A Phase 2/3 Randomized and Placebo-Controlled Study of ANA001 in Moderate and Severe COVID-19 Patients

Investigational Product(s)	ANA001 (Niclosamide capsules)
Protocol Number	ANA001-001
Version Number	5.0 (ANA001-001.05)
Version Date	03-Feb-2022
Amendment	Amendment 4
Sponsor	NeuroBo Pharmaceuticals, Inc. 200 Berkeley Street, 19th Floor Boston, MA 02116
Sponsor Medical Representative	Douglas Rank, MD Director, Clinical Development drank@neurobopharma.com

Confidentiality Statement

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCP) as outlined by International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use E6 (R2), and all applicable local and national regulatory requirements. Screening at any clinical study site may not begin prior to Ethics Committee (EC) or Institutional Review Board (IRB) approval.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment, unless allowed by regulatory guidelines (e.g., when necessary to eliminate immediate hazard to the participants). Reconsent of previously enrolled participants may be necessary depending on the nature of the amendment.

The principal investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the IRB of record, unless such a change is necessary to eliminate an immediate hazard to the study participants.

All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training as outlined by their governing institution.

SPONSOR'S APPROVAL

Study Title	A Phase 2/3 Randomized and Placebo-Controlled Study of ANA001 in Moderate and Severe COVID-19 Patients
Protocol Number	ANA001-001
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The design of this study as outlined by this protocol has been reviewed and approved by the Sponsor's responsible personnel as indicated in the signature table below.

Sponsors Responsible Personnel			
Name:	**Title:**	**Signature:**	**Date:**
Doug Rank	Director, Clinical Development	DocuSigned by: Doug Rank Signer Name: Doug Rank Signing Reason: I approve this document Signing Time: 2/4/2022 | 7:06:33 PM PST 4B48F1AF5162489FB2A513290AD7BE86	[DD-MMM-YYYY] 2/4/2022

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study ANA001-001 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all investigational products provided by the Sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the IRB/EC of record for my clinical site, and GCP as outlined by ICH E6 (R2).
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent and updated consent in the event of new information or amendments, as required from all participants (or their legally authorized representative) enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those participants
- To maintain records of each participant's participation and all data required by the protocol
- To permit monitoring, auditing, and inspection by the Sponsor, its designated representatives, and regulatory authorities

Name [Last, First Name]	**Title at Institution**	**Site Number**
Signature		**Date** [DD-MMM-YYYY]

Site Name	**Site Address**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE2	Angiotensin converting enzyme 2
ADAM17	ADAM Metallopeptidase Domain 17
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMP	Amplifier
ANGII	Angiotensin II
aPTT	Partial thromboplastin
AR	Adverse reaction
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
AT1R	Angiotensin II receptor type 1 receptor
BID	Twice daily
BL	Baseline
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CATB/L	Cathepsin B and L
CBC	Complete blood count
CCR	Chemokine receptor
C_{max}	Maximum observed serum concentration
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
CPE	Cytopathic effects
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DAIDS	Division of AIDS
DIC	Disseminated intravascular coagulation
DG	Dose group
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EC	Ethics Committee
ECMO	Extracorporeal membrane oxygenation
EC_{50}	Half maximal effective concentration
eCRF	Electronic case report form
EDC	Electronic data capture
EOS	End of study

Abbreviation	Definition
EOT	End of treatment
FIO_2	Fraction of inspired oxygen
GCP	Good Clinical Practices
GI	Gastrointestinal
GRAS	Generally recognized as safe
GU	Genitourinary
HPMC	Hydroxypropylmethylcellulose
HR	Heart rate
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
IC_{100}	Total inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonization
ICU	Intensive care unit
IEC	Independent ethics committee
IL	Interleukin
IL-6	Interleukin-6
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
JAK	Janus kinase
LDH	Lactate dehydrogenase
LRTI	Lower respiratory tract infection
LTFU	Long-term follow-up
Mabs	Monoclonal antibodies
MERS-CoV	Middle East respiratory syndrome coronavirus
MODS	Multiple organ dysfunction syndrome
N	Sample size
NDA	New Drug Application
NEWS2	National Early Warning Score 2
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NIPVV	Noninvasive positive pressure ventilation
NG	Nasogastric
NP	Nasopharyngeal
OG	Orogastric
PaO_2	Partial pressure of oxygen
PD	Pharmacodynamics
PEG	Percutaneous endoscopic gastrostomy
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/Pharmacodynamic
PO	By mouth
PRRs	Pattern-recognition receptors

Abbreviation	Definition
PTT	Prothrombin time
RR	Respiratory rate
RT-PCR	Reverse transcriptase polymerase chain reaction
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Suspected adverse reaction
SARS-CoV	Severe acute respiratory syndrome coronavirus
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SOC	Standard-of-care
SOE	Schedule of events
SOFA	Sequential Organ Failure Assessment
SpO_2	Peripheral capillary oxygen saturation
STAT	Signal transducers and activators of transcription
STAT3	Signal transducer and activator of transcription 3
SUSAR	Suspected unexpected serious adverse reaction
T2D	Type 2 diabetes
TEAE	Treatment-emergent adverse event
TF	Tissue factor
TID	Thrice daily
t_{max}	Time at which C_{max} is observed
TMPRSS2	Transmembrane serine protease 2
TNF-α	Tumor necrosis factor alpha
WBC	White blood cell
WHO	World Health Organization

1 SYNOPSIS

Title	A Phase 2/3 Randomized and Placebo-Controlled Study of ANA001 in the Treatment of Moderate and Severe COVID-19 Patients
Phase	2/3
Study Design	This is a randomized, double blind, placebo-controlled multicenter study to investigate the safety and efficacy of ANA001 in the treatment of subjects with moderate and severe coronavirus disease 2019 (COVID-19). A total of 436 subjects who meet all eligibility criteria at Screening will be randomized to be treated with ANA001 1,000 mg twice daily (BID) or matching placebo administered orally (PO). Randomization will be stratified by oxygenation (SpO_2 >93 and <98% on room air versus SpO_2 ≤93% on room air), diarrhea (presence/absence), and age (<65/≥65). Each subject will be treated for 7 consecutive days. Additionally, every subject will be followed up for safety and efficacy up to day 60 (+2 days) after first dose. The study consists of 2 parts: Study Part 1: It includes 60 subjects randomized in 1:1 ratio to receive ANA001 or matching placebo to assess the safety and tolerability of ANA001 1,000 mg BID for 7 days. An independent Data Monitoring Committee will review the safety profile of ANA001 1,000 mg PO BID prior to the initiation of Part 2 of the study. Study Part 2: It includes 376 subjects randomized in 1:1 ratio to receive ANA001 or matching placebo to demonstrate the statistical superiority of ANA001 1,000 mg PO BID for 7 days compared with matching placebo in the treatment of subjects with moderate and severe COVID-19. Additionally, the safety profile of ANA001 will be assessed compared with placebo.
Rationale	Niclosamide has demonstrated both antiviral and immunomodulatory activity with possible beneficial downstream effects on coagulation abnormalities observed in COVID-19. These effects support the development of ANA001, an oral formulation of niclosamide, for the treatment of COVID-19. Hypothesis: ANA001 will reduce viral load and inflammation associated with cytokine dysregulation, acute respiratory distress syndrome (ARDS), and coagulation abnormalities and thus improve time to clinical improvement defined as hospital discharge recorded using the WHO Ordinal Scale for Clinical Improvement (Appendix 1).
Target Population	Patients with moderate and severe COVID-19 who fulfill the study entry criteria
Number of Participants	Total: Approximately 436 participants Part 1 (60 participants): 30 ANA001 + 30 matching placebo Part 2 (approximately 376 participants): 188 ANA001 + 188 matching placebo
Intervention	ANA001 1,000 mg PO BID or matching placebo for 7 days (i.e., 14 scheduled doses comprised of 56 capsules in total): All participants will also receive unrestricted access to standard-of-care as defined by the respective study sites.
Primary Objective and Primary Endpoints/Parameters (Part 1)	Objective: • To evaluate the safety and tolerability of ANA001 as therapy for moderate and severe COVID-19 patients Endpoints/Parameters: • Treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), deaths, and discontinuations due to a TEAE • Vital signs and laboratory (hematology, chemistry, and coagulation) parameters
Secondary Objectives and Secondary Endpoints (Part 1)	Objectives: • To evaluate the efficacy of ANA001 as therapy in moderate and severe COVID-19 patients

	• To evaluate the PK of ANA001 Endpoints: • 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 • Plasma concentrations of ANA001 will be explored on Day 1, 2, 3, or Day 4
Exploratory Objectives and Exploratory Endpoints (Part 1)	Objectives: • To evaluate clinical improvement using National Early Warning Score 2 (NEWS2) • To evaluate the need and duration of rescue therapy • To evaluate the effect on subjective symptoms of COVID-19 • To evaluate progression of COVID-19 from moderate or severe to more severe (i.e., moderate to severe, moderate to critical, or severe to critical) • To evaluate the effect of ANA001 on requirement for oxygen and/or assisted ventilation • To evaluate time to resolution of the WHO Ordinal Scale for Clinical Improvement • To evaluate the effect of ANA001 on thromboembolic events • To evaluate the relationship of ANA001 and markers of inflammation associated with acute respiratory distress syndrome (ARDS) • To evaluate the relationship between ANA001 plasma concentrations and viral dynamics Endpoints: • Mean change from baseline (BL) in NEWS2 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 (Appendix 4) within 15 days after enrollment • Proportion of participants requiring ICU admission within 15 days after enrollment • Mean change from baseline (BL) in SOFA score on Day 8 and Day 15 • Proportion of participants requiring supplemental O_2, high-flow nasal cannula (HFNC) oxygen, noninvasive positive pressure ventilation (NIPPV) or mechanical ventilation on Day 8 and Day 15 • 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 in the WHO Ordinal Scale for Clinical Improvement (Appendix 1) on Day 8 and Day 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 (CRP, IL-6, TF, MCP-1, and IP-10) on Day 8 • Mean change in viral load from baseline (BL) on Days 1, 4, 8, 15, and 28 • Mean time (in days) to viral load undetectable by nasopharyngeal (NP) swab
Primary Objectives and Primary Endpoints (Part 2)	Objectives: • To evaluate the efficacy of ANA001 as therapy in moderate and severe COVID-19 patients • To evaluate the safety and tolerability of ANA001 as therapy for moderate and severe COVID-19 patients Endpoints/Parameters: • Time to clinical improvement as measured by 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) • TEAEs, treatment-emergent SAEs, deaths, and discontinuations due to a TEAE • Vital signs and laboratory (hematology, chemistry, and coagulation) parameters
Secondary Objectives and Secondary Endpoints (Part 2)	Objectives: • To evaluate clinical improvement using NEWS2 • To evaluate the need and duration of rescue therapy Endpoints: • Mean change from baseline (BL) in NEWS2 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
Exploratory Objectives and Exploratory Endpoints (Part 2)	Objectives: • To evaluate the effect on subjective symptoms of COVID-19 • To evaluate progression of COVID-19 from moderate or severe to more severe (i.e., moderate to severe, moderate to critical, or severe to critical) • To evaluate the effect of ANA001 on requirement for oxygen and/or assisted ventilation • To evaluate time to resolution of the WHO Ordinal Scale for Clinical Improvement • To evaluate the effect of ANA001 on thromboembolic events • To evaluate the relationship of ANA001 and markers of inflammation associated with acute respiratory distress syndrome (ARDS) • To evaluate the relationship between ANA001 and viral dynamics Endpoints: • 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 (Appendix 4) within 15 days after enrollment • Proportion of participants requiring ICU admission within 15 days after enrollment • Mean change from baseline (BL) in SOFA score on Day 8 and Day 15

