STATISTICAL ANALYSIS PLAN

for Part 1 for ANA001-001 Study

Protocol Number	ANA001-001
Protocol Title:	A Phase 2/3 Randomized and Placebo-Controlled Study of ANA001 in Moderate and Severe COVID-19 Patients
Product:	Niclosamide (ANA001)
Indication:	Moderate and Severe COVID-19 Infection
Development Phase:	2/3
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Table of Contents

1. INTRODUCTION

The purpose of this document is to outline the planned statistical analyses at the end of Part 1 of data captured according to NeuroBo Pharmaceuticals protocol ANA001-001 titled "A Phase 2/3 Randomized and Placebo-Controlled Study of ANA001 in Moderate and Severe COVID-19 Patients" Version 4.0 (Amendment 3) dated 25 February 2021. This trial was registered on ClinicalTrials.gov Identifier NCT04603924 by ANA Therapeutics, which was acquired by NeuroBo Pharmaceuticals.

Tables, listings, and figures planned for the final analyses of Part 1 will be provided in a separate document.

2. STUDY OBJECTIVES

2.1 Primary Objectives

Part 1 of the study has one primary objective:

- Evaluate the safety and tolerability of ANA001 as therapy for moderate and severe COVID-19 patients

2.2 Secondary Objectives

The following is the secondary objective of Part 1 of the study:

- Evaluate the efficacy of ANA001 as therapy in moderate and severe COVID-19 patients
- Evaluate pharmacokinetics (PK) of ANA001

2.3 Exploratory Objectives

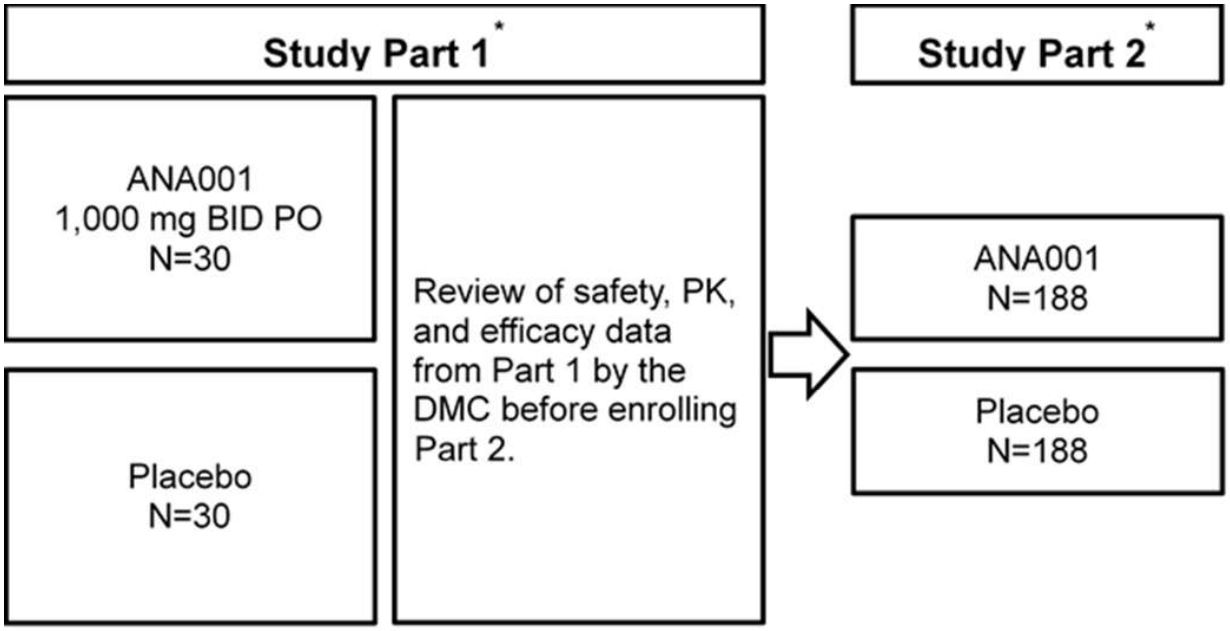
The exploratory objectives of Part 1 of the study:

- Evaluate clinical improvement using National Early Warning Score 2 (NEWS2)
- Evaluate the need and duration of rescue therapy
- Evaluate the effect on subjective symptoms of COVID-19
- Evaluate progression of COVID-19 from moderate or severe to more severe (i.e., moderate to severe, moderate to critical, or severe to critical)
- Evaluate the effect of ANA001 on requirement for oxygen and/or assisted ventilation
- Evaluate time to resolution of the WHO Ordinal Scale for Clinical Improvement
- Evaluate the effect of ANA001 on thromboembolic events
- Evaluate the relationship of ANA001 and markers of inflammation associated with acute respiratory distress syndrome (ARDS)

- Evaluate the relationship between ANA001 plasma concentrations and viral dynamics

3. STUDY DESIGN

This is a 2-part, multicenter, randomized, placebo-controlled clinical study of ANA001 in patients with moderate and severe COVID-19. The study duration for each participant will be approximately 62 days, including a 36-hour screening window. Screening and Day 1 may occur on the same day if screening criteria are met to confirm participant eligibility. After provision of informed consent, participants who satisfy all inclusion and no exclusion criteria will be randomized in a 1:1 ratio to be treated with ANA001 1000 mg BID or matching placebo. Randomization of participants will be stratified by oxygenation (SpO2 > 93 and < 98% on room air versus ≤ 93% on room air), diarrhea (presence versus absence), and age (< 65 and ≥ 65). Participants will be dosed within 36 hours of screening and as soon as possible following hospital presentation.



Participants will receive capsules of ANA001 or matching placebo for 7 consecutive days (defined as 14 doses administered BID) according to the assignment made by the randomization and trial supply management (RTSM) system. Additionally, participants will receive continued standard of care therapy (per study site policies or guidelines). Dosing will continue until the treatment course is completed. If the participant requires mechanical ventilation or for any other reason is unable to swallow oral medication over the course of the study, ANA001 will be administered via nasogastric (NG) or orogastric (OG) tube in accordance with the appropriate section in the study Pharmacy Manual. If the participant is discharged prior to completing the

treatment course, the remaining study drug will be dispensed for at-home administration. Every effort will be made to complete the remaining study assessments for participants who are not able to complete the 7-day consecutive course of study drug.

