yes.

The Investigator will make a determination of the relationship of the AE to the study drug using a four-category system according to the following guidelines:

- Not related: when the AE is definitely caused by the patient's clinical state, or the study procedure/conditions.
- Unlikely Related: when the temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- Possibly Related: when the AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the patient's clinical state or the study procedures/conditions.
- Related: when the AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Related to study treatment will be identified as possibly related or related as per reported on eCRF Form "Adverse Event".

5.2 Serious Adverse Events

An SAE is any AE occurring at any dose that meets 1 or more of the following criteria:

- Results in death,
- Is life-threatening;
- Requires patient hospitalization or prolongation of an existing hospitalization;
- Results in persistent or significant disability or incapacity;
- Results in a congenital anomaly or birth defect;
- Results in an important medical event.

5.3 Laboratory Parameters

Laboratory evaluations are done at screening, Day 10 and follow-up visit 2 (Day 28). Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

Hematology laboratory tests include: hematocrit (L/L), hemoglobin (g/L), MCH (pg), MCHC (g/L), MCV (fL), Platelet count (GI/L), RBC count (TI/L), WBC count (GI/L) and WBC differentials (Neutrophils, Eosinophils, Basophils, Lymphocytes and Monocytes) in both percent (%) and absolute (GI/L).

Biochemistry laboratory tests include: albumin (g/L), alkaline phosphatase (U/L), ALT (U/L), AST (U/L), bicarbonate (mmol/L), BUN (mmol/L), calcium (mmol/L), chloride (mmol/L), cholesterol (mmol/L), creatinine (umol/L), GFR CKD-EPI (mL/min/1.73m^2) , GGT (U/L), glucose (mmol/L), LDH (U/L), phosphorus (mmol/L), potassium (mmol/L), sodium (mmol/L), total bilirubin (umol/L), total protein (g/L), triglycerides (mmol/L) and uric acid (umol/L).

5.4 Other Safety Parameters

Pulse oximetry and saturation measurements will take place on screening, Days 1, 3, 5, 7, 10, follow-up visit 1 (Day14) and follow-up visit 2 (Day28/EOS).

6 STATISTICAL METHODOLOGY

6.1 Determination of Sample Size

As per protocol, it was anticipated that 208 patients will be randomized into the study in a 1:1:1:1 ratio to 900, 1800, or 3600 mg dalcetrapib or placebo.The original sample size was calculated for the sustained resolution endpoint and was described in the protocol as follows: The purpose of the proof-of-concept study is to identify whether there is sufficient promise of efficacy to justify conducting a Phase 3 study in a larger sample size and to determine efficacious dose to be used in Phase 3. While the entirety of data will be considered at the end of study, the sample size has been chosen to ensure that a positive trend will be present with alpha of 0.2 when considering the two highest doses combined compared to placebo. One-hundred twenty-seven (127) resolution events provides 80% power to demonstrate a positive trend if the average hazard ratio (HR) of the two dalcetrapib groups is 1.4 relative to placebo. Allowing for 20% of patients not resolving, 156 patients (52 per treatment arm) will be enrolled across the two highest dose levels and placebo arms, and an additional 52 will be randomized to 900 mg for a total sample size of 208 patients.

6.2 Statistical Considerations

Continuous variables will be summarized by the standard descriptive statistics: number of patients (n), mean, standard deviation, median, Q1, Q3, minimum, and maximum, along with confidence interval (CI) for outcome measures when appropriate. Frequency of patient or events and percentages will be summarized for categorical variables, again with CI when appropriate. Time to event variables will be summarized using Kaplan-Meier methods.

All statistical tests will be conducted at a two-sided 0.20 significance level.

Statistical analyses will be performed using SAS Version 9.4 or higher.

6.2.1 Interim Analysis

The study will be overseen by an independent Data Monitoring Committee (DMC). The DMC will review safety data throughout the study. The DMC will review efficacy data at the interim analysis and at the end of the study. A DMC Charter, which includes detailed processes, will be prepared.