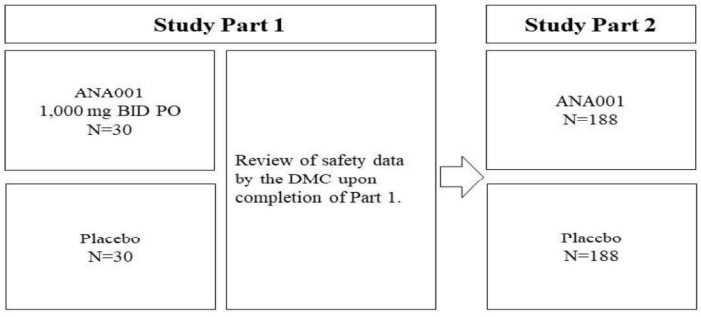
	• Proportion of participants requiring supplemental O_2, high-flow nasal cannula (HFNC) oxygen, noninvasive positive pressure ventilation (NIPPV) or mechanical ventilation on Day 8 and Day 15 • Mean number of days on mechanical ventilation within 15 days after enrollment • Mean number of oxygenation-free days within 15 days after enrollment • Proportion of participants who achieve a score of 1 in the WHO Ordinal Scale for Clinical Improvement (Appendix 1) on Day 8 and Day 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 (CRP, IL-6, TF, MCP-1, and IP-10) on Day 8 • Mean change in viral load from baseline (BL) on Days 1, 4, 8, 15, and 28 • Mean time (in days) to viral load undetectable by nasopharyngeal (NP) swab
Number of Sites	Approximately 20 study sites in the United States
Participant Duration	Treatment Duration: 7 consecutive days (defined as 14 doses administered BID) Total study duration (including screening period through the end of study visit): Approximately 60 (+2) days
Study Duration	The study will last approximately 1.5 years.
Inclusion Criteria	To be included in this study, an individual must satisfy all the following criteria: 1. Willing and able to provide written informed consent (or their legally authorized representative) prior to performing study procedures. If necessary, emergency consent may be obtained per local procedures. 2. Hospitalized. 3. Understands and agrees to comply with planned study procedures, including ability and willingness to swallow multiple small capsules. 4. Male or female adult ≥18 years of age at the time of informed consent. 5. Positive for SARS-CoV-2 by a standard RT-PCR assay or alternative Sponsor approved assay within 7 days of randomization and no more than 36 hours after hospitalization. 6. Presence of symptoms of lower respiratory tract infection (LRTI) including at least 1 of the following: fever, cough, sore throat, malaise, headache, muscle pain, or more significant lower respiratory tract symptoms, including shortness of breath (at rest or with exertion). 7. At least 1 of the following: respiratory rate (RR) ≥20 breaths per minute, room air SpO_2 <98%, requirement for supplemental oxygen, heart rate (HR) ≥90 beats per minute, or temperature >38.3°C. 8. Access to a telemedicine platform for outpatient visits in cases where visits to the study site are not possible (e.g., telephone, smartphone, tablet, or computer). 9. Women of childbearing potential must agree to abstinence from heterosexual intercourse or use at least 1 form of contraception not including hormonal contraception from the day of screening through Day 30.
Exclusion Criteria	If an individual meets any of the following criteria at screening, he or she is ineligible for this study: 1. Hospitalized, but no longer requires ongoing inpatient medical care (i.e., hospital discharge is anticipated in ≤24 hours. 2. Per the clinical judgment of the Investigator, the patient is not anticipated to survive >48 hours OR is under palliative care.

	3. Evidence of critical illness, defined by at least 1 of the following: • 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) • Shock (defined by systolic blood pressure (BP) <90 mm Hg, or diastolic BP <60 mm Hg or requiring vasopressors), OR • Multi-organ dysfunction/failure 4. Severe CNS conditions, e.g., acute stroke, severe confusion, or other acute mental status changes that may significantly determine duration of hospitalization and patient outcomes. 5. Chronic kidney disease requiring dialysis. 6. Anticipated transfer to another facility, which is not a study site, within 72 hours. 7. Known allergy to the study drug or salicylate containing medications. 8. Suspected and/or confirmed pregnancy or breastfeeding. 9. Current or planned participation in any other interventional clinical trial under a US IND or EUA. 10. Patients receiving chemotherapeutic agents and/or immunomodulators (including glucocorticoids, monoclonal antibodies (Mabs), or plasma transfusions) for chronic disease conditions (e.g., malignancies, rheumatoid arthritis or other autoimmune diseases).

1.1 Study Schematic

The study schematic is presented in Figure 1. Both Study Part 1 and Part 2 are double-blinded, randomized, and placebo-controlled.

Figure 1 Study Schematic



BID=twice daily; DMC=data monitoring committee; N=number of observed participants;

PO=by mouth. NOTE: In addition to the safety evaluation at the end of Part 1, the DMC will conduct periodic evaluations during Part 1 and Part 2.

1.2 Schedule of Events

The schedule of events (SOE) for Study Part 1 and Part 2 is presented in Table 1.

Table 1 Schedule of Events (Study Part 1 and Study Part 2)

Study Day (All Study Days are calendar days.)	**Screening[a]**	**Day 1 BL**	**Day 2[b]**	**Day 3[b]**	**Day 4**	**Day 5[b]**	**Day 6[b]**	**Day 7[b]**	**Day 8 or EOT[s]**	**Day 15**	**Day 28**	**Day 60 EOS[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,s], vital signs, COVID-19 severity and subjective symptoms of COVID-19[n,s]	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,s]	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-dimer (central laboratory)[j]		X			X				X			
CRP (central laboratory)[j]		X			X				X			
Cardiac troponin (central laboratory)[j]		X			X				X			
LDH (central laboratory)[j]		X			X				X			
Ferritin (central laboratory)[j]		X			X				X			
NP swab for confirmation of SARS-CoV-2 with RT-PCR[k] (local site laboratory)	X	Per local SOC										

Table 1 Schedule of Events (Study Part 1 and Study Part 2)

Study Day (All Study Days are calendar days.)	**Screening[a]**	**Day 1 BL**	**Day 2[b]**	**Day 3[b]**	**Day 4**	**Day 5[b]**	**Day 6[b]**	**Day 7[b]**	**Day 8 or EOT[s]**	**Day 15**	**Day 28**	**Day 60 EOS[b]**
NP swab for confirmation of SARS-CoV-2 with RT-PCR[k] (central laboratory)		X			X				X	X	X	
PK sampling[l] (Part 1 Only)		X										
WHO Ordinal Scale for Clinical Improvement[e,m,s]	X	X	X	X	X	X	X	X	X	X	X	X
Chest X-ray	Per local SOC											
AE assessment[e,s]	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant medications[e,r,s]	X	X	X	X	X	X	X	X	X	X	X	X
SOFA[e,o,s]		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 subject eligibility (SARS-CoV-2-positive NP swab confirmed with RT-PCR or alternative Sponsor approved assay).

[b] It may not be possible to conduct all study visits in-person following discharge due to quarantine and other infection control measures. In case where in-person visits are not possible, telemedicine appointments should be conducted. If the participant is discharged home with study drug for self-administration, visits appropriate for the telemedicine platform are Days 2, 3, 5, 6, 7, and the EOS/Day 60 visit. For telemedicine appointments, all data should be collected, and the following should be reviewed/discussed in detail with the participant: AEs, concomitant medication, clinical status, and hospital re-admission. Due to the blood and NP swab collection requirements for central laboratory testing on Days 4, 8, 15, and 28, these visits should be conducted in person, either at the stie or with a home visit. If neither is possible, then a telemedicine appointment combined with a home nursing appointment for blood and NP sample collection could be arranged.

[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.

Table 1 Schedule of Events (Study Part 1 and Study Part 2)

Study Day (All Study Days are calendar days.)	Screening[a]	Day 1 BL	Day 2[b]	Day 3[b]	Day 4	Day 5[b]	Day 6[b]	Day 7[b]	Day 8 or EOT[s]	Day 15	Day 28	Day 60 EOS[b]

[e] All assessments should be collected daily while hospitalized **including any day after Day 8** that the patient remains in the hospital. Assessments should be performed 2 to 6 hours post-first dose per day. In addition to the once daily assessment, the WHO Ordinal Scale for Clinical Improvement should be collected/recorded any time the numerical score changes to include the corresponding date and time.

[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, OG, or PEG tube. Please refer to the Pharmacy Manual for instructions for NG, OG, or PEG administration. Total duration of study drug administration is a 7-day course of treatment. Participants may be discharged before completing 14 doses and are to be given dosing instructions, the remainder of their therapy, and a diary to record all study drug doses taken.

[h] Chemistry laboratories to be collected daily while hospitalized **including any day after Day 8** 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 to be collected daily while hospitalized **including any day after Day 8** pre-dose (prior to first study drug dose of the day) and include a CBC (consisting of hemoglobin, hematocrit, total WBC count with 5-part differential, platelet count) plus a partial thromboplastin time (aPTT), a thrombin time (PT), and an international normalized ratio (INR).

[j] Test sample is for central laboratory assessment and is to be collected pre-dose (prior to first study drug dose of the day). Additionally, a central laboratory 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 will be performed by an external central laboratory. 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. PK samples should be collected in relation to the morning dose of study drug. 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. All assessments should be collected daily while hospitalized **including any day after Day 8** that the patient remains in the hospital. Assessments should be performed 2 to 6 hours post-first dose per day. In addition to the once daily assessment, the WHO Ordinal Scale for Clinical Improvement should be collected/recorded any time the numerical score changes to include the corresponding date and time..

[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),

Table 1 Schedule of Events (Study Part 1 and Study Part 2)

Study Day (All Study Days are calendar days.)	Screening[a]	Day 1 BL	Day 2[b]	Day 3[b]	Day 4	Day 5[b]	Day 6[b]	Day 7[b]	Day 8 or EOT[s]	Day 15	Day 28	Day 60 EOS[b]

and temperature), severity of the participant's COVID-19 (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 made 2 to 6 hours post-first dose per day and 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 assessments to be collected pre-dosing at baseline (Day 1) for all participants and post-baseline only for participants admitted to the ICU. SOFA score criteria should be assessed 2 to 6 hours post-first dose per day for participants in the ICU.

[p] Appendix 5 Laboratory Assessments.

[q] Appendix 6 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 within 14 days prior to screening (considered prior medications) and from randomization through the Day 60 visit (considered concomitant medications). For the purpose of 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 (if the participant is in the ICU), should be collected daily while hospitalized **including any day after Day 8** that the patient remains in the hospital. In addition to the once daily assessment, the WHO Ordinal Scale for Clinical Improvement should be collected/recorded any time the numerical score changes to include the corresponding date and time. Results will be collected on an Unscheduled Visit eCRF.

2 INTRODUCTION

2.1 Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of a global pandemic (Huang *et al*., 2020, Zhu *et al*., 2020, Chen *et al*., 2020b). The World Health Organization (WHO) named the novel coronavirus SARS-CoV-2 and the disease caused by the virus as coronavirus disease 2019 (COVID-19).

WHO declared the COVID-19 pandemic a Public Health Emergency of International Concern on 30 January 2020 (WHO 2020), and the United States (US) declared a national emergency on 13 March 2020 (White House Press Release 2020).

No acquired immunity to this novel viral infection appears to exist in the human population globally, and no effective treatment or preventative agent is licensed at this time.

Rigorous self-isolation and lockdown have been required to contain SARS-CoV-2, causing entire societies to abruptly stop normal life.

COVID-19 presents with a variety of conditions, including acute respiratory distress syndrome (ARDS) and rapid multiple organ dysfunction syndrome (MODS) and death. Proposed mechanisms for MODS in COVID-19 include a hypercoagulable state with micro- and macro-circulatory thrombosis.

Effective interventions are urgently needed to not only reduce viral load but also to decrease the processes that drive morbidity and mortality associated with the infection.

2.1.1 Target Indication and Population

The study population includes hospitalized adults with clinical signs and symptoms of moderate and severe COVID-19 and SARS-CoV-2 infection confirmed by the site using reverse transcriptase polymerase chain reaction (RT-PCR) or Sponsor approved equivalent assay.

2.1.2 ANA001 Pharmacology relative to COVID-19

2.1.2.1 Introduction

Niclosamide (5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide) is an anthelmintic that has antiviral activity as well as anti-inflammatory, bronchodilator, and antineoplastic activity.

Niclosamide was approved by the Food and Drug Administration (FDA) for use in humans to treat tapeworm infection in 1982 under the New Drug Application (NDA) 018669. It is included in the WHO's list of essential medicines and has been used to treat tapeworm in thousands of patients in a number of other countries since 1960. The adult dose is 2 g either as a single dose or once daily for 7 days, depending on the infection.

Niclosamide is also a potent antiviral that has been shown to inhibit replication of severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) in vitro at submicromolar concentrations. SARS-CoV, MERS-CoV, and SARS-CoV-2 share 86% homology (Wilder-Smith *et al*., 2020), and niclosamide is therefore being developed as a potential treatment for COVID-19.

2.1.2.2 ANA001 Inhibits SARS-CoV-2 Viral Replication

Niclosamide efficacy against SARS-CoV-2 replication was shown in 3 independent in vitro studies resulting in half maximal inhibitory concentrations (IC_{50}) of 0.15 µM (Shi 2020, unpublished results), 0.28 µM (Jeon *et al*., 2020), and 0.17 µM (Gassen *et al*., 2020). In contrast, the IC_{50} values of remdesivir, chloroquine, and lopinavir are 11.41 µM, 7.28 µM, and 9.12 µM, respectively (Jeon *et al*., 2020).

Niclosamide was found to suppress cytopathic effects (CPE) of SARS-CoV-2 at concentrations as low as 1 µM, with a half-maximal effective concentration (EC_{50}) of less than 0.1 µM in Vero E6 cells (Xu *et al*., 2020a, Jeon *et al*., 2020).

Niclosamide likely exerts its antiviral activity by enhancing autophagy, which was first shown in MERS-CoV-infected cells by Gassen and colleagues. This study demonstrated that niclosamide inhibits the activity of SKP2, a small protein that regulates autophagy. Inhibition of SKP2 facilitates autophagy and inhibits virus replication. The IC_{50} of niclosamide to block MERS-CoV replication was 0.32 µM (Gassen *et al*., 2019). This serves as a strong argument to expect that niclosamide has the same mechanism of action against SARS-CoV-2.