Upon successful completion of Part 1, the safety and efficacy of ANA001 1,000 mg PO BID for 7 consecutive days will be evaluated in a larger population of patients in Part 2.

4. STUDY ENDPOINTS AND COVARIATES

The following endpoints will be considered for Part 1.

4.1 Demographic and Baseline Disease Characteristics

Demographics characteristics include:

- Age at baseline (including number of participants 18 – <40, 40 – < 65, and ≥ 65 years)
- Sex at birth
- Ethnicity
- Race
- Height (m)
- Weight at Baseline (kg)
- Body mass index at Baseline (kg/m2) (including number of participants > 30 kg/m^2).

Baseline disease characteristics include:

- WHO Ordinal Scale for Clinical Improvement score
- Number of days from first symptom to randomization
- Number of COVID-19 symptoms
- Number of co-existing conditions (0, 1, 2, 3, ≥4) as determined by medical history and other screening data, including
    - Age at screening >60 years
    - Obesity, which is defined BMI at screening >30 kg/m^2
    - Hypertension
    - Cardiovascular disease
    - Chronic lung disease
    - Chronic kidney disease
    - Chronic liver disease
    - Chronic immunosuppression, and
    - Diabetes
- Respiration rate (<20, ≥ 20 to <25, ≥ 25 to <30, and ≥ 30 breaths per minutes)
- Pulse rate (<90, ≥ 90 to <100, ≥ 100 to <125, and ≥ 125 beats per minute)
- Temperature (≤ 38.3 versus > 38.3C)

- Peripheral capillary oxygen saturation (SpO_2) (>93% and <98% on room air versus <93% on room air)
- Fraction of Inspired Oxygen (SpO_2/FiO_2) (≤ or > 200)

4.2 Efficacy Endpoints

The primary endpoints for Part 1 of the study are safety endpoints including treatment-emergent adverse events (TEAEs), vital signs and laboratory (hematology, chemistry, and coagulation) parameters and are described in Section 4.3. The secondary and exploratory efficacy endpoints for Part 1 are described in the following sections.

4.2.1 Secondary Efficacy Endpoints

The secondary efficacy endpoint of Part 1 of this study is the median time (in hours) to hospital discharge (where discharge is defined as a score of 1 or 2 in the WHO Ordinal Scale for Clinical Improvement). For the purpose of deriving this efficacy endpoint, hospital discharge is defined as achieving WHO Ordinal Scale for Clinical Improvement score of:

- 1: Not hospitalized, no limitations on activities or
- 2: Not hospitalized, limitation on activities and/or requiring home oxygen.

4.2.2 Exploratory Efficacy Endpoints

The following are the exploratory efficacy endpoints of Part 1 of this study:

- Mean change from baseline in the NEWS-2 total score on Day 15
- Mean number of days on rescue treatment (COVID-19 therapies that are FDA approved or have emergency-use authorization) within 15 days after enrollment.
- Median time (in days) to resolution of subjective symptoms assessed by the Investigator to be potentially due to COVID-19 including: fever, cough (productive or non-productive), sore throat, malaise, headache, muscle pain, gastrointestinal symptoms (i.e., nausea, vomiting, or diarrhea), shortness of breath (with or without exertion), and respiratory distress
- Proportion of participants who's COVID-19 progresses to Severe or Critical within 15 days after enrollment
- Proportion of participants requiring ICU admission within 15 days after enrollment
- Mean change from baseline in SOFA score on Days 8 and 15
- Proportion of participants on Days 8 and 15 requiring:
    - Supplemental oxygen
    - High flow nasal cannula (HFNC) oxygen
    - Non-invasive positive pressure ventilation (NIPPV)
    - Mechanical ventilation
- Mean number of days on mechanical ventilation within 15 days after enrollment
- Mean number of oxygenation-free days within 15 days after enrollment

- Proportion of participants who achieve a score of 1 on the WHO Ordinal Scale for Clinical Improvement on Days 8 and 15
- Median time (in hours) to a 2-point improvement in the WHO Ordinal Scale for Clinical Improvement
- Incidence and severity of thromboembolic events within 15 days after enrollment
- Incidence of abnormal markers of inflammation to include CRP, IL-6, TF, MCP-1, and IP-10 on Day 8
- Mean change in viral load from baseline on Days 1, 4, 8, 15, and 28
- Median number of days to viral load undetectable by nasopharyngeal (NP) swab

4.3 Safety Endpoints

The following endpoints will be used to assess the safety and tolerability of ANA001:

- Incidence of treatment-emergent adverse events, serious adverse events, adverse events leading to study treatment discontinuation and adverse events leading to death
- Incidence of treatment-emergent potentially clinically significant laboratory abnormalities, including test results in the hematology, blood chemistry, and coagulation panels
- Incidence of vital signs abnormality, including temperature ($^{\circ}$C), systolic and diastolic blood pressure (mmHg), pulse (beats/min), and respiratory rate (breaths/min).

4.4 Covariates

Sample size permitting, the following randomization factors will be considered as covariates:

- Oxygenation (SpO2 > 93 and < 98% on room air, ≤ 93% on room air)
- Diarrhea (presence, absence), and
- Age at screening (<65, ≥65).

Additionally, baseline score of the WHO Clinical Improvement Scale and the number of co-existing conditions will be used as covariates.

5. ANALYSIS POPULATIONS AND SUBGROUPS

5.1 Analysis Populations

The following populations will be considered for analysis:

Randomized Set: It includes all randomized participants who satisfied the inclusion and exclusion criteria described in this protocol.

Full Analysis (or Intent-to-Treat [ITT]) Set: It is the analysis population for the primary efficacy analysis. It includes all randomized participants classified according to the treatment arm into which they were randomized regardless of the actual treatment received.