One interim analysis will be conducted for efficacy once 120 patients with a follow-up of 28 days have occurred. No decision to stop the trial will be made based on these efficacy findings as the review of data will occur around the time the last patients enrolled in the study complete the treatment period.

The members of the committee will include appropriately qualified medical personnel, and other members, as required. Detailed responsibilities of the DMC will be provided in the DMC Charter.

6.2.2 Handling of Missing Data

6.2.2.1 Imputation

Severity Symptom Score: Missing values on severity symptom score will not be imputed. However, where a patient has died, their symptom score will not be considered missing, but will be imputed with the maximum severity score (3) for each symptom at each time point.

Clinical Outcome Scale: Missing values on clinical outcome scale will not be imputed. However, where a patient has died, their clinical outcome scale will not be considered missing, but will be imputed with maximum clinical outcome scale (7 [maximum severity if alive] or 8 [maximum severity if dead]) at each time point.

Viral load: Prior to the log 10 transformation, non-numeric viral load results reported as below the limit of detection will be replaced by the limit of detection divided by 2. As an example, results reported as "<2228cp/mL SARSCoV2 detected" will be replaced by 1114 cp/mL. Non-numeric viral load results reported as "No SARS-CoV2 detected" will be replaced by 1 cp/mL. Replacing by 1 (instead of by zero) will be done so that the log 10 of viral load will be defined in all subjects (and equal to zero when no SARS-CoV2 is detected).

6.2.2.2 Censoring

Severity Symptom Score: For time to resolution, a patient will be censored if the patient has not had the required time point assessment if not due to death. If patient has died or received another antiviral therapy prior to the assessment endpoint, then the patient will be considered as having a moderate or severe COVID-19 symptom for all COVID-19 symptoms and imputed to maximum severity score at the assessment day.

Viral Clearance: For time to viral clearance, a patient will be censored if the patient has not had the required time point assessment.

6.2.3 Multiplicity/Multiple Testing

The primary analysis compares the combined two highest dalcetrapib dose groups against placebo as well as each treatment group individually. No adjustments will be made for multiple testing.

6.3 Study Subjects

6.3.1 Subject Disposition

Number of subjects randomized, number of subjects who took at least one dose of study medication, number of subjects completing the study and reasons for not completing the study will be summarized by randomized treatment group, for all randomized subjects as well as for the ITT population.

A listing of subject disposition will be presented (Section 7, Listing 1).

Subject disposition will also be presented with a flow chart reporting the following information: subjects who signed informed consent, subjects who are screen failures, subjects randomized (excluding screening failures that were randomized), subjects who took at least one dose of study medication, subjects completing the study and reasons for study discontinuation (Section 7, Figure 1).

Which visits were done will also be summarized overall and by treatment group, for the ITT population.

6.3.2 Protocol Deviations

Protocol deviations will be summarized overall and by treatment group for the ITT population.

A listing will also be provided (Section 7, Listing 3).

6.3.3 Datasets Analyzed

The number of subjects in the ITT population, PP population and Safety population will be summarized overall and by treatment group.

A listing of datasets analyzed will be presented and will include subject ID, randomization group, ITT population (Yes/No), reason for exclusion from the ITT population, PP population, reason for exclusion from the PP population, Safety population (Yes/No) and reason for exclusion from the Safety population (Section 7, Listing 2).

6.3.4 Demographic and Baseline Characteristics

Demographic data such as age, sex, ethnicity, race and smoker will be summarized overall and by treatment group for the ITT population.

In case the date of birth is incomplete [in the eCRF Demographics], the following imputation will be done:

- the partial date will be replaced by the fifteenth day of the month if month and year are known;
- the partial date will be replaced by the first day of July if only the year is known.

A listing of demographic data will be provided (Section 7, Listing 4).

Medical and surgical history such as diabetes, hypertension, prior cardiovascular disease, respiratory disease, renal disease and liver disease will also be summarized overall and by treatment group for the ITT population.

Delays since first symptoms of COVID-19 will be summarized overall and by treatment group, for the ITT population. The number of days between the date of first symptom of COVID-19 and the following dates will be presented in this table: date of positive diagnosis for COVID-19, date of randomization and date of first dose of study medication. In addition, the number of days between the date of positive diagnosis of COVID-19 and the date of randomization will be presented, as well as how the diagnosis of COVID-19 was established.