Indeed, it was shown recently that pretreatment of VeroFM cells with 5 µM niclosamide for 24 hours before infection reduced SARS-CoV-2 replication significantly (Gassen *et al*., 2020).

2.1.2.3 ANA001 inhibits NF-κB and STAT3, Drivers of Cytokine Release Syndrome

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) is a transcription factor that induces the expression of pro-inflammatory cytokines. In vitro experiments with U2OS cells demonstrated that niclosamide inhibited NF-kB transcription, its binding to deoxyribonucleic acid (DNA), tumor necrosis factor (TNF)-induced phosphorylation of IκBα, translocation of p65 into the nucleus, and expression of NF-κB-regulated downstream genes. The IC_{50} of niclosamide to inhibit NF-kB transcription was 0.13 µM (42.5 ng/mL) (Jin *et al*., 2010).

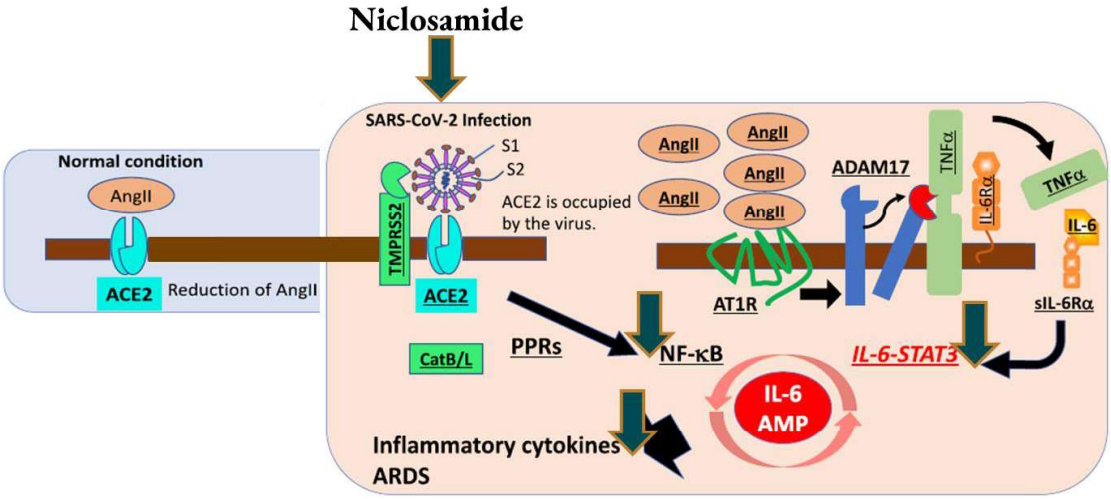
Signal transducers and activators of transcription (STATs) are a class of transcription factors that regulate cellular and biological processes, including immune responses and angiogenesis, by modulating the expression of specific target genes (Yu *et al*., 2007). Upon stimulation by cytokines such as interleukin 6 (IL-6), tyrosine residue 705 (Tyr-705) in the STAT3 SH2 domain is phosphorylated, consequently inducing STAT3 to dimerize, translocate into the nucleus, and induce its binding to specific DNA response elements of target genes (Schuringa *et al*., 2000). Niclosamide was shown to inhibit activation and transcriptional function of STAT3 in vitro. HeLa cells were transfected with a luciferase reporter driven by a promoter sequence with 7 STAT3 binding sites so that luciferase becomes active upon STAT3 binding. Niclosamide prevented binding and thus the transcriptional function of STAT3 with an IC_{50} of 0.25 µM (81.8 ng/mL) and an IC_{100} (total inhibitory concentration) of 5.0 µM (1,635.5 µg/mL) after a 24-hour incubation (Ren *et al*., 2010).

ARDS is a life-threatening condition caused by pneumonia, sepsis, or aspiration. The pathogenesis due in part to "cytokine storms," in which immune cells and nonimmune cells release large amounts of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6, and IL-8) that cause damage to the host. Hyperactivation of the NF-kB pathway is involved in the phenotype, and SARS-CoV-2 is a potential initiator of this scenario (Figure 2).

Angiotensin converting enzyme II (ACE2) and transmembrane serine protease 2 (TMPRSS2) serves as cell entry receptors for SARS-CoV-2. Since ACE2 is either occupied by the virus or internalized with it, the density on the cell surface is reduced and angiotensin 2 increases in serum. Angiotensin 2 acts as a pro-inflammatory cytokine that activates NF-kB which, in turn,

leads to the production of IL-6. IL-6 activates STAT3 that further enhances activation of the NF-kB pathway. It is therefore likely that SARS-CoV-2 infection of the respiratory system activates both NF-kB and STAT3, which in turn can activate the IL-6 amplifier (IL-6 Amp), a mechanism for the hyperactivation of NF-kB by STAT3, leading to multiple inflammatory and autoimmune diseases (Hirano and Murakami 2020).

Figure 2 Potential Therapeutic Targets to Treat COVID-19 and Anticipated Activity of ANA001 (Modified from Hirano and Murakami, 2020)



ACE2: Angiotensin converting enzyme 2; ADAM17: ADAM Metallopeptidase Domain 17; ANGII: Angiotensin II; ARDS: Acute respiratory distress syndrome; AT1R: Angiotensin II receptor type 1 receptor; CATB/L: Cathepsin B and L; IL-6: Interleukin-6; AMP: Amplifier; STAT3: Signal transducer and activator of transcription 3; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; PPRs: Pattern-recognition receptors; SARS-COV-2: Severe acute respiratory syndrome coronavirus 2; TMPRSS2: Transmembrane serine protease 2; TNFα: Tumor necrosis factor alpha.

Although ACE2 as the SARS-CoV-2 receptor for cellular entry provides a key target for prophylactic and therapeutic development during the initial phase of the infection, patients will often be seen at a later timepoint, many of which are downstream of ACE2-mediated cytokine release syndrome. These COVID-19 patients will likely require targeting of cytokine pathways, including the NF-κB and the IL-6-STAT3 axis.

ANA001 (niclosamide) was shown in in vitro experiments to inhibit binding of NF-kB and STAT3 to DNA thus blocking the expression of genes that code for inflammatory cytokines. This suggests that ANA001 may prevent or reduce the severity of uncontrolled cytokine release in COVID-19 patients.

2.1.2.4 STAT3 Mediates IL-6 Associated TH17 Orientation

The janus kinase 2 (JAK2) inhibitor fedratinib is currently in clinical development for reducing mortality of COVID-19 in patients with TH17-type immune profiles.

STAT3 is activated by ILs through JAK1 (IL-6 and IL-21), JAK2 (IL-6 and IL-23), and JAK3 (IL-23). STAT3 mediates, e.g., IL-6 signals for TH17 cell initial differentiation and effector function. IL-6 activates STAT3 through JAK1 and JAK2, IL-23 activates STAT3 through JAK2, and IL-21 activates STAT3 through JAK1 and JAK3. It was shown recently that peripheral blood of a patient with severe COVID-19 had a strikingly high number of chemokine receptor CCR6+ TH17 cells, further supporting a TH17-type cytokine storm in this disease. Generally, a TH17-type response contributes to the cytokine storm in pulmonary viral infection

that likely promotes pulmonary edema. Therefore, patients with TH17 dominant immune profiles may benefit from an intervention that targets the TH17 pathway (Wu and Yang 2020).

Niclosamide inhibited STAT3 in HeLa cells with an IC_{50} of 0.25 µM (81.8 ng/mL) and an IC_{100} of 5.0 µM (1,635.5 µg/mL) in an in vitro assay (Ren *et al*., 2010). These data indicate potential for beneficial anti-inflammatory effects of ANA001 in COVID-19 patients independent of its anti-viremic effects at similarly low micromolar concentrations.

2.1.2.5 STAT3 Upregulates Tissue Factor, the Key Initiator of Blood Coagulation

IL-6-triggered STAT3 activation induces the expression of tissue factor (TF). TF initiates the blood clotting process by thrombin formation (Park *et al*., 2013, Yeh *et al*., 2013). Complement and neutrophils are sentinels of innate immunity and modulate thrombogenic pathways that are likely related to C5a receptor/TF crosstalk mediated by neutrophils. Neutrophilia in COVID-19 patients could be an index of the extent of complement activation that is associated with a poor outcome (Gralinski *et al*., 2018, Yen *et al*., 2006, Magro *et al*., 2020).

COVID-19 pneumonia triggers the expression of active TF, both on endothelial cells and on activated infiltrating macrophages and neutrophils. The net effect is local presentation of blood-borne TF within the lungs, which will further amplify activation of the coagulation cascade. Endothelial cell disruption, TF expression, and initiation of the coagulation cascade will be progressively exacerbated by local hypoxia, leading to a deleterious positive thrombo-inflammatory feedback loop within the lung capillaries resulting in thrombosis and haemorrhage.

Thrombin generation and fibrin deposition within the bronchoalveolar system are associated with severe pneumonia and ARDS. These changes are mainly driven by upregulation of TF expression within the alveoli and correlate with severity of inflammation (McGonagle *et al*., 2020).

ANA001 (niclosamide) is a STAT3 inhibitor and therefore may reduce the increased expression of TF and associated blood coagulations abnormalities often observed in COVID-19 patients.

2.1.2.6 Relevance of Tissue Factor in High-Risk Patients with COVID-19

Coagulopathy is a hallmark of severe COVID-19. In 1 report, 71.4% of patients who died of COVID-19 met the International Society on Thrombosis and Haemostasis criteria for disseminated intravascular coagulation (DIC), whereas only 0.6% of patients that survive met these criteria. This is a predominantly pro-thrombotic DIC with elevated D-dimer levels, high venous thromboembolism rates, and elevated fibrinogen levels in combination with low antithrombin levels. Additionally, it is accompanied by pulmonary congestion with microvascular thrombosis and high rates of central line thrombosis and vascular occlusion (e.g., stroke, ischemic limbs, etc.) in patients with severe COVID-19 (Wang *et al*., 2020).

ANA001 (niclosamide) is a STAT3 inhibitor and therefore may reduce the increased expression of TF and associated blood coagulations abnormalities often observed in COVID-19 patients.

2.1.2.6.1 Acute Respiratory Distress Syndrome

COVID-19 is associated with the development of ARDS. ARDS is a result of acute inflammation within the alveolar space and prevents normal gas exchange. Damaged alveolar endothelial cells and leukocytes exposing TF promote fibrin deposition (Whyte *et al*., 2020).

STAT3 may be one of the key regulatory genes in the underlying dysfunction of sepsis induced ARDS (Zhang *et al*., 2019). ANA001 (niclosamide) inhibits STAT3 and therefore may reduce the severity of ARDS.

2.1.2.6.2 Association of Tissue Factor with Obesity and Type 2 Diabetes Mellitus

Obesity is a major risk factor for the development of type 2 diabetes mellitus (T2D) and associated with increased severity of COVID-19. Clinical studies have established an increased incidence of thrombosis and cardiovascular disease as a primary cause of mortality in diabetic patients. T2D is associated with accelerated and premature atherosclerosis as well as other cardiovascular and thrombotic complications including myocardial infarction, ischemic stroke, and peripheral vascular disease (Samad and Ruf 2013).

T2D patients show elevated levels of circulating TF, the main activator of blood coagulation, due to hyperglycemia and hyperinsulinemia. This procoagulant state predisposes such individuals to acute cardiovascular events (Boden *et al*., 2007) and may also predispose such patients to increased cardiovascular events in COVID-19.

2.1.3 Gastrointestinal System and Dosing of Niclosamide

2.1.3.1 Introduction

Interstitial cells of Cajal are important for gastrointestinal (GI) motility and express protein transmembrane member 16A (TMEM16A), a calcium-activated chloride channel (Cil *et al*., 2019). Given that niclosamide was shown to inhibit TMEM16A in vitro with an IC_{50} of 0.132 to 0.3 µM (43 to 98 ng/mL) (Miner *et al*., 2019), oral administration of 1 to 2 g of ANA001 may transiently decrease gastric emptying or intestinal motility. This could explain why most of the reported transient side effects of niclosamide as an anthelmintic medication are upper GI-tract related.

The clinical implications of the potential inhibition of gastric emptying and intestinal motility in intubated patients in the intensive care unit (ICU) setting is currently unknown. Patients receiving ANA001 administered with their enteral nutrition in the ICU setting should be closely monitored for potential impaired gastric emptying. There was only a low (~10%) incidence of documented upper GI adverse events (AEs) reported in the original studies performed with niclosamide. According to the NDA 018669 Review Documentation, niclosamide was administered to 6365 patients under an Investigational New Drug (IND) in the US between 1971 and 1978. Of the 2385 evaluable patients, 4.1% reported nausea/emesis, 3.4% reported abdominal discomfort/loss of appetite, 1.6% reported diarrhea, and 1.4% reported drowsiness/dizziness/headache.

2.1.3.2 Administration Regimen

ANA001 is supplied as a capsule containing 250 mg of niclosamide for oral administration. ANA001 should be taken with meal. A placebo capsule that matches the size and appearance of the ANA001 drug product capsules is also supplied.

2.1.3.3 Justification for Dosing Strategy

Niclosamide was originally developed as an anthelmintic drug (Perera *et al*., 1970) but has also been found to demonstrate broad antiviral activity in cell culture models.