Safety Analysis Set: It includes all randomized participants, classified according to the actual treatment received regardless of randomization assignment, who received any amount of study drug and have at least one post-baseline safety evaluation. This is the analysis population for all planned safety analyses.

5.2 Subgroups

Sample size permitting, the following subgroups will be considered:

- Age at baseline: 18 – 40, 40 – <65, ≥ 65 years
- Sex: Male, Female
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino
- Race: While, African American/Black, Asian, Other
- Symptoms duration: < 7 days, ≥ 7 days
- Baseline score of the WHO Clinical Improvement Scale: 3, 4
- Co-existing conditions: chronic lung disease, cardiovascular or cerebrovascular disease, hypertension, diabetes, obesity, an immunocompromised state
- Peripheral Capillary Oxygen Saturation (SpO_2): > 93% and < 98% on room air versus ≤ 93% on room air.

6. ANALYTIC DEFINITIONS

Baseline Measurements will be the last measurement for the corresponding endpoint prior to the first dose of study drug.

Age at Baseline is the last non-missing age collected before the first dose of study drug.

Body Mass Index is calculated as (Weight in kg / (Height in meter)^2). The last non-missing weight and height collected before the first dose of study treatment will be used to calculate the baseline body mass index.

Study Drug Exposure is calculated as number of days from first dose day to last. That is:

Study Drug Exposure = Last Study Drug Date – First Study Drug Date + 1.

Study Drug Compliance (%) for a participant is calculated as: 100*total number of doses taken/total number of doses the participant was supposed to have taken during the treatment period. That is, 100*total number of doses taken ÷ (8* Study Drug Exposure [in Days]).

A Treatment-Emergent Adverse Event (TEAE) is any adverse event that occurs on or after first dosing and up through Day 28.

COVID-19 Rescue Treatments that are defined as any treatment approved under NDA or Emergency Use Authorization (EUA) for COVID-19 or off label medications given as direct treatment of COVID-19.

Concomitant Medication will be defined as the medications used on/after the first dose of study drug or started before first dose of study drug and continued during the study.

7. STATISTICAL ANALYSIS AND METHODOLOGY

The statistical analysis of the data of this protocol will be performed using SAS® version 9.4 or higher.

Unless otherwise specified, continuous endpoints will be summarized with number of non-missing observations (n), mean, standard deviation (SD), median, 25th quartile (Q_1) and 75th quartile (Q_3), minimum and maximum. In general, the same number of decimal places as in the raw data will be presented when reporting minimum and maximum, one more decimal place than in the raw data will be presented when reporting mean and median, and two more decimal places than in the raw data will be presented when reporting SD. If the raw data have 3 decimals or more, 3 decimals will be presented for mean, median, minimum, maximum, and standard deviation.

Categorical endpoints will be described using the number and percentage of participants in the various categories of the endpoint. One decimal will be presented for percentages. Percentages equal to 100 will be presented as 100%.

All two-sided inference tests will be performed at the 0.05 significance level and all one-sided inference tests will be performed at the 0.025 significance level.

7.1 Participant Disposition and Protocol Deviations

Participants' disposition will be described by reporting the number of randomized participants, the number and percentage of participants randomized but not treated, number and percentage of participants in each of the stratification factors, the number and percentage of participants in each analysis set by treatment group. Additionally, the number and percentage of participants who completed treatment and those who discontinued treatment early along with the reason for early treatment discontinuation as well as the number and percentage of participants who completed the study or withdrew early from the study along with the reason for early withdrawal from the study will be presented by treatment group.

Number and percentage of participants randomized by site number and investigator name will also be reported by treatment group.

Incidence of major protocol deviation will be tabulated by protocol deviation category and deviation for all participants in the Full Analysis Set.

7.2 Demographics and Baseline Disease Characteristics

Demographics characteristics listed in Section 4.1 will be summarized by treatment group for participants in the Full Analysis Set.

For baseline height, weight, and BMI, 24 hours window will be added for baseline values. To be more specific, the baseline value is defined as last non-missing value prior to first dose date + 1 day. For participants who are randomized but not dosed, baseline will be the last non-missing value prior to date of randomization.

Baseline disease characteristics listed in Section 4.1 will be summarized by treatment group for participants in the Full Analysis Set. It should be noted that:

- Co-existing medical conditions of interests include the following:
  - Age at screening >60
  - Obesity, which is defined BMI at screening >30 kg/m^2
  - Hypertension
  - Cardiovascular disease
  - Chronic lung disease
  - Chronic kidney disease
  - Chronic liver disease
  - Chronic immunosuppression, and
  - Diabetes

  Participants in immunocompromised will be identified during the blinded medical review of participants' baseline data.

- In calculating baseline SOFA score assume the following:

  - SOFA score for respiratory system could be calculated as follows:

SOFA Respiratory System Score	**PaO_2/FiO_2 (mmHg)**	**SpO_2 (%)**
0	> 400	> 96 on Room Air
1	301 – 400	> 93 and < 97 on Room Air > 93 on 1 L/min > 96 on 2 L/min
2	201 – 300	94 – 96 on 2 L/min

    For participants do not have SOFA score collected at baseline, the last non-missing SpO2 respiration score prior to the first dose will be used for the baseline value.
  - For participants not admitted to ICU, assume Glasgow Coma Score of 16

- Fraction of Inspired Oxygen (SpO_2/FiO_2) can be calculated as follows:

Oxygen Tank Flow Rate	FiO_2
Room Air	0.21
1 L/min Nasal Cannula	0.24
2 L/min Nasal Cannula	0.28

7.3 Treatment Exposure and Compliance

Number of doses received, treatment duration (in days) and percent of treatment compliance and compliance category (<80%, 80%-120%, >120%) will be summarized by treatment group for all participants in the Full Analysis Set.

COVID-19 rescue medications will be classified according to the anatomical therapeutic chemical (ATC) codes in the World Health Organization Drug (WHODRUG) dictionary; version B3 WHO Drug DDE – March 2020. The incidence rate of each classified medication will be tabulated by treatment group for all participants in the intent-to-treat population.