Delays will be calculated as:

- Date of positive diagnosis for COVID-19 - Date of first COVID-19 symptoms
- Date of randomization - Date of first COVID-19 symptoms
- First treatment start date - Date of first COVID-19 symptoms
- Date of randomization - Date of positive diagnosis for COVID-19

6.3.5 Treatment Compliance

Compliance will be assessed if subject took all the pills at each study visit and will be summarized using frequencies and percentages, by treatment group, for the subjects of the ITT population. If subject did not take all the pills, then the number of missed pills will be reported as number of patients (n), mean, standard deviation, median, Q1, Q3, minimum, and maximum.

6.3.6 Prior and Concomitant Medications

Prior and concomitant medications will be coded with respect to indication and generic name using the WHO drug dictionary (version MAR2021).

Frequency of use of medications at randomization will be presented for the subjects of the ITT population by therapeutic class and preferred term, overall and for each treatment group.

A medication will be flagged as being ongoing at the time of randomization if:

- Medication start date < randomization date
  AND
- (Medication end date ≥ randomization date OR Medication is ongoing)

In case of missing or incomplete medication start / end dates, the following rules will be applied:

- If 1) the medication start date is completely missing, or 2) only the year is specified, it is the same as the randomization year and randomization did not occur the first day of the year or 3) only the month/year are specified, they are the same as the randomization month/year, then the medication will be assumed to have started before randomization.
- If 1) the medication end date is completely missing, or 2) only the year is specified and it is the same as the randomization year or 3) only the month/year are specified and they are the same as the randomization month/year, then the medication will be assumed to have ended after randomization.
- Otherwise, partial medication start / end dates (month/year or year only) will be compared to the randomization date and the medication will be classified accordingly.

Frequency of use of prior and concomitant medications will also be presented for the subjects of the ITT population by therapeutic class and preferred term, overall and for each treatment group.

A listing of concomitant medication(s) taken by the subject will be provided (Section 7, Listing 5).

6.4 Efficacy Analysis

The analysis of treatment efficacy will be based on the Intent-to-Treat Population. The PP population will be used for sensitivity analysis. This section is a summary of the planned efficacy analyses of the most important efficacy endpoints including primary and key secondary efficacy endpoints.

6.4.1 Primary Analysis

The primary endpoint is time to sustained clinical resolution of symptoms (excluding cough, sense of smell and taste) as determined by symptom score. Sustained clinical resolution of symptoms (excluding cough, sense of smell and taste) is defined in Section 4.1. Time to sustained clinical resolution will be calculated as date of resolution – date of randomization + 1. Subjects who did not resolve will be censored at the last time point where they were not resolved [see Section 9 Appendix 1]. The number and percentage of patients whose symptoms resolved will be presented, and to summarize the time to resolution, censored subjects will be imputed with a time to resolution of 29 days and simple medians with 80% confidence intervals will be provided.

The differences in time to sustained clinical resolution of symptoms (excluding cough, sense of smell and taste) between the treatment groups will be evaluated using 2-sided log-rank tests, The combined two highest treatment groups will be compared to placebo in addition to the comparison of individual doses.

The cumulative incidence curve for sustained clinical resolution (excluding cough, sense of smell and taste) will also be presented using 1 – Kaplan-Meier estimates(Section 7, Figure 2). Should there be several deaths, the cumulative incidence curve will be presented under a competing risk model.

A listing with the score of each symptom at each time point will be provided (Section 7, Listing 7).

6.4.2 Key Secondary Analysis

6.4.2.1 Change from Baseline in log10 Viral Load

Log10 viral load, as assessed using the saliva and as assessed using the nasal swab, will be summarized by treatment group using descriptive statistics (N, mean, median, standard deviation, minimum, and maximum) for each visit as well as for changes from baseline where an 80% CI will also be presented.