Several recent publications have shown that niclosamide has very low IC_{50} to inhibit replication of various coronaviruses: 1.56 µM against SARS-CoV (Wu *et al*., 2004), 0.32 µM against MERS-CoV (Gassen *et al*., 2019), and 0.15 to 0.28 µM against SARS-CoV-2 (Shi 2020,

unpublished results, Jeon *et al*., 2020, Gassen *et al*., 2020). These data become relevant in the context of the GI and lung exposures projected for niclosamide as both have been demonstrated to be sources of viral shedding (He *et al*., 2020, Chen *et al*., 2020a).

Niclosamide pharmacokinetics (PK) information from the literature was extrapolated assuming monoexponential elimination to estimate the niclosamide concentrations for the doses planned in this study. The physicochemical properties of niclosamide suggest that niclosamide has minimal protein binding in plasma and is thus available for distribution into the lungs at concentrations that are anticipated to be equivalent to or higher than the free concentrations in plasma. Projections based on available clinical data (Schweizer *et al*., 2018) suggest that oral dosing within the dose range to be evaluated in Part 1 of the study can achieve therapeutic concentrations in both compartments at or above in vitro IC_{50} for a substantial portion of, if not the entirety of, a dosing interval.

The proposed dose is the same total daily dose as approved for anthelmintic use (2,000 mg/day), although it will be given as 1,000 mg twice daily (BID). The Sponsor expects that the proposed dosing regimen will achieve therapeutic effects while preserving an adequate safety margin.

2.1.4 Summary of Nonclinical Toxicology and Pharmacokinetics

ANA001 (niclosamide) is a member of the salicylanilide class of pharmacologic agents and is a derivative of salicylic acid. ANA001 contains an aryl beta-hydoxyl-carbonyl pharmacophore motif that is resident in a large number of natural products and multiple approved medicines, including salicylic acid (aspirin), mycophenolate, doxycycline, and others. Niclosamide has pleiotropic activities (Chen *et al*., 2018, Kadri *et al*., 2018, Jurgeit *et al*., 2010), with in vitro evidence of benefit in diseases ranging from viral to helminthic disease, as well as inflammatory conditions and even diabetes mellitus.

Daily oral doses of up to 100 mg/kg in rabbits for 11 days, 900 mg/kg in cats for 24 days, and 4,500 mg/kg in dogs for 24 days were found nontoxic clinically, based on routine laboratory tests and toxicology. Male cats were noted to have a mild reduction in white blood cells (WBCs), and dogs showed a tendency toward watery stools, but otherwise adverse treatment effects were not evident. Other studies reported that doses of 250 mg/kg may cause vomiting in dogs and cats. The conclusion of these studies was that niclosamide was low risk for dosing orally in humans at the standard therapeutic regimen of 2,000 mg/day (Bayer NDA 018669; Summary Basis for Approval).

In light of the extensive use and safety record niclosamide has shown, several groups have subsequently evaluated niclosamide in cell-culture as part of efforts to identify and/or repurpose agents with activity against multiple viruses, including SARS-CoV2, the etiologic agent of COVID-19. Niclosamide was found to suppress CPE of SARS-CoV-2 at concentrations as low as 1 µM (327 ng/mL), with an EC_{50} of less than 0.1 µM (33 mg/mL) in Vero E6 cells (Xu *et al*., 2020a).

Predictions of niclosamide partitioning to the lungs based on its physio-chemical properties have suggested that niclosamide partitions into lung with resulting concentrations in excess of the in vitro EC_{50} required to demonstrate a clinical effect.

2.1.5 Summary of Supportive Clinical Data

Clinical experience for niclosamide consists primarily of its use as an anthelmintic drug, where its success in treating thousands of patients has led it to be included in the WHO list of essential medicines. This is the first study we are aware of evaluating niclosamide for use in the treatment of moderate and severe COVID-19.

2.1.5.1 Clinical Pharmacology and Pharmacokinetics

Niclosamide, with a hydrophobic structure, is a Biopharmaceutical Classification System class II drug, with limited absorption and low bioavailability (F=10%) when administered orally to rats, with the absorbed fraction rapidly eliminated by the kidneys (Chang *et al*., 2006).

In a cohort of healthy male and female volunteers administered a single 2,000 mg by mouth (PO) dose of carbonyl-^{14}C-labeled niclosamide, the fraction of ^{14}C-activity eliminated in the urine was 2% to 25% over 4 days. The remainder was eliminated in the feces. Elimination was almost complete within 1 to 2 days. In this study, maximum observed serum concentration (C_{max}) was found to be 0.25 to 6.0 µg/mL (0.76 to 18.35 µM) (Andrews *et al*., 1982). A study with prostate cancer patients showed that 149-182 ng/mL (0.46-0.56 µM) became available after a single oral dose of 1,000 mg (Schweizer *et al*., 2018). Colorectal cancer patients received 2,000 mg of niclosamide orally once per day until disease progression or toxicity (up to four months). Plasma levels mainly peaked 40 minutes after the first niclosamide administration with a median C_{max} of 0.43-0.85 µg/ml (1.31-2.60 µM) (Burock *et al*., 2020). The lower bounds of the reported C_{max} values all fall within the range of *in vitro* concentrations shown to exert an antiviral effect on SARS-CoV-2 (0.15-0.28 µM, 49-92 ng/mL) (Shi, 2020, unpublished results, Jeon et al., 2020, Gassen et al., 2020). These studies strongly suggest that the dose regimen foreseen for clinical development – 1,000 mg twice daily (BID) - will provide sufficient systemic and intracellular drug levels for effective antiviral and anti-inflammatory activity.

2.1.5.2 Clinical Safety

Niclosamide has been used extensively to treat helminthic disease at daily doses of up to 2,000 mg in both adults and children.

The primary risks noted in the label include GI upset, including nausea, vomiting, and abdominal pain. Additionally, in some cases hypersensitivity reactions have been reported (erythema, pruritis, and exanthema). All reported side effects were transitory and did not require stopping treatment. ANA001 should be taken with a meal to prevent stomach upset.

Several studies have explored the use of niclosamide as adjunctive care in patients with malignancies (Schweizer *et al*., 2018). In one of these studies, niclosamide was evaluated at doses up to 1500 mg PO TID for up to 28 days and was dosed in conjunction with enzalutamide (Schweizer *et al*., 2018). In this study no dose-limiting toxicities were seen in the cohort treated at 500 mg PO TID. Two participants, however, in the 1,000 mg TID regimen were found to have a dose limiting toxicity (DLT). One participant had grade 3 nausea, vomiting, and diarrhea lasting >72 hours beginning on Day 26 of treatment. The second participant, also on an immune checkpoint inhibitor, developed a grade 3 colitis, abdominal pain and diarrhea on Day 8 of treatment, with the colitis constituting a dose limiting toxicity (DLT). The participant was treated with aggressive intravenous (IV) hydration and antibiotics and the event resolved to grade 1 by time of discharge. These observations may be related to a dosing duration (>7 days) which exceeds the dosing duration foreseen in the present study, the underlying disease (stage 4 castration-resistant prostate cancer), and concomitant treatment with enzalutamide (XTANDI®). The prescribing information for XTANDI reports that diarrhea and nausea are some of the most common adverse reactions (ARs) (≥10%) that occurred more frequently (≥2% over placebo) in XTANDI-treated patients.

2.1.5.3 Clinical Efficacy

This is the first study of oral niclosamide for this indication.

2.1.6 Other Relevant Data

Several groups have observed that the primary modes of SARS-CoV-2 shedding are pulmonary and GI (Xu *et al*., 2020b, Ong *et al*., 2020, Guan *et al*., 2020) with both sputum and stool containing PCR detectable virus. As niclosamide has limited absorption, it is anticipated that GI concentrations of niclosamide will be significantly in excess of the IC_{50} for SARS-CoV-2.

2.1.7 Benefit:Risk Assessment

Niclosamide is typically used to treat helminthic disease. Niclosamide has been found to be safe and well tolerated at daily oral doses of up to 2,000 mg and is on the WHO list of essential medications.

As COVID-19 is currently a cause of significant excess global mortality and niclosamide has been shown to have potent antiviral and anti-inflammatory effects on key pathways associated with cytokine storm and abnormal coagulation in sepsis, at concentrations which are expected to be achievable in both the GI tract, systemically and the lungs, the potential benefits of ANA001 outweigh the known and potential risks.

Coadministration of niclosamide with drugs that are metabolized by Cytochrome P450 (CYP450) 1A2 may prolong plasma concentrations of such drugs. However, such data are based on theoretical modeling and to date, no proven drug-drug interactions have been reported for niclosamide since its approval by the FDA as an anthelmintic in 1982. Significant effects on plasma concentration of concomitant medications metabolized by CYP450 1A2 are not expected due to the short duration of ANA001 treatment.

2.2 Study Rationale

There is an urgent need to develop innovative and cost-effective oral therapies to treat COVID-19. Based on available data from nonclinical studies and previous experience with marketed products, the use of ANA001 could represent a potent and safe oral treatment for COVID-19.

3 OBJECTIVES AND ENDPOINTS

The objectives and endpoints for Part 1 and Part 2 of the study are detailed in Table 2 and Table 3, respectively.

Table 2 Objectives and Endpoints of Study Part 1

Objectives	Endpoints/Parameters
Primary	
To evaluate the safety and tolerability of ANA001 as therapy for moderate and severe COVID-19 patients	• TEAEs, treatment-emergent SAEs, deaths and discontinuations due to a TEAE • Vital signs and laboratory (hematology, chemistry, and coagulation) parameters
Secondary	
To evaluate the efficacy of ANA001 as therapy in moderate and severe COVID-19 patients	• 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)
To evaluate PK of ANA001	• Plasma concentrations of ANA001 will be explored on Day 1, 2, 3, **or** Day 4
Exploratory	
To evaluate clinical improvement using NEWS2	• Mean change from baseline (BL) in NEWS2 on Day 15
To evaluate the need and duration of rescue therapy	• Mean number of days on rescue treatment (COVID-19 therapies that are FDA approved or have emergency-use authorization) within 15 days after enrollment
To evaluate the effect on subjective symptoms of COVID-19	• 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
To evaluate progression of COVID-19 from moderate or severe to more severe (i.e., moderate to severe, moderate to critical, or severe to critical)	• Proportion of participants who's COVID-19 progresses to Severe or Critical (Appendix 4) within 15 days after enrollment • Proportion of participants requiring ICU admission within 15 days after enrollment • Mean change from baseline (BL) in SOFA score on Day 8 and Day 15
To evaluate the effect of ANA001 on requirement for oxygen and/or assisted ventilation	• Proportion of participants requiring supplemental O2, high-flow nasal cannula (HFNC) oxygen, noninvasive positive pressure ventilation (NIPPV) or mechanical ventilation on Day 8 and Day 15 • Mean number of days on mechanical ventilation within 15 days after enrollment • Mean number of oxygenation-free days within 15 days after enrollment
To evaluate time to resolution of the WHO Ordinal Scale for Clinical Improvement	• Proportion of participants who achieve a score of 1 in the WHO Ordinal Scale for Clinical Improvement (Appendix 1) on Day 8 and Day 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
To evaluate the effect of ANA001 on thromboembolic events	• Incidence and severity of thromboembolic events within 15 days after enrollment
To evaluate the relationship of ANA001 and markers of inflammation associated with	• Incidence of abnormal markers of inflammation to (CRP, IL-6, TF, MCP-1, and IP-10) on Day 8

acute respiratory distress syndrome (ARDS)	
To evaluate the relationship between ANA001 plasma concentrations and viral dynamics	• Mean change in viral load from baseline (BL) on Days 1, 4, 8, 15, and 28 • Mean time (in days) to viral load undetectable by nasopharyngeal (NP) swab

Table 3 Objectives and Endpoints of Study Part 2

Objectives	Endpoints/Parameters
Primary	
To evaluate efficacy of ANA001 as therapy for COVID-19 patients, AND To evaluate the safety and tolerability of ANA001 as therapy for COVID-19 patients	• Time to clinical improvement measured as 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) • TEAEs, treatment-emergent SAEs, deaths and discontinuations due to a TEAE • Vital signs and laboratory (hematology, chemistry, and coagulation) parameters
Secondary	
To evaluate clinical improvement using NEWS2	• Mean change from baseline (BL) in NEWS2 on Day 15
To evaluate the need and duration of rescue therapy	• Mean number of days on rescue treatment (COVID-19 treatments that are FDA approved or have emergency-use authorization) within 15 days after enrollment
Exploratory	
To evaluate the effect on subjective symptoms of COVID-19	• 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
To evaluate progression of COVID-19 from moderate or severe to more severe (i.e., moderate to severe, moderate to critical, or severe to critical)	• Proportion of participants who's COVID-19 progresses to Severe or Critical (Appendix 4) within 15 days after enrollment • Proportion of participants requiring ICU admission within 15 days after enrollment • Mean change from baseline (BL) in SOFA score on Day 8 and Day 15
To evaluate the effect of ANA001 on requirement for oxygen and/or assisted ventilation	• Proportion of participants requiring supplemental O_2, high-flow nasal cannula (HFNC) oxygen, noninvasive positive pressure ventilation (NIPPV) or mechanical ventilation on Day 8 and Day 15 • Mean number of days on mechanical ventilation within 15 days after enrollment • Mean number of oxygenation-free days within 15 days after enrollment
To evaluate time to resolution of the WHO Ordinal Scale for Clinical Improvement	• Proportion of participants with an improvement in the WHO Ordinal Scale for Clinical Improvement (Appendix 1) on Day 8 and Day 15 • Median time (in hours) to 2-point improvement in the WHO Ordinal Scale for Clinical Improvement
To evaluate the effect of ANA001 on thromboembolic events	• Incidence and severity of thromboembolic events within 15 days after enrollment
To evaluate the relationship of ANA001 and markers of inflammation associated with acute respiratory distress syndrome (ARDS)	• Incidence of abnormal markers of inflammation (CRP, IL-6, TF, MCP-1, and IP-10) on Day 8
To evaluate the relationship between ANA001 and viral dynamics	• Mean change in viral load from baseline (BL) on Days 1, 4, 8, 15, and 28 • Mean time (in days) to viral load undetectable by nasopharyngeal (NP) swab

4 STUDY PLAN

4.1 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 is met to confirm subject eligibility. Randomization of subjects will be stratified by oxygenation (SpO_2 >93 and <98% on room air versus SpO_2 ≤93% on room air), diarrhea (presence versus absence), and age (<65 and ≥65).