Concomitant medications will be classified and tabulated in a manner similar to rescue medications.

7.4. Efficacy Analysis for Secondary Endpoint

The secondary efficacy endpoint for Part 1 of this study is the median time (in hours) from randomization to hospital discharge (where discharge is defined as a score of 1 or 2 in the WHO Ordinal Scale for Clinical Improvement).

Kaplan-Meier curves will be constructed to display time-to- hospital discharge. Participants who are lost to follow-up or ended study early prior to achieving clinical improvement will be censored at the day of the last obtained assessment of their WHO Ordinal Scale for Clinical Improvement. Participants who complete follow-up without hospital discharge will be censored at the day of their Day 60 visit. Participants who die for any reason during the study will be right-censored at Day 60 or date of death, whichever is earlier. For the analysis of this efficacy endpoint, missing scores of the WHO Ordinal Scale for Clinical Improvement will be assumed to be > 2 (*i.e.*, no hospital discharge). Median time-to-clinical improvement and corresponding 95% confidence interval will be estimated from the Kaplan-Meier curves and tabulated for each treatment group.

The Cox proportional hazard method will be used to calculate the hospital discharge rate ratio of ANA001 relative to placebo while controlling for the stratification factors, baseline WHO Ordinal Scale for Clinical Improvement, and number of co-existing conditions. Hospital discharge rate ratio is akin to a hazard ratio but for the beneficial outcome of hospital discharge.

A hospital discharge rate ratio > 1 indicates a benefit for ANA001. Treatment groups will be compared using a stratified log-rank test.

The above analyses will be produced for all participants in the Full Analysis Set and by baseline WHO Ordinal Scale for Clinical Improvement scores. Additionally, the same analysis will be produced for participants in the Per-Protocol Analysis Set and Safety Analysis Set.

If WHO Ordinal Scale are missing at baseline, 6 hours window after first dose will be added for baseline values.

7.5 Efficacy Analysis for Exploratory Endpoints

As a general strategy, analyses of the exploratory efficacy endpoints will be presented for all participants in the Full Analysis Set.

7.5.1 Change from Baseline in NEWS-2

NEWS-2 will be administered daily for hospitalized participants. NEWS-2 total score will be calculated according to authors' instructions (Appendix B.1). For participants who get discharged from the hospital before Day 15, their last available NEWS-2 total score will be carried forward to Day 15.

Mean observed and mean change from baseline in NEWS-2 total score at Day 15 will be tabulated by treatment group. Additionally, the difference in the least-squares means and their standard errors adjusted for baseline NEWS-2 score, stratification factors, baseline WHO Ordinal Scale for Clinical Improvement score, and number of co-existing conditions will be tabulated. Corresponding 95% confidence interval of the difference between two least-squares means and p-value will also be reported.

7.5.2 Number of Days on COVID-19 Rescue Therapy

According to the protocol, participants are allowed to receive concomitant treatments during the course of the study per the standard-of-care at the investigational site. Some concomitant treatments (*e.g.*, treatments granted US FDA approval, Emergency Use Authorization or glucocorticoid therapy) may aid the cure of COVID-19. For the purpose of this analysis, medications that may have direct anti-viral effects or systemic effects on the acute inflammatory processes of the virus/COVID and are given more than 24 hours after study drug started and no more than 240 hours (10 days) after enrollment will be considered COVID-19 rescue therapy. All concomitant medications will be reviewed in a blinded fashion prior to the database lock by team members with appropriate background and training to identify concomitant treatment that may be considered COVID-19 rescue therapy.

Mean number of days on COVID-19 rescue treatment within 15 days after enrollment will be tabulated by treatment group. The difference in the least-squares mean and their standard errors adjusted for stratification factors, baseline WHO Ordinal Scale for Clinical Improvement score, and number of co-existing conditions will be tabulated. Corresponding 95% confidence interval of the difference between two least-squares means and p-value will also be reported.

Participants who do not require any COVID-19 rescue treatment during the study will be excluded from the analysis of this endpoint.

7.5.3 Duration of COVID-19 Symptoms

Subjective symptoms assessed by the investigators to be potentially due to COVID-19, including fever, cough (productive or non-productive), sore throat, malaise, headache, muscle pain, gastrointestinal symptoms (i.e., nausea, vomiting, or diarrhea), shortness of breath (with or without exertion), and respiratory distress will be captured and followed up until resolution.

Duration (in days) to resolution of subjective COVID-19 symptoms will be defined as:

End date of last COVID-19 symptom – Start date of first COVID-19 symptom+1.

Participants who did not have resolution of COVID-19 symptoms are censored at date of completion/withdrawal. Kaplan-Meier curves will be constructed to duration of COVID-19 symptoms for participants in each treatment group. The curves will be constructed in a manner similar to the primary efficacy endpoint (Section 7.4). Median duration of COVID-19 symptoms and corresponding 95% confidence interval will be presented for each treatment group.

7.5.4 Progression of COVID-19

The table below describes the criteria FDA adapted for severe and critical COVID-19:

Severity	**Criteria**
Severe	Development of one of the following: 1. Symptoms suggestive of severe illness, which could include any symptom of moderate illness PLUS shortness of breath at rest or respiratory distress, OR 2. Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate ≥30 breaths per minute, heart rate ≥125 beats per min, SpO_2 ≤93% on room air, AND No criteria for Critical Severity
Critical	Evidence of critical illness, defined by at least 1 of the following: 1. Respiratory failure requiring at least 1 of the following:

	a. Endotracheal intubation and mechanical ventilation, oxygen delivered by high flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5) b. Noninvasive positive pressure ventilation (NIPPV), OR c. Extracorporeal membrane oxygenation (ECMO) or clinical diagnosis of respiratory failure (i.e., clinical need for 1 of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation) 2. Shock (defined by systolic blood pressure (BP) <90 mm Hg, or diastolic BP <60 mm Hg or requiring vasopressors), OR 3. Multi-organ dysfunction/failure

The proportion of participants whose COVID-19 infection progresses to Severe or Critical at Day 15 along with the corresponding 95% binomial confidence interval will be reported by treatment group. Sample size permitting, reported binomial confidence intervals will be based on Wilson's score. Additionally, the difference in proportions will be reported along with the corresponding 95% confidence interval using Newcombe's method. Should the number of Severe or Critical COVID-19 infection be small, the exact distribution will be used instead of the normal approximation to derive the confidence intervals.