Mean changes from baseline will be analyzed using a repeated measures ANCOVA model including effects of treatment, visit (Day 3, Day 5, Day 10 and Day 28/EOS), and treatment-by-visit interaction, as well as baseline value of log10 viral load and baseline value of log10 viral load-by-visit-interaction. An unstructured covariance structure will be used to model the within-patient errors and the Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The combined two highest treatment groups will be compared to placebo in addition to the comparison of individual doses at the following study visits (Day 3, Day 5, Day 10 and Day 28/EOS).

Since oragene and nasal samples are collected by the subjects themselves (visit identifiers may be unreliable), an algorithm (presented in Appendix 2) was developed to classify the day of assessment into their respective visit identifiers. This algorithm is based on the fact that Day 1 corresponds to the date of the first dose and as such, will be used as baseline when available. This is in alignment with the study protocol that identifies Day 1 as the date of first dose. It is understood that all protocol assessments collected on Day 1 were to be done PRIOR to the first dose. Therefore, Day 1 will correspond to baseline when available. Please refer to Appendix 2 for more details.

A plot of mean change from baseline in log10 viral load with 80% CI at each study visit will also be presented (Section 7, Figure 4).

6.4.2.2 AUC in log10 Viral Load

The area under the curve (AUC) of log10 viral load, as assessed using the saliva and as assessed using the nasal swab, will be calculated from randomization to Day 10 and summarized by treatment group using descriptive statistics (N, mean, median, standard deviation, Q1, Q3, minimum, and maximum). The AUC will be calculated using the trapezoidal rule on the period from baseline to Day 10. In subjects who will not have a viral load assessment up to Day 10, the last observation carried forward will be used so that the AUC is calculated on 10 days in all subjects. An ANOVA model will be performed to analyze the difference between treatment groups. The model will include only the treatment group. Contrasts under this model will allow for the comparisons across treatment groups. The results will be presented as mean treatment difference with associated 80% CI and p-value.

6.4.2.3 Time to Sustained Clinical Resolution

Sustained clinical resolution is defined in Section 4.2.

Same statistical methods as those described in section 6.4.1 will be used to analyze the time to sustained clinical resolution.

6.4.3 Other Secondary Analysis

6.4.3.1 Time to Viral Clearance Based on PCR Test for SARS-CoV-2

Each subject will be tested to determine if the subject has COVID-19 by obtaining a PCR or rapid antigen test as it confirms the presence of SARS-CoV-2. A subject will be considered to no longer have COVID-19 if two consecutive PCRs do not detect SARS-CoV-2. Time to viral clearance using PCR test for SARS-CoV-2, as assessed using the saliva and using the nasal swab, will be calculated as date of the first negative PCR test for SARS-CoV-2 – date of randomization + 1. Subjects who did not obtain two consecutive negative PCRs will be censored at the date of study completion.

Same statistical methods as those described in section 6.4.1 will be used to analyze the time to viral clearance.

6.4.3.2 Time to Complete Clinical Resolution (excluding cough, sense of taste and smell)

Complete clinical resolution (excluding cough, sense of taste and smell) is defined in Section 4.2.

Same statistical methods as those described in section 6.4.1 will be used to analyze the time to complete clinical resolution (excluding cough, sense of taste and smell).

6.4.3.3 Time to Complete Clinical Resolution

Time to complete clinical resolution is defined in Section 4.2

Same statistical methods as those described in section 6.4.1 will be used to analyze the time to complete clinical resolution.

6.4.3.4 Change from Baseline in COVID-19 Total Symptom Score

COVID-19 total symptom score will be summarized by treatment group using descriptive statistics (N, mean, median, standard deviation, minimum, and maximum) for each visit as well as for changes from baseline where an 80% CI will also be presented.

Mean changes from baseline will be analyzed using a repeated measures ANCOVA model including effects of treatment, visit (Day5, Day10, Day14 & Day28/EOS), and treatment-by-visit interaction, as well as baseline value of total symptom score and baseline value of total symptom score-by-visit-interaction. An unstructured covariance structure will be used to model the within-patient errors and the Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The combined two highest treatment groups will be compared to placebo in addition to the comparison of individual doses at the following study visits (Day5, Day10, Day14 and Day 28/EOS).