The Sponsor will review blinded safety data on an ongoing basis, and an independent Data Monitoring Committee (DMC) will review available unblinded safety and efficacy data in accordance with the DMC Charter.

Part 1 will primarily evaluate safety and tolerability of ANA001 compared with matching placebo and explore PK parameters. Blood samples (Primary and Back-Up) for PK are to be collected 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.

Part 2 will evaluate safety, tolerability, and efficacy of the proposed clinical dosing regimen of ANA001 as compared with matching placebo.

After provision of informed consent, participants who satisfy all inclusion and no exclusion criteria will be dosed within 36 hours of screening and as soon as possible following hospital presentation.

Part 1

Participants in Part 1 will be randomly assigned to either ANA001 or matching placebo in a 1:1 ratio. 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 (SOC) 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 should be administered via nasogastric (NG), orogastric (OG), or percutaneous endoscopic gastrostomy (PEG) 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 should be made to complete the remaining study assessments for participants who are not able to complete the 7-day course of study drug.

An emergency DMC meeting will convene if 3 or more blinded participants in Part 1 or 10 or more blinded participants in Part 2 experience AEs leading to premature discontinuation of study drug.

DMC assessments: After enrollment into Part 1 is completed, the independent DMC will conduct an unblinded review of safety, tolerability, and efficacy. If safety issues are identified or no potential for benefit is seen when compared with the placebo group, the DMC may recommend that the study be terminated for safety concerns or for futility. Further discussion of the terms for termination of the study are provided in Section 6.4.2.

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.

Part 2

Participants in Part 2 will be randomly assigned to either ANA001 or matching placebo in a 1:1 ratio according to the assignment made by the randomization and trial supply management (RTSM) system. Participants will receive ANA001 or matching placebo for 7 consecutive days (defined as 14 doses administered BID). Additionally, participants will continue to receive SOC therapy (per study site policies or guidelines).

Dosing will continue until the treatment course is completed. If the participant requires mechanical ventilation over the course of the study, ANA001 may be administered via nasogastric, orogastric, or percutaneous endoscopic gastrostomy (NG, OG, or PEG) tube in accordance with the appropriate section in the study Pharmacy Manual. If the participant is discharged from the hospital prior to completing the treatment course, remaining study drug will be dispensed for at-home administration. Every effort should be made to complete the all remaining study assessments for all participants including those who are not able to complete the 7-day course of study drug.

For both Part 1 and Part 2, following discharge from the hospital, follow-up visits that do not require laboratory evaluations may be performed via the study approved telemedicine platform on Days 2, 3, 5, 6, 7, and the EOS/Day 60 visit. Assessments at the follow-up visits for Part 1 and Part 2 will be performed according to Table 1.

4.2 Design Rationale

Niclosamide has been established as a well-tolerated and effective anthelmintic agent at doses of up to 2,000 mg daily. Recently, several groups have demonstrated *in vitro* potency of niclosamide against SARS-CoV-2 at IC_{50} values ranging from 0.15 to 0.28 µM (49 to 92 ng/mL) (Shi 2020, unpublished results, Jeon *et al*., 2020, Gassen *et al*., 2020). C_{max} values reported in humans ranged from 149 to 182 ng/mL (0.46 to 0.56 µM) after a single oral dose of 1,000 mg (Schweizer *et al*., 2018). In humans that received oral doses of 2,000 mg, C_{max} ranged from 0.25 to 6.0 µg/mL (0.76 to 18.35 µM) (Andrews *et al*., 1982) and 0.43-0.85 µg/ml (1.31-2.60 µM) (Burock *et al*., 2020). It is therefore highly likely that the proposed dosing regimen (1,000 mg BID daily for 7 days) will achieve concentrations of niclosamide in infected tissues with effective antiviral and anti-inflammatory activity. Pharmacokinetic models suggest that partitioning of niclosamide to lung and GI parenchyma may provide adequate therapeutic coverage.

This study will explore ANA001 to evaluate its safety, tolerability, and efficacy as an oral therapy for the treatment of patients with moderate and severe COVID-19. It is anticipated that 60 patients in Study Part 1 will provide sufficient information on safety, tolerability, and potential for efficacy to proceed to a statistically powered test of the efficacy and further assessment of safety and tolerability in a larger patient cohort in Study Part 2.

5 POPULATION

5.1 Recruitment

Approximately 436 participants will be enrolled from approximately 20 study sites in the US.

5.2 Definitions

Participants officially enter the screening period following provision of written informed consent either directly or via a legally authorized representative.

A screen failure is a consented participant who has been deemed ineligible on the basis of 1 or more eligibility criteria or who has withdrawn consent prior to treatment assignment. Screen failures may be rescreened if COVID-19 is suspected based on worsening clinical criteria (e.g., worsening oxygenation status or development of bilateral lower lobe pneumonia or fever >38.3°C) and dosing should be initiated within 36 hours of re-screening.

An enrolled participant is one who has been deemed eligible and has been randomized to a treatment group.

5.3 Inclusion Criteria

To be included in this study, an individual must satisfy all the following criteria:

1. Willing and able to provide written informed consent (or their legally authorized representative) prior to performing study procedures. If necessary, emergency consent may be obtained per local procedures.
2. Hospitalized.
3. Understands and agrees to comply with planned study procedures, including ability and willingness to swallow multiple small capsules.
4. Male or female adult ≥18 years of age at the time of informed consent.
5. Positive for SARS-CoV-2 by a standard RT-PCR assay or alternative Sponsor approved assay within 7 days of randomization and no more than 36 hours after hospitalization.
6. Presence of symptoms of lower respiratory tract infection (LRTI) including at least 1 of the following: fever, cough, sore throat, malaise, headache, muscle pain, or more significant lower respiratory tract symptoms, including shortness of breath (at rest or with exertion).
7. At least 1 of the following: respiratory rate (RR) ≥20 breaths per minute, room air SpO_2 <98%, requirement for supplemental oxygen, heart rate (HR) ≥90 beats per minute, or temperature >38.3°C.
8. Access to a telemedicine platform for outpatient visits in cases where visits to the study site are not possible (e.g., telephone, smartphone, tablet, or computer).
9. Women of childbearing potential must agree to abstinence from heterosexual intercourse or use at least 1 form of contraception not including hormonal contraception from the day of screening through Day 30.

5.4 Exclusion Criteria

If an individual meets any of the following criteria at screening, he or she is ineligible for this study:

1. Hospitalized, but no longer requires ongoing inpatient medical care (i.e. hospital discharge is anticipated in ≤24 hours.

2. Per the clinical judgment of the Investigator, the patient is not anticipated to survive >48 hours OR is under palliative care.
3. Evidence of critical illness, defined by at least 1 of the following:
   - 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 (NIPVV), 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)
   - Shock (defined by systolic blood pressure (BP) <90 mm Hg, or diastolic BP <60 mm Hg or requiring vasopressors), OR
   - Multi-organ dysfunction/failure
4. Severe CNS conditions, e.g., acute stroke, severe confusion, or other acute mental status changes that may significantly determine duration of hospitalization and patient outcomes.
5. Chronic kidney disease requiring dialysis.
6. Anticipated transfer to another site, which is not a study site, within 72 hours.
7. Known allergy to the study drug or salicylate containing medications.
8. Suspected and/or confirmed pregnancy or breastfeeding.
9. Current or planned participation in any other interventional clinical trial under a US IND or EUA.
10. Patients receiving chemotherapeutic agents and/or immunomodulators (including glucocorticoids, monoclonal antibodies (Mabs), or plasma transfusions) for chronic disease conditions (e.g., malignancies, rheumatoid arthritis or other autoimmune diseases).

5.5 Exceptions to Eligibility Criteria

Prospective approval of a protocol deviation of an enrollment criterion, also known as a protocol waiver or exemption, is not permitted.

The Medical Monitor should be consulted if there are questions about interpretation of eligibility criteria.

6 STUDY CONDUCT

The study duration for each participant will be approximately 62 days including a 36-hour window allowed for screening assessments prior to randomization. Study procedures for Study Part 1 and Study Part 2 are presented in the schedule of events, Table 1.

6.1 Screening Period Assessments

The screening procedures and evaluations are to be carried out prior to the start of treatment. Screening assessments are to be performed and completed no more than 36 hours before randomization, and as soon as possible following hospital presentation. Randomization and initiation of treatment should occur as soon as possible following confirmation that all inclusion and no exclusion criteria have been met. Screening and Day 1 may occur on the same day if eligibility criteria are met. Assessments to be performed and information to be collected for the Screening period include:

- Obtain informed consent. No study specific assessments will be conducted until after provision of written informed consent.
- Demographics.
- Eligibility assessment.
- Medical 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 the presence of comorbidities, especially cardiovascular disease, pulmonary disease (e.g., COPD, asthma), hypertension, diabetes, and obesity, is to be recorded as well.
- NEWS2 (Appendix 2), vital signs, severity of the participant's COVID-19 (Appendix 4), and assessment for presence of 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.
- Record SpO_2 on room air and need for supplemental nasal cannula oxygen (including flow rate) if applicable. If clinically possible, SpO_2 should be recorded on room air for all patients and if applicable a value should be recorded on supplemental oxygen (with at least 30 continuous minutes of oxygen administration).
- Targeted physical examination.
- Nasopharyngeal (NP) swab for confirmation of SARS-CoV-2 with RT-PCR or Sponsor approved alternative test (e.g., local laboratory analysis used for screening).
- WHO Ordinal Scale for Clinical Improvement score (Appendix 1) assessment.
- Chest X-ray per local standard-of-care.
- AE assessment (AEs are to be recorded from the time of signing of informed consent to the end of the study participation).
- All systemic prior medications within 14 days prior to screening (Section 7.4).
- Serum pregnancy test for females of childbearing potential.

6.2 Randomization (Day 1-Baseline)

Participants who have provided written informed consent, completed all screening procedures and assessments, and who meet all of the inclusion and none of the exclusion criteria will be randomized. Randomization should occur as soon as possible following confirmation that all

inclusion and no exclusion criteria have been met and within no more than 36 hours following initiation of screening.

6.3 Dosing Period (Day 1 through Day 8)

After provision of informed consent, participants who satisfy all necessary eligibility criteria will receive doses of ANA001 or matching placebo to begin within approximately 36 hours of site screening and as soon as possible following hospital presentation.

6.3.1 Day 1 Assessments

Procedures to be performed and information to be collected on Day 1:

- Height and weight for body mass index (BMI). If a participant is unable to be measured for height and weight, stated height and weight is acceptable.
- NEWS2 (Appendix 2), vital signs, severity of the participant's COVID-19 (Appendix 4), and assessment for presence of 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. Day 1 assessments should be done before the first dose of study drug.
- Record SpO_2 on room air and need for supplemental nasal cannula oxygen (including flow rate) if applicable. For patients on supplemental oxygen, SpO_2 should be recorded with at least 30 continuous minutes of oxygen.
- A complete physical examination, excluding a genitourinary (GU) examination.
- Administration of study drug (ANA001 or matching placebo). Study drug should be taken with a meal (or NG/OG/PEG tube feeding if applicable).
- Serum chemistry (to be collected before initial dosing), including blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, carbon dioxide, glucose, direct bilirubin, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT).
- Hematology and coagulation tests (to be collected before initial dosing) including a complete blood count (CBC), which consists of hemoglobin, hematocrit, total WBC count with a 5-part differential, platelet count, plus a partial thromboplastin time (aPTT), prothrombin time (PT), and an international normalized ratio (INR).
- D-dimer, CRP, cardiac troponin, LDH, and ferritin samples collected for central laboratory testing (to be collected before initial dosing).
- NP swab for confirmation of SARS-CoV-2 with RT-PCR (local site laboratory) per site SOC (to be collected before initial dosing) if part of standard-of-care.
- NP swab for confirmation of SARS-CoV-2 with RT-PCR (central laboratory) (to be collected before initial dosing).
- PK sample collection: Study Part 1 Only: See Appendix 6 for PK sample collection schedule. Refer to the Central Laboratory Manual for additional sample collection and processing instructions. PK samples should be collected in relation to the morning dose of study drug administration.
- WHO Ordinal Scale for Clinical Improvement score (Appendix 1) assessment should be collected/recorded daily and any time the WHO Ordinal Scale for Clinical Improvement score changes. The WHO Ordinal Scale for Clinical Improvement should be recorded with the corresponding date and time of assessment (if unchanged) or with the date and time reflecting the numerical change in the score (if changed).