7.5.5 ICU Admission

The number and proportion of participants requiring ICU admission at any time within the first 15 days after enrollment will be tabulated by treatment group and Baseline WHO Ordinal Scale for Clinical Improvement score. The corresponding 95% binomial confidence interval will also be reported. Sample size permitting, Wilson's method will be used to derive these confidence intervals. The difference in proportions will also be reported with the corresponding 95% confidence interval using Newcombe's method. Should the number of observed admissions be small, the exact distribution will be used instead of the normal approximation to derive the confidence intervals.

Participants who did not get admitted to ICU will not contribute to this analysis

7.5.6 Sequential Organ Failure Assessment (SOFA) Score

The Sequential Organ Failure Assessment (SOFA) will be administered for all participants who get admitted to ICU. The SOFA will be scored according to authors' instructions (Appendix B.2). For participants who get discharged from ICU before Day 8 or Day 15, their last available SOFA score will be carried forward to Day 8 or Day 15, respectively.

Mean observed and mean change from baseline in SOFA score at Days 8 and 15 will be tabulated by treatment group. Additionally, the difference in the least-squares means and their standard errors adjusted for baseline SOFA score, stratification factors, WHO Ordinal Scale for Clinical Improvement score, and number of co-existing conditions will be tabulated. Corresponding 95% confidence interval of the difference between two least-squares means will also be reported.

Participants who did not get admitted to ICU will not contribute to this analysis.

7.5.7 Oxygen and Assisted Ventilation

Number and proportion of participants requiring each of the following on Days 8 and 15 will be tabulated by treatment group:

- Supplemental oxygen only: This is defined as nasal cannula and oxygen level 1-15 L/min or FiO2≤35%, or simple facemask, or non-rebreather
- High-flow nasal cannula (HFNC) oxygen: This is defined as nasal cannula and oxygen level>15L/min or FiO2>40% and up to 100%.
- Noninvasive positive pressure ventilation (NIPPV): This is defined as non-invasive CPAP or non-invasive - BIPAP
  Mechanical ventilation: This is defined as invasive – mechanical PPV, invasive – negative pressure, or invasive ECMO

Each proportion will be analyzed in a way similar to the analysis of proportion of participants requiring ICU Admission in Section 7.5.5. Additionally, the proportion of subjects requiring any of the above will also be analyzed.

Mean number of days on mechanical ventilation within 15 days after enrollment and mean number of oxygenation-free days within 15 days after enrollment will be tabulated by treatment group. Participants who are not off mechanical ventilation are censored at date of completion/withdrawal. Participants without requiring oxygenation within 15 days after enrollment are censored at Day 15 or date of completion/withdrawal, whichever is earlier.

Sample size permitting, these endpoints will be compared in a way similar to the analysis of the Duration of COVID-19 Symptoms in Section 7.5.3.

7.5.8 WHO Ordinal Scale for Clinical Improvement

Number and proportion of participants who achieve a score of 1 on the WHO Ordinal Scale for Clinical Improvement on Days 8 and 15 will be tabulated by treatment group and Baseline WHO Ordinal Scale and compared in a way similar to the analysis of ICU Admissions in Section 7.5.5.

The corresponding 95% binomial confidence interval will also be reported. Sample size permitting, Wilson's method will be used to derive these confidence intervals. The difference in proportions will also be reported with the corresponding 95% confidence interval using Newcombe's method. Should the number of observed admissions be small, the exact distribution will be used instead of the normal approximation to derive the confidence intervals.

Similarly, the number and proportion of participants who achieve 2-point improvement from baseline in the WHO Ordinal Scale for Clinical Improvement on Days 8 and 15 will be analyzed based on Full Analysis Set. Median number of days to a 2-point improvement will be tabulated by treatment group and compared in a way similar to the analysis of duration of COVID-19 symptoms in Section 7.5.3. The same analysis will be provided in the Safety Analysis Set.

7.5.9 Thromboembolic Events

All adverse events will be reviewed in a blinded fashion prior to the database lock by team members with appropriate background and training. The team will identify adverse events with an onset date within 15 days after enrollment that may be considered thromboembolic.

Incidence and severity of thromboembolic events will be tabulated by treatment group and compared in a way similar to the analysis of ICU Admissions in Section 7.5.5.

7.5.10 Inflammation Markers Associated with Acute Respiratory Distress Syndrome (ARDS)

The following inflammation markers associated with acute respiratory distress syndrome will be analyzed at a central lab: CRP, IL-6, TF, MCP-1, and IP-10. An inflammation marker is considered abnormal if the reported value is > ULN.

Incidence of abnormal inflammation markers at Day 8 will be tabulated by treatment group and compared in a way similar to the analysis of ICU Admissions in Section 7.5.5.

7.5.11 Viral Dynamics

Observed mean and mean change in log-transformed viral load from baseline on Days 1, 4, 8, 15, and 28 will be tabulated by treatment group and compared similar to the analysis of the SOFA score in Section 7.5.6.

Time-to-viral load undetectable (*i.e.*, <LOD) by nasopharyngeal swab is defined as the number of days from randomization to achieving undetectable viral load. That is:

(Date/Time to Undetectable Nasopharyngeal Swap – Date/Time of Randomization)/24.

Participants who are lost to follow-up or ended study early prior to achieve Undetectable Nasopharyngeal Swap will be censored at the day of the last obtained assessment. Median

number of days to undetectable will be tabulated by treatment group and compared in a way similar to the analysis of duration of COVID-19 symptoms in Section 7.5.3.

7.6 Safety Endpoints

Safety data will be summarized descriptively. No inferential statistics will be provided. All safety analyses and summaries will be based on the Safety analysis set.