Symptom scores were either reported electronically by the subject or by the site through telephone calls. Except for the assessments done at screening reported in the eCRF, no visit identifiers were attached to these evaluations, only the date of the assessment. Therefore, similar to viral load, the day of assessment of the symptom scores will be classified into visit identifiers as per the algorithm presented in Appendix 2. This will ensure that Day X for symptom score will correspond to Day X for viral load.

A plot of mean change from baseline in COVID-19 total symptom score with 80% CI at each study visit on the ITT population will be presented (Section 7, Figure 6).

6.4.3.5 Scoring of WHO Clinical Outcome Scale (9-point Scale)

The number and percentage of patients for each WHO clinical outcome score will be summarized.

The combined two highest treatment groups will be compared to placebo in addition to the comparison of individual doses at the following visits (Baseline, Day3, Day5, Day10, Day14 and Day 28/EOS) using the Mann-Whitney-Wilcoxon test. Since Day 1 corresponds to the date of first dose, Day 1 will be used for baseline. A frequency distribution plot of WHO clinical outcome scale at each study visit on the ITT population will also be presented (Section 7, Figure 9).

A listing of the WHO clinical outcome scale score at each time point will be provided (Section 7, Listing 8).

6.4.3.6 Rate of Hospitalization Through Day 28

The number and percentage of patients who were hospitalized will be presented. The percentage of patients who were hospitalized will be compared using a binary logistic regression analysis. The model will include only the treatment group. Contrasts under this model will allow for the comparisons across treatment groups. The results will be presented as odds ratios, with associated 80% CIs and p-value. The period will cover from the time of randomization to 28 days after, any hospitalization for which date of hospitalization > date of randomization + 28 would be excluded.

A listing with details on hospitalizations will be incorporated as part of the AE listing (Section 7, Listing 9).

6.4.3.7 Rate of Progression to Oxygen Therapy Through Day 28

The analysis of this endpoint will be performed on the ITT population. The number and percentage of patients who progress to oxygen therapy and type of oxygen therapy will be presented. The percentage of patients who had progressed to oxygen therapy will be compared using a binary logistic regression analysis. The model will include only the treatment group. Contrasts under this model will allow for the comparisons across treatment groups. The results will be presented as odds ratios, with associated 80% CIs and p-value. The period will cover from the time of randomization to 28 days after, any progression to oxygen therapy for which date of progression > date of randomization + 28 would be excluded.

6.4.3.8 Duration of Hospitalization

The duration of hospitalization will be from the date of first hospitalization until date of discharge [(Date of hospitalization – date of discharge) in the eCRF Form “Adverse Event”]. The duration of hospitalization will be the total number of days hospitalized in case of more than one hospitalization.

The duration of hospitalization will be analyzed on the ITT population in subjects who were hospitalized. Duration of hospitalization will be summarized by treatment group using descriptive statistics (N, mean, median, standard deviation, Q1, Q3, minimum, and maximum). An ANOVA model will be performed to analyze the difference between treatment groups. The model will include only the treatment group.

Contrasts under this model will allow for the comparisons across treatment groups. The results will be presented as mean treatment difference with associated 80% CI and p-value.

6.4.3.9 Mortality Rate

The analysis of this endpoint will be performed on the ITT population. The number and percentage of patients who died will be presented. The percentage of patients who died will be compared using a binary logistic regression. The model will include only the treatment group. Contrasts under this model will allow for the comparisons across treatment groups. The results will be presented as odds ratios, with associated 80% CIs and p-values. The period will cover from the time of randomization to 28 days after, any death for which date of death > date of randomization + 28 would be excluded.

A listing with details on deaths will be provided (Section 7, Listing 10).

6.4.4 Sensitivity Analysis

As a sensitivity analysis, the primary analysis described in section 6.4.1 will be repeated on the PP population.

As an additional sensitivity analysis, the primary endpoint will be derived using the algorithm of Appendix 1, but prior to applying the algorithm, the last observation carried forward will be used in alive patients with no assessment at Day 28. In other words, in alive patients, the missing assessment at Day 28 will be imputed as the last available assessment.