- Chest X-ray per local standard-of-care.
- AE assessment.
- All systemic concomitant medications (Section 7.4).
- Sequential Organ Failure Assessment (SOFA) score (to be performed at baseline for all participants; Appendix 3).
- Blood for exploratory tests (e.g., IL-6, tissue factor, MCP-1 and IP-10). Blood sample is to be collected before initial dosing.

6.3.2 Daily Assessments (Day 2 through Day 8)

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. If the participant is discharged home with study drug for self-administration, visits appropriate for the telemedicine platform are Days 2, 3, 5, 6, 7, and the EOS/Day 60 visit.

For telemedicine appointments, all data should be collected, and the following should be reviewed/discussed in detail with the participant: AEs, concomitant medication, clinical status, and hospital re-admission. Due to the blood and NP swab collection requirements for central laboratory testing on Days 4, 8, 15, and 28, these visits should be conducted in person, either at the stie or with a home visit. If neither is possible, then a telemedicine appointment combined with a home nursing appointment for blood and NP sample collection could be arranged.

Procedures to be performed and information to be collected on Day 2 through Day 8 include:

- NEWS2 (Appendix 2), vital signs, severity of the participant's COVID-19 (Appendix 4), and assessment for presence of subjective clinical signs and symptoms of COVID-19 will be assessed daily 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. This should be performed between 2-6 hours after first dose of the day with study drug. Assessments should be collected daily while hospitalized including any day after Day 8 that the participant remains in the hospital.
- Record daily SpO_2 on room air and need for supplemental nasal cannula oxygen (including flow rate) if applicable. For patients on supplemental oxygen, SpO_2 should be recorded with at least 30 continuous minutes oxygen. Also record any noninvasive ventilation (i.e., 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. Assessments should be collected daily while hospitalized including any day after Day 8 that the participant remains in the hospital.
- Daily administration of study drug (ANA001 or matching placebo). Study drug should be taken with a meal (or NG/OG/PEG tube feeding if applicable). Total duration of study drug administration is a 7-day course of treatment (i.e., 14 scheduled doses comprised of 56 capsules in total). Participants may be discharged before completing 14 doses and are to be given dosing instructions, the remainder of their therapy, and a diary to record all study drug doses taken.
- Daily serum chemistry (pre-dose), including blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, carbon dioxide, glucose, direct bilirubin, total bilirubin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT).

- Daily hematology and coagulation tests (pre-dose) including a complete blood count (CBC), which consists of hematocrit, hemoglobin, total WBC count with a 5-part differential, platelet count, plus a partial thromboplastin time (aPTT), prothrombin time (PT), and an international normalized ratio (INR).
- D-dimer, CRP, and ferritin (to be collected pre-dose on Day 4 and Day 8 only) for central laboratory testing. Cardiac troponin and LDH (to be collected Day 8 or EOT) for central laboratory testing.
- NP swab for confirmation of SARS-CoV-2 with RT-PCR (local site laboratory) per site SOC if part of standard-of-care.
- NP swab for SARS-CoV-2 testing with RT-PCR (to be collected on Day 4 and 8) for central laboratory testing.
- PK sample collection: Study Part 1 Only: See Appendix 6 for PK sample collection schedule. Refer to the Central Laboratory Manual for additional sample collection and processing instructions (Day 1, 2, 3 **or** Day 4). PK samples should be collected in relation to the morning dose of study drug.
- Daily WHO Ordinal Scale for Clinical Improvement score (Appendix 1) assessment should be collected/recorded daily and any time the WHO Ordinal Scale for Clinical Improvement score changes. The WHO Ordinal Scale for Clinical Improvement should be recorded with the corresponding date and time of assessment (if unchanged) or with the date and time reflecting the numerical change in the score (if changed).
- Chest X-ray per local standard-of-care.
- Daily AE assessment.
- All systemic concomitant medications (Section 7.4).
- SOFA score (to be performed daily only for participants who are admitted in the ICU; Appendix 3).
- Blood for exploratory tests (e.g., IL-6, tissue factor, MCP-1 and IP-10) on Day 8.

6.4 Day 15 (±3 days), and Day 28 (+2 days) Assessments

Procedures to be performed and information to be collected on Day 15 and Day 28:

- NEWS2 (Appendix 2), severity of the participant's COVID-19 (Appendix 4), and assessment for presence of subjective clinical signs and symptoms of COVID-19 including 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 participant remains in the hospital.
- Record SpO_2 on room air and need for supplemental nasal cannula oxygen (including flow rate) if applicable. For patients on supplemental oxygen, SpO_2 should be recorded with at least 30 continuous minutes of oxygen Also record any noninvasive ventilation (i.e., 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.
- NP swab confirmation of SARS-CoV-2 with RT-PCR (local site laboratory) per site SOC.
- NP swab for confirmation of SARS-CoV-2 with RT-PCR on Day 15 (±3 days), and Day 28 (+2 days) for central laboratory testing.
- WHO Ordinal Scale for Clinical Improvement score (Appendix 1) assessment should be collected/recorded daily and any time the WHO Ordinal Scale for Clinical Improvement score changes. The WHO Ordinal Scale for Clinical Improvement should

be recorded with the corresponding date and time of assessment (if unchanged) or with the date and time reflecting the numerical change in the score (if changed).
- Chest X-ray per local standard-of-care.
- AE assessment.
- All systemic concomitant medications (Section 7.4).
- SOFA score (to be performed only for participants who are admitted in the ICU; Appendix 3).

6.5 Day 60 (+2 days)/End of Study (EOS)Assessments

Procedures to be performed and information to be collected on Day60/EOS include:

- NEWS2 (Appendix 2), vital signs, severity of the participant's COVID-19 (Appendix 4), and assessment for presence of subjective clinical signs and symptoms of COVID-19 including 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 participant remains in the hospital.
- Record SpO_2 on room air and need for supplemental nasal cannula oxygen (including flow rate) if applicable. For patients on supplemental oxygen, SpO_2 should be recorded with at least 30 continuous minutes of oxygen Also record any noninvasive ventilation (i.e., 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.
- NP swab confirmation of SARS-CoV-2 with RT-PCR (local site laboratory) per site SOC.
- NP swab for confirmation of SARS-CoV-2 with RT-PCR for central laboratory testing.
- WHO Ordinal Scale for Clinical Improvement score (Appendix 1) assessment should be collected/recorded daily and any time the WHO Ordinal Scale for Clinical Improvement score changes. The WHO Ordinal Scale for Clinical Improvement should be recorded with the corresponding date and time of assessment (if unchanged) or with the date and time reflecting the numerical change in the score (if changed).
- Chest X-ray per local standard-of-care.
- AE assessment.
- SOFA score (to be performed only for participants who are admitted in the ICU; Appendix 3).

6.6 Discontinuation or Withdrawal

6.6.1 Individual Participants

6.6.1.1 Withdrawal from Study and Lost to Follow-up

An individual participant may withdraw from the study at any time at his/her own request (withdrawal of consent) or may be withdrawn at any time for the following reasons:

- At the request of the primary care provider if he/she thinks the study is no longer in the best interest of the participant.

- The participant is judged by the Investigator or Sponsor to be at significant risk of failing to comply with the provisions of the protocol so as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the Institutional Review Board (IRB)/ Ethics Committee (EC)/ or government agencies as part of their duties.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data/samples collected before such withdrawal of consent.

At the time of withdrawal from study all procedures scheduled for that study day plus additional assessments (not already planned for that study day) which are scheduled for the end of study drug administration (Study Day 8) or the End of Study (EOS/Day 60) visit should be completed if possible AND if the participant is agreeable. See SOE (Table 1) for data to be collected at the time of withdrawal from study.

A participant will be considered lost to follow-up if unable to be contacted by the study site. The following actions must be taken if a participant fails to present for a study required assessment:

- The site must attempt to contact the participant as soon as possible and counsel the participant on the importance of maintaining the assigned procedure schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary and practical, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6.6.1.2 Discontinuation of Study Drug

Participants may be prematurely discontinued from study drug prior to completing a full 7 consecutive days of study drug (i.e., 14 doses administered BID) for any of the following reasons:

- Withdrawal from study or Lost to follow-up (due to reasons listed in Section 6.6.1.1)
- Participant decision (i.e., to be used as reason if participant desires to stop study drug but not withdrawal consent of the study). A participant is free to discontinue study drug therapy at any time without prejudice to further treatment. The Investigator must verify on the eCRF that the participant decision was not based on an adverse event (AE). In such cases, the reason must be recorded as premature discontinuation from study drug due to an AE.
- AE (e.g., continuation of study drug poses a risk to the participant as judged by the Investigator)
- Positive pregnancy test at any time during study drug treatment, OR
- Early discontinuation/termination of the study by Sponsor

In the event that a participant prematurely discontinues study drug, all study procedures and assessments should continue to be performed and collected until the participant completes the EOS/Day 60 visit to the extent possible.

6.6.1.3 Replacement of Participants

Randomized participants may not be replaced.

6.6.2 Discontinuation or Termination of the Study

An independent Data Monitoring Committee (DMC) will be formed and constituted according to appropriate regulatory agency guidelines. Detailed information regarding the composition of the committee and detailed procedures will be provided in a separate DMC charter. The independent DMC will review the safety, tolerability, and efficacy data of Study Part 1 and Study Part 2 as described in the DMC charter.

An emergency DMC meeting will convene if 3 or more blinded participants in Study Part 1 or 10 or more blinded participants in Study Part 2 experience AEs leading to premature discontinuation of study drug.

The Sponsor may discontinue further enrollment of the study at any time (including after unblinding of Study Part 1 study data and before enrollment of Study Part 2).

Additionally, the Sponsor may (before beginning enrollment of Study Part 2):

- Exclude a specific patient subgroup due to potential safety concerns
- Modify allowed concomitant medication due to potential safety concerns, OR
- Modify other protocol criteria due to potential safety concerns (e.g., safety laboratory monitoring or PK sampling)
- Modify the sample size and/or endpoints of Study Part 2 if Study Part 1 efficacy data suggests that such changes may be necessary to adequately power Study Part 2

The DMC may also recommend interruption of recruitment at ANY time during Study Part 1 or Study Part 2 for further analysis. The DMC may also recommend termination of the study if any one of the following are observed and not associated with the natural course of COVID-19 (based on CTCAE v5: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf):

- Grade 4 or greater nausea, vomiting, diarrhea, or abdominal pain lasting >72 hours in participants who have received maximal medical care
- Grade 4 or greater anemia, neutropenia, or thrombocytopenia without an alternative etiology

The DMC will review the study on a regular basis as outlined in the DMC charter and evaluate the study for safety, futility or lack of efficacy. The DMC may recommend interruption of recruitment or termination of the study at any time. Any recommendations for safety review, as summarized in section 6.4. are non-binding. The DMC is fully independent and is at liberty to use additional or modified criteria as a basis for determination of the safety, tolerability and potential futility in Study Part 1 or Study Part 2.

7 STUDY INTERVENTIONS

7.1 Description of Products

The investigational product is a capsule containing 250 mg of active pharmaceutical ingredient (API) or matching placebo.

7.1.1 Active Intervention – ANA001

7.1.1.1 Formulation, Storage, Preparation, and Handling

For Study Part 1 and Study Part 2 ANA001 (proprietary niclosamide formulation) 250 mg capsules will be provided in bottles containing a sufficient number of capsules (56 per patient) to cover the 7-day treatment period and should be stored at room temperature out of direct sunlight.

7.1.1.2 Dosing and Administration

ANA001 will be administered as 1,000 mg (4 capsules; 250 mg each) PO BID for 7 consecutive days and should be given with a meal. If the participant requires mechanical ventilation over the course of the study, niclosamide may be administered via NG, OG, or PEG tube and, if possible, should be administered with a scheduled NG, OG, or PEG feeding. Please refer to the study Pharmacy Manual for additional dosing and study drug administration information.

7.1.2 Control - Placebo

7.1.2.1 Formulation, Storage, Preparation, and Handling

For Study Part 1 and Study Part 2, matching placebo (size 0, hydroxypropylmethylcellulose [HPMC]) will be provided in bottles containing a sufficient number of capsules (56 per patient) to provide for dosing for the 7-day treatment duration. Placebo should be stored at room temperature out of direct sunlight.