7.6.1 Adverse Events

Treatment-emergent adverse events reported during the study will be coded using a MedDRA dictionary. Incidence of treatment-emergent adverse events will be summarized by treatment group and the following:

- Preferred term
- System organ class and preferred term.

These summaries will be presented for the following subsets:

- All adverse events
- Serious adverse events
- Drug-related adverse events
- All adverse events with severity ≥Grade 3
- All adverse events leading to death
- All adverse events leading to study treatment discontinuation.

A participant with multiple occurrences of the same adverse event or a continuing adverse event will only be counted once for tables reporting adverse events by preferred term and system organ class.

For tables reporting adverse events by severity, if a participant has multiple occurrences of an adverse event with the same organ class and preferred term, the most severe event will be presented. Adverse events with missing severity will be imputed to Grade 3. Additionally, for tables reporting adverse events by relationship, if a participant has multiple occurrences of an adverse event with the same organ class and preferred term, only the strongest relationship level will be presented in the relationship summary. Adverse events with missing relationship will be imputed as drug-related. Details on the treatment of missing data are provided in Section 11.2.

7.6.2 Clinical Laboratory Evaluation

Laboratory parameters will be summarized by treatment group at each visit. Each summary will include the values of the laboratory parameters and their change from baseline. Shift tables from baseline will be presented for laboratory values in the chemistry and hematology panels that are captured categorically. Parameters will be classified as potentially clinically significant according to the criteria described in Appendix C. In addition, the laboratory results will be

graded by CTCAE v5.0 and the summary of treatment-emergent laboratory results by highest CTCAE grade will be summarized.

7.6.3 Vital Signs

Vital signs, including pulse, blood pressure, temperature, respiratory rate and body weight will be summarized by treatment group and time point. For each assessment of vital signs, change and percent change in vital signs from baseline will be summarized by treatment group.

8. VISIT WINDOW

Implementation of visit windows is not planned for the analysis of this study. Results will be analyzed according to reported visits.

9. MULTIPLICITY ADJUSTMENT

There are no plans to implement any adjustment to type-I error for Part 1 analyses as the primary endpoint is safety.

10. HANDLING OF MISSING DATA

10.1 Missing Efficacy Data

Missing data for the secondary efficacy endpoint is discussed in Section 7.4. Limited imputation of missing data is planned for exploratory efficacy endpoints.

10.2 Adverse Events Missing Data

Treatment-emergent adverse events (TEAEs) with missing severity will be considered Grade 3 and TEAEs with missing relationship will be counted as drug-related.

In cases where the start date is not complete, the assumption will be made that the adverse event is a treatment-emergent event unless there is evidence to the contrary. The first treatment start date will be used as the AE start date if the start date is missing. Missing adverse event end dates will not be imputed. The adverse event will be assumed to be ongoing if end date is missing.

10.3 Concomitant Medications Missing Dates

In cases where the start or stop dates are not complete, the assumption will be made that the medication is a concomitant medication unless there is evidence to the contrary.

If the year and month are available (and only day is missing) the first day of the month will be used to impute the start date, and the last day of the month will be used to impute the stop date.

If only the year is available and it is before the year of first study treatment date, January will be used to impute the start date and December will be used to impute the stop date. If the year is equal to the year of the first study treatment date, month and day of the first study treatment date

will be used to impute the start date, and month of the last study treatment date will be used to impute the stop date.

If the start or stop date is completely missing, the first study treatment date will be used to impute the start date, and the last study treatment date to impute the stop date.

Imputed dates will be used for categorization of medications to concomitant or prior, but data listings will present the date as recorded on the Case Report Forms.

APPENDIX A. SCHEDULE OF EVENTS (STUDY PART 1 AND STUDY PART 2)

Study Day (All Study Days are calendar days)	**Screening[a]**	**Day 1**	**Day 2[b]**	**Day 3[b]**	**Day 4**	**Day 5[b]**	**Day 6[b]**	**Day 7[b]**	**Day 8/ET[s]**	**Day 15**	**Day 28**	**Day 60/ES[b]**
Window	**36 hours[a]**									**±3 days**	**+2 days**	**+2 days**
Informed consent	X											
Demographics	X											
Eligibility assessment	X											
Medical history[c]	X											
Height and weight for BMI[d]		X										
Randomization		X										
NEWS2[e,n], vital signs, COVID-19 severity and subjective symptoms of COVID-19 [n]	X	X	X	X	X	X	X	X	X	X	X	X
Record SpO_2 and supplemental oxygen, and type of ventilation, if applicable[e,f]	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination (excluding GU)		X							X			
Targeted physical examination	X											
Study drug administration[g]		X	X	X	X	X	X	X	X			
Serum chemistry[h, p]		X	X	X	X	X	X	X	X			
Hematology and coagulation[i, p]		X	X	X	X	X	X	X	X			
D-dimers (central lab) [j]		X			X				X			
CRP (central lab) [j]		X			X				X			
Cardiac troponin (central lab) [j]		X			X				X			
LDH (central lab) [j]		X			X				X			
Ferritin (central lab) [j]		X			X				X			
NP swab for confirmation of SARS-CoV-2 with RT-PCR[k] (local site lab)	X	Per local SOC										

Window	**36 hours[a]**									**±3 days**	**+2 days**	**+2 days**
NP swab for confirmation of SARS-CoV-2 with qRT-PCR [k] (central lab)		X			X				X	X	X	
PK sampling [l] (Part 1 Only)		X										
WHO Ordinal Scale for Clinical Improvement[e,m]	X	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray	Per local SOC											
AE assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[e,r]	X	X	X	X	X	X	X	X	X	X	X	X
SOFA[e,o]		X	X	X	X	X	X	X	X	X	X	X
Blood for exploratory tests [j] (e.g., IL-6, Tissue Factor, MCP-1 and IP-10)		X							X			
Serum pregnancy test for females of childbearing potential	X											

[a] Screening assessment are to be completed within 36 hours of randomization. Screening and Day 1 may occur on the same day if results are available to confirm participant eligibility (SARS-CoV-2-positive NP swab confirmed with RT-PCR or alternative Sponsor approved assay at screening).