6.4.5 Subgroup Analysis

A subgroup analysis for the variants might be done on the primary endpoint, time to sustained clinical resolution of symptoms (excluding cough, sense of smell and taste). The analysis described in section 6.4.1 would be repeated in subjects presenting a specific variant. These analyses would however be done at a later time point when the information on the variants become available.

6.5 Safety Analysis

The safety analyses described in this section will be conducted on the safety population. No formal statistical testing is planned for the safety parameters.

6.5.1 Treatment Exposure

Duration of exposure will be defined as number of days on treatment for each subject. Duration will be calculated as: [treatment end date – treatment start date + 1] from the eCRF Form “Study Drug Administration”.

Duration of exposure will be summarized by treatment arm using N, mean, median, standard deviation, Q1, Q3, minimum and maximum.

Duration of exposure will also be categorized according to day intervals ([1-3], [4-5], [6-7], [8-9], [10], [>10]) and summarized using frequencies and percentages, overall and by treatment group.

In addition, if subject interrupted/discontinued the study medication, then the reason will also be reported using frequencies and percentages overall and by treatment group.

Duration of exposure will be presented for the safety population.

A listing with details on the administration of study medication will be provided (Section 7, Listing 6).

6.5.2 Adverse Events and Serious Adverse Events

6.5.2.1 Adverse Events

AEs will be coded by system organ class and preferred term according to the MedDRA dictionary (version 24).

Treatment-emergent AEs (TEAEs) will be summarized. Number and proportion of subjects experiencing a treatment-emergent AE will be presented by system organ class and preferred term overall and for each treatment group.

An overall summary of TEAEs that includes the total number of TEAEs reported, the number and proportion of subjects experiencing at least one TEAE, at least one severe TEAE, at least one TEAE related to the study treatment, at least one TEAE leading to treatment discontinuation and a TEAE leading to death will also be presented.

TEAEs related to study treatment will also be summarized. Number and proportion of subjects experiencing a treatment-emergent AE related to study treatment will be presented by system organ class and preferred term overall and for each treatment group.

An overall summary of TEAEs related to study treatment that includes the total number of TEAEs reported, the number and proportion of subjects experiencing at least one TEAE, at least one severe TEAE, at least one TEAE leading to treatment discontinuation and a TEAE leading to death will also be presented.

TEAEs leading to treatment discontinuation will also be summarized. Number and proportion of subjects experiencing a treatment-emergent AE leading to treatment discontinuation will be presented by system organ class and preferred term overall and for each treatment group. Severe TEAEs will be presented similarly.

All AEs will also be listed (Section 7, Listing 9).

6.5.2.2 Serious Adverse Events

Treatment-emergent serious AEs (TESAE) will be summarized. Number and proportion of subjects experiencing a treatment-emergent serious AE will be presented by system organ class and preferred term overall and for each treatment group.

An overall summary of the total number of TESAEs reported, the number and proportion of subjects experiencing at least one TESAE, at least one severe TESAE, at least one TESAE related to the study treatment, at least one TESAE leading to treatment discontinuation, a TESAE leading to death, at least one TESAE requiring supplemental oxygenation, at least one TESAE requiring mechanical ventilation and at least one TESAE requiring ECMO will also be presented.

Treatment-emergent serious AEs (TESAE) related to study treatment will also be summarized. Number and proportion of subjects experiencing a treatment-emergent serious AE related to study treatment will be presented by system organ class and preferred term overall and for each treatment group.

An overall summary of TESAEs related to study treatment that includes the total number of TESAEs related to study treatment reported, the number and proportion of subjects experiencing at least one TESAE related to study treatment, at least one severe TESAE related to study treatment, at least one TESAE related to study treatment leading to treatment discontinuation, a TESAE related to study treatment leading to death, at least one TESAE related to study treatment requiring supplemental oxygenation, at least one TESAE related to study treatment requiring mechanical ventilation and at least one TESAE related to study treatment requiring ECMO will also be presented.

All SAEs will also be listed (Section 7, Listing 9).

A separate listing for deaths will be also provided (Section 7, Listing 10).