Placebo formulation is comprised of generally recognized as safe (GRAS) excipients and contains fillers (microcrystalline cellulose and mannitol), a binder (hydroxypropyl cellulose), a disintegrant (sodium starch glycolate), a wetting agent (sodium lauryl sulfate), a glidant (colloidal silica), and a lubricant (sodium stearyl fumarate). No biologically active or potentially immunogenic compounds are included in the placebo formulation.

7.1.2.2 Dosing and Administration

Placebo will be administered as 4 HPMC capsules PO BID for 7 consecutive days and should be given with a meal. If the participant requires mechanical ventilation over the course of the study, placebo may be administered via NG, OG, or PEG tube and, if possible, should be administered with a scheduled NG, OG, or PEG feeding. Please refer to the study Pharmacy Manual for additional dosing and study drug administration information.

7.2 Dosing Assignment and Bias Minimization

Both Study Part 1 and Study Part 2 are randomized and double-blinded to reduce bias.

7.2.1 Dosing Allocation

During Study Parts 1 and 2, participants will receive either ANA001 as a 1,000 mg PO BID dose or matching placebo dose for 7 days.

7.2.2 Randomization Strategy and Procedure

During Study Part 1 and Study Part 2 participants will be randomized in a 1:1 ratio to ANA001 or matching placebo.

The randomization plan will be overseen by the study statistician. The randomization code and resulting allocation list will be generated and overseen by the study statistician. The list will be blocked and stratified by oxygenation (SpO_2 <93 and <98% on room air versus SpO_2 ≤93% on room air), diarrhea (presence/absence), and age (<65/≥65).

7.2.3 Extent and Maintenance of Blinding

Both Study Part 1 and Study Part 2 will be blinded. The containers of study drug product allocated to each participant will not identify treatment allocation. Treating Investigators will be blinded. The DMC statistician and the DMC itself will be unblinded for analysis purposes as described in the DMC charter. The Sponsor may also be unblinded at any time if the Sponsor deems this necessary to adequately evaluate potential safety issues. The Sponsor may also be unblinded in accordance with procedures outlined in the statistical analysis plan (SAP).

7.2.4 Unblinding Procedures

7.2.4.1 Planned Unblinding

The Sponsor and/or principal investigator may decide to unblind the study drug for a given participant if medically necessary. The investigator may request being unblinded to treatment assignment of a participant, in accordance with procedures outlined in the Randomization and Trial Supply Management (RTSM) Manual

7.2.4.2 Unplanned or Unintentional Unblinding

The Sponsor or designated representative must be notified immediately if an Investigator and/or blinded site study team member becomes unblinded unintentionally.

7.3 Assessment and Verification of Compliance

ANA001 or matching placebo will be administered to the participants by clinical staff. For participants who are discharged prior to completing the 7-day course of treatment, the remainder of the 7-day course of study drug will be provided for at-home administration in a bottle along with a diary card on which they are to record the dates/times/amount of study drug self-administered. Participants are to return the bottle and the diary card at the time of their follow-up visit to the Investigator. In the event that telemedicine follow-up is necessary arrangements to obtain the bottle and the diary card must be made as outlined in the Randomization and Trial Supply Management (RTSM) Manual.

Participants should be advised not to consume alcohol or alcohol containing products while on study drug due to the potential for ANA001 to potential increased impairment (Yomesan [PI] 2008: https://www.bayer.co.za/static/documents/MSDS/PIs/YOMESAN_EN_PI.pdf).

7.4 Prior and Concomitant Therapies

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 the purpose of this study, all enteral nutrition and administration of blood products will also be considered as medication.

The medication, dose, route of administration, duration (e.g., start date and time and stop date and time), and reason for the medication (including if the medication was given as a primary or supportive therapy for COVID-19) must be documented on the appropriate eCRF(s).

At each assessment timepoint post-hospitalization, the participant will be asked about any medications taken and these will be recorded in the participant's record and documented on the appropriate eCRF(s).

Any medication, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and must be recorded in the appropriate sections of the participant's record and documented on the appropriate eCRF(s).

The Sponsor recognizes that new therapies for COVID-19 may become available during the time this study is being conducted. Therapeutics approved by the FDA and listed in CDC guidelines, or FDA authorized medications (i.e., under the emergency-use authorization program) to prevent or treat COVID-19 and offered by the respective study site as standard-of-care may be administered and must be meticulously documented as outlined above.

7.4.1 Prohibited Therapies

Patients receiving chemotherapeutic agents and/or immunomodulators (e.g., systemic glucocorticoids, Mabs or plasma transfusions) for chronic disease conditions (e.g., malignancies, rheumatoid arthritis or other autoimmune diseases) at screening will not be eligible for enrollment into this study. Such agents may be administered as standard-of-care after enrollment and should be captured on the appropriate eCRF(s) as outlined above.

Participants should be advised not to consume alcohol or alcohol containing products while on study drug due to the potential for ANA001 to potential increased impairment (Yomesan [PI] 2008: https://www.bayer.co.za/static/documents/MSDS/PIs/YOMESAN_EN_PI.pdf).

7.4.2 Permitted Therapies

Therapeutics approved by the FDA and listed in CDC guidelines, or FDA authorized medications (i.e., under emergency-use authorization program) to prevent or treat COVID-19 and offered by the respective study site as standard-of-care may be administered and must be meticulously documented as outlined above.

Specifically, patients who deteriorate such that they fulfill criteria for more severe COVID-19 (e.g., require mechanical ventilation or increased oxygen support) may receive all treatments and FDA approved or FDA authorized medications determined by the respective investigative site to constitute standard-of-care for the treatment of severe or critical COVID-19 and should remain in the study.

7.4.3 Rescue Therapies

Rescue therapy is defined as any therapy that is either FDA approved (or has FDA emergency-use authorization) for COVID-19 or is administered to a participant to treat COVID-19 based on the potential for clinical efficacy against SARS-CoV-2. As the available FDA approved or authorized therapies are likely to evolve during enrollment of this study, a complete list of such therapies identified in the course of this study will be generated prior to unblinding.

8 SAFETY MONITORING

8.1 Definitions

Adverse event (AE) - An AE is any untoward medical occurrence associated with the use of a drug in humans whether or not it is considered drug-related. An AE can be any unfavorable and unintended sign (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug and does not imply any judgement about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug and with any route of administration, formulation, or dose including an overdose). Events that are related to the disease under study, COVID-19, should not be considered or recorded as AEs unless the event fits the definition for a serious adverse event (SAE), in which case the SAE must be reported to the electronic data capture (EDC) system for safety reporting purposes in the appropriate time frame.

Laboratory abnormalities should not be recorded as AEs or SAEs unless they are associated with clinical signs or symptoms or require medical intervention. However, each laboratory abnormality (e.g., clinically significant changes detected on hematology, chemistry, or coagulation test) independent from any underlying medical condition that requires medical or surgical intervention, or that leads to interruption of study drug administration or discontinuation, must be recorded as an AE or SAE, if applicable. If the laboratory abnormality is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than as the individual laboratory abnormality. In addition, laboratory abnormalities or other abnormal test assessments that are associated with signs or symptoms that are not part of a clinical condition or syndrome must be recorded as AEs or SAEs if they meet the definition of an AE or SAE.

Serious adverse event (SAE) - An event is considered "serious" if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE (An event is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the patient or participant at immediate risk of death. It does not include an AE or suspected adverse reaction (AR) that, had it occurred in a more severe form, might have caused death.)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Treatment-emergent – All AEs will be collected from the signing of informed consent until the EOS visit/Day 60. Non-treatment-emergent AEs are defined from the signing of informed consent to randomization. Treatment-emergent AEs (TEAEs) are defined from randomization through Day 28.

Causality or relatedness - A treatment-related AE (TEAE) is defined as any new AE that begins or any preexisting condition that worsens in severity, after informed consent until the EOS visit (i.e., Day 60+2) and is considered by the investigator to be related to ANA001. All AEs and SAEs should have attribution recorded as treatment- or not treatment-related, in the judgment of the site investigator.

- Related: There is a temporal relationship between the study drug and event, and the AE is known to occur with the study drug or there is a reasonable possibility that the study drug caused the AR. Reasonable possibility means that there is evidence to suggest a causal relationship between the study drug and the AE.
- Not related: There is not a reasonable possibility that the administration of the study drug caused the event, there is no temporal relationship between the study drug and event onset, or an alternate etiology has been established.

Adverse reaction - An AR is any AE caused by a drug.

Suspected adverse reaction (SAR) - An SAR is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of the IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. SAR implies a lesser degree of certainty about causality than AR.

Unexpected event- An event is considered unexpected if it is not listed in the Investigator's Brochure (IB), is not listed at the specificity or severity that has been observed, or, if an IB is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the IND. Unexpected also refers to events that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

Severity or intensity - All AEs that are recorded must have their severity graded. To grade AEs, study sites should refer to the Common Terminology Criteria for Adverse Events (CTCAE v5) criteria (USDHHS 2017: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).

8.2 Documenting Adverse Events

AEs will be recorded in the appropriate electronic case report form (eCRF).

8.2.1 Time Frame for Collection

AEs will be collected from the signing of informed consent through study completion (EOS visit; Day 60+2) or study withdrawal.

8.3 Recording Adverse Events

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., dizziness, light-headedness, and fall should be reported as "syncopal episode"). Investigators must record their opinion concerning the relationship of the (S)AE to the study drug and record a severity grade (using the criteria defined in the CTCAE v5 [USDHHS 2017: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf]) on the appropriate eCRF. All measures required for (S)AE management must be recorded in the source documents and reported according to the Sponsor's instructions.

All (S)AEs occurring at any time during the study (including the follow-up period) must be followed by the Investigator until resolution, return to baseline, or until the event is deemed stable or irreversible.

8.4 Communicating an SAE/SUSAR to the Sponsor and/or CRO

As soon as a clinical site investigator or other staff member becomes aware of a possible SAE in a study participant, regardless of attributability to study treatment, he/she should enter the AE/SAE information into the EDC system and reported on the SAE report within 24 hours of awareness for reporting to the Sponsor/CRO. The Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study participant safety and protocol conduct.

8.5 Expedited Reporting of SAE/SUSAR to IEC/IRB and Regulatory Authorities

With documentation support from the CRO and Sponsor, US Investigators must promptly submit all expedited safety reports to their IRB/EC within 7 days for fatal and life-threatening events and 15 days for other reportable events. The Sponsor or designee will be responsible for reporting an SAE/suspected unexpected serious adverse reaction (SUSAR) to regulatory authorities.

The FDA will be notified for any subject who is withdrawn from the study for safety reasons and for any DMC decision to pause enrollment or terminate the study.

8.6 Adverse Events of Special Interest

There are no identified AEs of special interest for ANA001.

8.7 Clinical Laboratory Findings

An AE can include any unfavorable and unintended abnormal laboratory findings temporally associated with the use of an investigational product whether or not considered related to the product.

Safety laboratory testing will be conducted as outlined in Section 9.3.6.2 and Appendix 5

8.8 Pregnancy

Pregnancies occurring in participants enrolled in this study must be reported and followed to outcome on the Pregnancy Notification Form. Pregnancy alone is not regarded as an AE unless there is a possibility that ANA001 may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be considered AEs unless they were therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered an SAE. Pregnancy is not considered an SAE unless there is an associated serious outcome. Spontaneous abortions should always be reported as SAEs.

8.9 Overdose or Misuse

ANA001 overdose, including misuse or abuse of the product and medication errors, must be reported in the Investigator’s notes and captured on the appropriate eCRF(s).

9 DATA ANALYSIS AND STATISTICAL METHODS

In this section, key details of the statistical analyses to be performed using data captured according to this protocol will be provided. This study consists of 2 main parts:

Study Part 1 is designed to primarily assess the safety and tolerability of ANA001 1,000 mg PO BID and

Study Part 2 is designed to primarily assess efficacy of ANA001 1,000 mg PO BID.

A complete statistical analysis plan (SAP) describing all planned analyses for each part will be finalized prior to unblinding of Study Part 1 (database freeze) and database lock after completion of Study Part 2. A DMC charter and DMC SAP will be finalized prior to initiation of Study Part 1.

9.1 Determination of Sample Size

9.1.1 Study Part 1

60 participants (30 randomized to ANA001 and 30 to placebo) are anticipated to provide sufficient data to assess safety and tolerability of ANA001 in patients with moderate and severe COVID-19. The sample size is based on clinical consideration and is consistent with the size of other studies with similar objectives.

9.1.2 Study Part 2

One study reported that subjects treated with placebo will have a median time to clinical improvement around 15 days (Beigel *et al*., 2020). Treatment with ANA001 is expected to reduce median time to clinical improvement to 11 days. At least 374 recoveries must be achieved for a log rank test to have 85% power at a two-sided significance level of 0.05.

Assuming a 6 months accrual period and the last enrolled subject will be followed for 30 days, at least 376 subjects must be randomized in 1:1 ratio. That is, at least 188 subjects must be randomized to be treated with ANA001 and 188 subjects to be treated with placebo.