[b] It may not be possible to conduct all study visits in-person due to quarantine and other infection control measures. In case where in-person visits are not possible, telemedicine appointments should be conducted. All visits are required to be conducted as in-person visits (due to sample collection requirements) except for Days 2, 3, 5 ,6, and 7 (if discharged home with study drug for self-administration) and the EOS/Day 60 (+2) visit which may be conducted by a telemedicine appointment. For telemedicine appointments, all data should be collected, and the following should be reviewed/discussed in detail with the participant: AEs, clinical status, and hospital readmission.

[c] Any history or current presence of signs and symptoms associated with COVID-19 within 14 days prior to screening, including fever, cough (productive or non-productive), sore throat, malaise, headache, muscle pain, gastrointestinal symptoms (i.e., nausea, vomiting, or diarrhea), shortness of breath (with or without exertion), and respiratory distress. Other medical history within 14 days prior to enrollment and presence of comorbidities especially cardiovascular disease, pulmonary disease (e.g., COPD, asthma), hypertension, diabetes, and obesity, is to be recorded.

[d] If the participant is unable to be measured for weight and height, stated weight and height is acceptable.

[e] Assessments should be collected daily while hospitalized **including any day after Day 8** that the patient remains in the hospital. NEWS2 (Appendix 2) score to be assessed 2 to 6 hours post-first dose per day. If first dose assessments are missed, use the same collection timepoint post-second dose of the day (2-6 hours post-dose).

[f] If mechanically ventilated (or ECMO), document PaO_2 and FiO_2. SpO_2 and any supplemental oxygen saturation and rate at SpO_2 determination timepoint; also, any noninvasive ventilation (No, yes; if yes, designate type). For intubated patients, record PaO_2 and FiO_2 values of the worst P-F ratio of the calendar day.

[g] Dosing should be performed within 36 hours of screening and continue until the treatment course is completed. Study drug is to be administered for 7 consecutive days (defined as 14 doses administered BID). ANA001 or matching placebo should be taken with a meal. If the participant is ventilated, study drug may be administered via NG or OG tube. Please refer to the Pharmacy Manual for instructions for NG or OG administration. Total duration of study drug administration is a 7-day course of treatment.

[h] Chemistry labs to be collected pre-dose (prior to first study drug dose of the day) and include the following: BUN, creatinine, sodium, potassium, chloride, carbon dioxide, glucose, direct bilirubin, total bilirubin, ALP, AST, and ALT

[i] Hematology and coagulation samples will be collected prior to first study drug dose of the day and include a CBC (consisting of hemoglobin, hematocrit, total WBC count with 5-part differential, and platelet count) plus a partial thromboplastin time (aPTT), a thrombin time (PT), and an international normalized ratio (INR).

[j] Test sample is for central lab assessment. Additionally, a central lab blood sample for each participant and timepoint collected will be stored for possible virology testing (e.g., genotypic resistance testing).

[k] NP swab for assessment of viral load is to be obtained at the indicated timepoints. Laboratory-confirmed SARS-CoV-2 infection as determined by RT-PCR, or other Sponsor approved assay used by the investigational site is to be obtained at Screening prior to baseline (Day 1). If a positive RT-PCR result for SARS-CoV-2 was collected as part of SOC during the study screening window, the result may be used to fulfill the applicable inclusion criteria. Quantitative assessment of viral load by qRT-PCR will be performed by an external central lab. Please refer Central Laboratory Manual for sample collection instructions. NP swab may be collected at any time during the day.

[l] PK samples will be collected for Part 1 ONLY. Blood samples (Primary and Back-Up) for PK are to be collected either on Day 1, 2, 3, **or** Day 4 at pre-dose (i.e., within 30 minutes), 1 hour (+/- 30 minutes) , 4 hour (+/- 30 minutes), 8 hour (+/- 30 minutes) and pre-dose to next study drug (i.e., within 30 minutes) administration. Remaining blood plasma volume may be used for exploratory analyses (e.g., IL-6 and TF). Please refer to the Central Laboratory Manual for additional sample collection and processing instructions (Appendix 6).

[m] Appendix 1 summarizes the criteria for daily WHO Ordinal Scale for Clinical Improvement score. The WHO Ordinal Scale for Clinical Improvement score should be determined concomitantly with the NEWS2 variables. Assessments should be collected daily while hospitalized including any day after Day 8 that the patient remains in the hospital.

[n] Appendix 2 summarizes the criteria for NEWS2. The parameters (e.g., vital signs, SpO_2, oxygen requirement) used to determine the NEWS2 score will be entered into the eCRF. Concurrently with determination of NEWS2, vital signs (including: pulse, respiratory rate, blood pressure (systolic and diastolic), and temperature), severity of the participant's COVID-19 infection (based on criteria in Appendix 4), and subjective clinical signs and symptoms of COVID-19 will be assessed and include presence or absence of: fever, cough (productive or non-productive), sore throat, malaise, headache, muscle pain, gastrointestinal symptoms (i.e., nausea, vomiting, or diarrhea), shortness of breath (with or without exertion), and respiratory distress. Assessments should be collected daily while hospitalized **including any day after Day 8** that the patient remains in the hospital.

[o] Appendix 3 summarizes the criteria for SOFA score. SOFA score to be calculated only for participants admitted to the ICU.

[p] Appendix 5 summarizes Laboratory Assessments.

[q] Appendix 6 summarizes PK Sample Collection Schedule (Part 1 Only).

[r] All prescription and over-the-counter systemic (i.e., oral, intravenous, intramuscular, inhaled, subcutaneous, or systemically absorbed transdermal) medications being administered or being taken by the participant from prior to randomization (considered prior medications) and from randomization through the Day 60 visit (considered concomitant medications). For this study, all enteral nutrition and administration of blood products will also be considered as medication.

[s] Assessments (including NEWS2, vital signs, severity of COVID-19, subjective symptoms of COVID-19, SpO_2, WHO Ordinal Scale for Clinical Improvement, AEs, concomitant medications, and SOFA score, should be collected daily while hospitalized **including any day after Day 8** that the patient remains in the hospital. Results will be collected on an Unscheduled Visit eCRF.