6.5.3 Laboratory Parameters

Laboratory data will be transferred electronically by Covance central lab. For all laboratory parameters, results at each visit and change from screening will be summarized overall and by treatment group using descriptive statistics (N, mean, median, standard deviation, Q1, Q3, minimum and maximum).

6.5.4 Other Safety Parameters

Vital signs [pulse oximetry and peripheral oxygen saturation] at each visit will be summarized overall and by treatment group using descriptive statistics (N, mean, median, standard deviation, Q1, Q3, minimum and maximum). Change from Day 1 will also be presented similarly using descriptive statistics since Day 1 corresponds to the date of first dose.

In addition, saturation will be characterized as: [<90%], [91%-95%], [>95%] at each visit overall and by treatment group. Number and proportion of subjects within each category will be provided.

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8 REFERENCES

NA

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APPENDIX 1

Algorithm used to classify sustained clinical resolution:

For each subject, all ePRO records will be sorted by the date/time. For each assessment, we characterize the record as clinically resolved (i.e., score of 0 for taste and smell and all other symptoms, a score of 0 or 1) or not.

From Day1 to Day10 (or last ePRO assessment before Day14)

a) If resolved at Day 10 (or last ePRO assessment), identify first date when resolution occurred with no relapse. This is the tentative date of resolution to be confirmed at Day 14 and Day 28.
b) If not resolved at Day 10 (or last ePRO assessment), re-assess at Day 14.

At Day14:

c) If resolved for the first time at Day 14 (i.e. was not resolved at Day 10 or before), use date of Day 14 as the tentative date of resolution to be confirmed at Day 28.
d) If still resolved at Day 14 (i.e. was already resolved at Day10 or before), use date of resolution identified in step a). This is the tentative date of resolution to be confirmed at Day 28.
e) If not resolved at Day 14, re-assess at Day28.

At Day28:

f) If resolved for the first time at Day 28 (i.e., was not resolved at Day 14), subject will be classified as resolved within 28 days and date of resolution will be the date of Day 28.

g) If still resolved at Day 28 (i.e. was already resolved at Day 14), subject will be classified as resolved within 28 days and date of resolution will be the date of resolution identified in step c) or d).

h) If not resolved at Day 28, subject will be classified as not resolved within 28 days and the date of censoring will be the date of Day 28.

It should also be noted that subjects who do not have an assessment at Day 28 will be classified as non-resolved REGARDLESS if symptoms were resolved up to their last assessment. Date of censoring will be the date of study discontinuation.

APPENDIX 2

To classify the symptom score and viral load assessments to their appropriate visit identifier, the difference in days between the date of the assessment and the date of the first dose will be calculated, and this difference will be classified according to the reporting windows below. This algorithm will ensure that Day X for symptom score will correspond to Day X for viral load. As per the study protocol, Day 1 corresponds to the date of 1st dose in which all assessments were to be done PRIOR to first dose.

Once the visit identifiers are sorted out, Day 1 will be used to establish a baseline visit. If a subject has no Day 1 assessment but a screening one, then the screening assessment is chosen.

In cases where more than one assessment falls within the same reporting window, the first assessment will be chosen.

Note: For the symptom score, if both ePRO and eCRF assessments were done on the same day, then the ePRO was favored.

Reporting windows for the classification of the visit identifiers for symptom score and viral load*

VISIT**	SCHEDULED WINDOW (± DAYS)	DIFFERENCE BETWEEN DATE OF ASSESSMENT AND DATE OF 1ST DOSE
*Screening	---	<0
*DAY 1	---	0
DAY 2	---	1
DAY 3	---	2
DAY 4	---	3
DAY 5	---	4
DAY 6	---	5
DAY 7	---	6
DAY 8	---	7
DAY 9	---	8
DAY 10	---	9
Follow-up visit 1 (DAY 14)	±2	11 to 15
Follow-up visit 2 (DAY 28/EOS)	±2	25 to 29

*Screening and Day 1 will not be reported separately but will be used to classify the baseline visit as detailed above.

**Viral loads are presented ONLY at baseline, Day 3, Day 5, Day 7, Day 10 & Day 28/EOS.