APPENDIX B. QUESTIONNAIRE SCORING

B.1 NATIONAL EARLY WARNING SCORE 2 (NEWS2)

The NEWS-2 is based on a simple aggregate scoring system in which a score is allocated to physiological measurements when participants present to, or are being monitored in hospital. Six simple physiological parameters form the basis of the scoring system:

- Respiration Rate (0 – 3)
- Oxygen Saturation (0 – 3)
- Systolic Blood Pressure (0 – 3)
- Pulse Rate (0 – 3)
- Level of consciousness or new confusion (0 – 3)
- Temperature (0 – 3)

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	

A score is allocated to each parameter as they are measured, with the magnitude of the score reflecting how extremely the parameter varies from the norm. The score is then aggregated and uplifted by 2 points for people requiring supplemental oxygen to maintain their recommended oxygen saturation. The higher the NEWS, the more critical is the state of the participant.

B.2 SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE

The SOFA score is based on a simple aggregate scoring system in which a score is allocated to the following six simple physiological parameters:

- Respiration (0 – 4)
- Coagulation (0 – 4)
- Liver (0 – 4)
- Cardiovascular (0 – 4)
- Central Nervous System (0 – 4)
- Renal (0 – 4)

SOFA score	0	1	2	3	4
Respiration[a]					
PaO_2/FIO_2 (mm Hg)	>400	301 – 400	201 – 300	101 – 200	≤100
Coagulation					
Platelets ($\times 10^3/mm^3$)	>150	101 – 150	51 – 100	21 – 50	≤20
Liver					
Bilirubin (mg/dL)	<1.2	1.2 – 1.9	2.0 – 5.9	6.0 – 11.9	≥12.0
Cardiovascular[b]					
Hypotension	None	MAP <70 mmHg	Dopamine ≤5 or dobutamine (any dose) [a]	Dopamine >5	Dopamine >15
Central Nervous System					
Glasgow Coma Score		13 – 14	10 – 12	6 – 9	<6
Renal					
Creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2 – 1.9	2.0 – 3.4	3.5 – 4.9 or <500	>5.0 or <200

FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen; MAP, mean arterial pressure; SaO_2, peripheral arterial oxygen saturation
[a] Vasoactive mediations administered for at least 1 hr (dopamine and norepinephrine µmg/kg/min)

A score is allocated to each parameter as they are measured, with the magnitude of the score reflecting how extremely the parameter varies from the norm. The score is then aggregated. The higher the SOFA score, the more critical is the state of the participant.

APPENDIX C. POTENTIALLY CLINICALLY SIGNIFICANT LABORATORY CRITERIA

Local Laboratory					
Parameter	**SI Unit**	**Lower Limit**	**Higher Limit**	**% Decrease from BSL**	**% Increase from BSL**
CHEMISTRY					
Blood urea nitrogen (BUN)	mmol/L	NA	>1.5*ULN	NA	>100
Creatinine	mg/dL	NA	>1.5*ULN	NA	>50
Sodium	mmol/L	<0.85*LLN	>1.1*ULN	>10	>10
Potassium	⌠mol/L	<0.8*LLN	>1.2*ULN	>20	>20
Chloride	mmol/L	<0.8*LLN	>1.2*ULN	>20	>20
Carbon dioxide (Bicarbonate)		<0.7*LLN	>1.3*ULN	>40	>40
Glucose	mmol/L	<0.6*LLN	>3.0*ULN	>40	>200
Total bilirubin	mg/dL	NA	>2.5*ULN	NA	>150
Direct bilirubin	mg/dL	NA	>1.5*ULN	NA	>150
Alkaline Phosphatase	U/L	<0.5*LLN	>2.0*ULN	>80	>100
Aspartate Aminotransferase (AST)	U/L	NA	>3.0*ULN	NA	>200
Alanine Aminotransferase (ALT)	U/L	NA	>3.0*ULN	NA	>200
HEMATOLOGY					
Hematocrit	Ratio	<0.8*LLN	>1.3*ULN	>20	>30
Hemoglobin	g/L	<0.8*LLN	>1.3*ULN	>20	>30
Platelet Count	10^9/L	<0.65*LLN	>1.5*ULN	>50	>100
White Blood Cell Count	10^9/L	<0.65*LLN	>1.6*ULN	>60	>100
Neutrophils, absolute cell count	10^9/L	<0.65*LLN	>1.6*ULN	>75	>100
Lymphocytes, absolute count	10^9/L	<0.25*LLN	>1.5*ULN	>75	>100
Eosinophils, absolute count	10^9/L	NA	>4.0*ULN	NA	>300
Monocytes, absolute count	10^9/L	NA	>4.0*ULN	NA	>300

Basophils, absolute count	10^9/L	NA	>4.0*ULN	NA	>300
COAGULATION					
Partial thromboplastin time (aPTT)	sec	<0.5*LLN	>2.0*ULN	>100	>100
Prothrombin time (PT)	sec	<0.5*LLN	>2.0*ULN	>100	>100
International normalized ratio (INR)	Ratio	<0.5*LLN	>2.0*ULN	>100	>100

LLN: Lower limit of normal value provided by the local laboratory
ULN: Upper limit of normal value provided by the local laboratory
BSL: Baseline

Central Laboratory Results

Parameter	SI Unit	Lower Limit	Higher Limit	% Decrease from BSL	% Increase from BSL
ADDITIONAL TESTING					
D-Dimer	ng/mL	NA	>1.0*ULN	NA	>20
Cardiac troponin	ng/mL	NA	>1.0*ULN	NA	>30
Ferritin	ng/mL	NA	>1.2*ULN	NA	>30
LDH	U/L	<0.4*LLN	>4.0*ULN	>60	>300
CRP	mg/dL	<1.0*ULN	>1.3*ULN	>80	>50

LLN: Lower limit of normal value provided by the local laboratory
ULN: Upper limit of normal value provided by the local laboratory
BSL: Baseline