9.2 Analysis Populations

The following populations will be considered for analysis of various endpoints:

Randomized Set: It includes all randomized subjects 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 subjects classified according to the treatment arm into which they were randomized regardless of the actual treatment received.

Per Protocol Set: It includes all subjects in the Full Analysis (or ITT) Set who satisfy COVID-19 disease criteria at baseline without any major protocol deviations which may affect the evaluation of the primary efficacy endpoints

Safety Set: It includes all randomized subjects, 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.

Pharmacokinetic (PK)-Evaluable Set: It consists of all randomized subjects, classified according to the actual treatment received regardless of randomization assignment, who receive at least one dose of study drug. A baseline and at least one pharmacokinetic blood sample following a dose of study treatment is required for inclusion in this analysis set. This is the analysis population for all planned pharmacokinetic analyses.

9.3 Planned Analyses

The analyses described in this section will be performed for data captured in Study Part 1 and Study Part 2 separately. No formal statistical inference is planned for data captured in Study Part 1.

As a general strategy, continuous efficacy and safety endpoints will be summarized using the five-number summary (mean, standard deviation, median, minimum, and maximum). Frequency distributions (counts and percentages) will be used to summarize categorical endpoints.

9.3.1 Disposition of the Study Participants

The disposition of subjects will be described with summaries by treatment group of the number of subjects in each analysis set described above, the number of subjects who completed the study (including the reasons for withdrawal), and the number of subjects for whom study drug was permanently discontinued (including the reasons for discontinuation). The ITT set will be used to produce this analysis.

9.3.2 Demographic and Baseline Disease Characteristics

Demographic and baseline disease characteristics will be summarized and compared by treatment group. Results will be reported using subjects in the ITT Analysis Set.

Medical history will be coded and reported by system organ class and body system.

Prior medications will be classified according to the anatomical therapeutic chemical (ATC) codes in the World Health Organization Drug (WHODRUG) dictionary. The incidence rate of each classified medication will be tabulated by treatment group. Tables will be sorted by the incidence use of the entire sample.

9.3.3 Exposure to Study Treatment and Compliance

Frequency distributions of the number of doses received will be presented by treatment group. Treatment duration and treatment compliance for all randomized subjects will also be described by treatment group.

Concomitant medications will be classified and reported in a manner similar to prior medications.

9.3.4 Analysis of Primary Efficacy Endpoints of Study Part 2

The primary efficacy endpoint in Study Part 2 is median time (in hours) to hospital discharge where discharge is defined as a score of 1 or 2 in the 8-point WHO Ordinal Scale for Clinical Improvement score. It is defined as the number of days from randomization to the first occurrence of discharge from the hospital (e.g., clinical recovery).

Median time (in hours) to hospital discharge and corresponding 95% confidence intervals will be estimated using the Kaplan-Meier method. Additionally, Cox proportional hazards model, with randomization factors as covariates, will be used to estimate the hospital discharge rate and corresponding 95% confidence interval. P-value will also be reported.

9.3.5 Analysis of Secondary Efficacy Endpoints

Mean change from baseline in continuous secondary efficacy endpoints will be compared using an analysis of variance model with baseline values and stratification factors as covariates. Difference in least-squares means and associated 95% confidence intervals will be reported. Sample size permitting, P-values will also be reported.

Logistic regression models, with stratification factors as covariates, will be used to compare categorical secondary endpoints. Odds ratio and corresponding 95% confidence intervals will be reported. P-values will also be reported.

9.3.6 Safety Analysis

All safety endpoints will be summarized using data from the safety set. Safety analyses will involve examination by treatment group of the incidence, relatedness, severity and type of treatment-emergent adverse events reported, changes from baseline (the assessment prior to first dose) in laboratory test results and in vital signs to specified timepoints throughout the study. Concomitant medications use will also be summarized by treatment group.

9.3.6.1 Treatment-Emergent Adverse Events

All adverse events reported during the study will be coded using a MedDRA (v21.1) dictionary. Non-treatment-emergent AEs will be captured on the appropriate eCRF and a listing will be generated for the randomized set. Only treatment-emergent AEs (TEAEs) will be summarized in the planned safety analyses. The incidence of treatment-emergent adverse events will be summarized by treatment group and the following:

Preferred term

System organ class and preferred term

System organ class, preferred term and severity

These summaries will be presented for the following subsets:

All adverse events

Serious adverse events

Drug-related adverse events

Adverse events leading to study treatment discontinuation.

For tables reporting adverse events by severity, if a subject has multiple occurrences of an adverse event with the same organ class and preferred term, the most severe event will be presented.

9.3.6.2 Clinical Laboratory Evaluation

Safety 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 hematology, chemistry, and coagulation tests. Parameters will be classified according to the laboratory reference normal ranges. A listing will be provided for out of normal range as well as potentially clinically significant abnormal laboratory values.

9.3.6.3 Vital Signs

Vital signs, including pulse, respiratory rate, blood pressure (i.e., systolic and diastolic), and temperature will be summarized by treatment group and timepoint. For each assessment of vital signs, change and percent change in vital signs from baseline will be summarized by treatment group.

9.4 Interim Analysis

Upon completion of Study Part 1, the independent DMC will conduct a review of safety and efficacy data to provide potential recommendations for early termination or possible study adaptations as outlined in the DMC charter. Additional details regarding interim analyses are outlined in the DMC statistical analysis plan (SAP) and the study SAP.

9.5 Independent Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be formed and constituted according to appropriate regulatory agency guidelines. Detailed information regarding the composition of the committee and detailed procedures will be provided in a separate DMC charter. The independent DMC will review the safety, tolerability, and efficacy data of Study Part 1 and Study Part 2 as described in the DMC charter.

9.6 Handling of Missing Data

Missing efficacy assessments will be imputed using a multiple imputation method appropriate to the pattern of missingness. Details of the considered patterns and associated sensitivity analyses will be described in the Statistical Analysis Plan.

9.7 Multiplicity Adjustment

A hierarchical testing scheme is planned to preserve the familywise type I error of the study. If statistical significance of the primary efficacy endpoint is established, secondary efficacy endpoints will be tested in the following order:

1. Mean change from baseline (BL) in National Early Warning Score (NEWS2)
2. Mean number of days on rescue treatment (COVID-19 treatments that are approved under NDA or EUA) within 15 days after enrollment

The testing scheme will be halted at the first secondary endpoint that fails to establish statistical significance.

9.8 Pharmacokinetic Analysis

Descriptive statistics of individual plasma concentrations for ANA001 will be summarized and listed according to the sampling schedule outlined in Appendix 6 for Study Day 1, 2, 3, or 4 for the PK-Evaluable set and will be reported in the CSR.

Derived PK parameters, population PK analyses, and potential pharmacokinetic/pharmacodynamic (PK/PD) relationships will be reported separately.

10 ETHICAL CONSIDERATIONS

10.1 Good Clinical Practice

This study will be conducted in compliance with Good Clinical Practices (GCP), i.e., International Council for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use guideline E6 (R2) on Good Clinical Practice, other ICH guidelines, and relevant national guidelines on GCP.

10.2 Ethics Review

The study protocol, site-specific informed consent forms (ICFs), participant education and recruitment materials, and other requested documents, including any subsequent modifications, will be reviewed and approved by the Independent Ethics Committee (IEC)/IRB.

10.3 Informed Consent

The principles of informed consent in the ICH GCP guideline E6 (R2) will be implemented before any protocol-specified procedures or interventions are carried out. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant, and this fact will be documented in the participant's record.

10.4 Data Privacy

Participants' study information will not be released without their written permission, except as necessary for oversight by:

- The principal investigators or designees
- IRB/IEC
- Sponsor or designees, AND/OR
- Regulatory authorities

10.5 Disclosure

Each study site will establish a standard operating procedure for confidentiality protection. Each site will ensure that study records including administrative documentation and regulatory documentation, as well as documentation related to each participant enrolled in the study, including ICFs, locator forms, CRFs, notations of all contacts with the participant, and all other source documents are stored in a secure manner.

10.6 Biological Specimens and Data

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality, unless otherwise required by local or state authorities, e.g., SARS-CoV-2 testing results, which are participant to local and state reporting that is name-based. Local public health agencies may contact participants diagnosed with SARS-CoV-2 for the purpose of surveillance and contact notification. Participants will be informed prior to SARS-CoV-2 testing that results are reportable and may lead to contact by local public health officials if results are positive for infection.

All records will be kept in a secure location. All computer entry and networking programs will be done with coded information. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the principal investigators

or designees, IRB/IEC, Office for Human Research Protections (or other local, US, and international regulatory entities as part of their duties), and/or the Sponsor or designees.

11 OVERSIGHT

11.1 Data Monitoring Committee

An independent DMC will be convened for this study consisting of at least 3 medical doctors, with expertise in infectious diseases, pulmonary/critical care, investigational drug development, and/or experienced in the management of hospitalized COVID-19 patients. The DMC will also include a biostatistician experienced in clinical trial design and analyses. The purpose of the DMC is to monitor the study for operational safety, and efficacy (including futility). The DMC will provide recommendations to the Sponsor as described in the DMC charter.

The DMC will conduct interim reviews when adequate data have been accrued. Open reports containing accrual and retention rates, participant characteristics, and SAEs will be sent to the DMC members prior to each scheduled or unscheduled DMC meeting. Only the DMC members (including the unblinded biostatistician) will receive password-protected closed reports containing unblinded study data. The DMC members will also have access to unblinded data at their request. Further details are contained in the DMC charter.

11.2 Quality Control and Assurance

11.2.1 Monitoring

Study conduct will be monitored by site-independent monitors. Monitors will visit participating clinical research sites to review the individual participant records, including consent forms, eCRFs, supporting data, laboratory specimen records, and endpoints through laboratory and medical records (physicians' progress notes, nurses' notes, and individuals' hospital charts), to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors also will inspect the sites' regulatory files to ensure that regulatory requirements are being followed and the sites' pharmacies to review product storage and management. When on-site visits to the participating clinical research sites are not feasible due to COVID-19 control measures and/or other institutional restrictions, remote monitoring visits will be performed per the study clinical monitoring plan.

11.2.2 Protocol Deviations

Prospective approval of a protocol deviation of an enrollment criterion, also known as a protocol waiver or exemption, is not permitted.

Protocol deviations will be liste**d** by treatment group for all randomized participants. Protocol deviations are defined as any variation from the protocol, including enrollment of a subject who did not meet all inclusion criteria or who met an exclusion criterion, or the failure to perform the assessments and procedures as specified in the protocol within the required time frames.

11.2.3 Records

11.2.3.1 Data Capture and Management

Participant information will be captured and managed by study sites on eCRFs by a web-based EDC tool.

11.2.3.2 Records Retention

Investigator shall retain all study records until **at least 2 years** after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or **at least 2 years** have elapsed since the formal discontinuation of clinical development of the study drug. In the event that study records are relocated to a different location from the site location during this study retention period, the Investigator must notify the Sponsor and/or its designees.

11.3 Study Completion/Termination

The Sponsor will register the study and post study results upon study completion or termination, regardless of outcome, on a publicly accessible website in accordance with the applicable laws and regulations.

The Sponsor also will notify, when required, the regulatory authorities and IECs/IRBs about the completion or termination of this study and send a copy of the study report synopsis in accordance with necessary timelines.

12 PUBLICATION POLICY

The Sponsor retains the rights to publish the results of this study. Details are included in the clinical trial agreement.

13 FUNDING

NeuroBo Pharmaceuticals, Inc. is the Sponsor of this study.

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15 APPENDICES

APPENDIX 1 WHO ORDINAL SCALE FOR CLINICAL IMPROVEMENT

Score	Status
1	Not hospitalized, no limitations on activities
2	Not hospitalized, limitation on activities and/or requiring home oxygen
3	Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care
4	Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)
5	Hospitalized, requiring supplemental oxygen
6	Hospitalized, on non-invasive ventilation or high flow oxygen devices
7	Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
8	Death

Reference: WHO R&D Blueprint: novel Coronavirus; COVID-19 Therapeutic Trial Synopsis. Geneva, Switzerland. 18 Feb 2020

APPENDIX 2 NATIONAL EARLY WARNING SCORE 2 (NEWS2)

The resulting observations are compared with a normal range to generate a single composite score, for instance based on the following diagram (an early modified NEWS):

Table 4 NEWS2

NEWS2 Score Select resp			Clinical risk		Response	
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 (air)	93-94 (O_2)	95-96 (O_2)	≥97 (O_2)
Air or O_2						
	O_2		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		35.1-36	36.1-38	38.1-39	≥39.1	

A summary of this scoring system can be accessed at https://www.rcplondon.ac.uk/projects/outputs/national-early-warning-score-news-2

For patients confirmed to have hypercapnic respiratory failure on blood gas analysis on either a prior or their current hospital admission and requiring supplemental oxygen should be noted. Scale 2 on the NEWS2 chart will be used to record and score the oxygen saturation for the NEWS.

The vital signs of the participant (including: pulse, respiratory rate, SpO2 (including room air or oxygen [with oxygen delivery and rate]), blood pressure (systolic and diastolic), and temperature will be entered into an eCRF. The individual parameters of the NEWS2 scoring system will be populated using these values.

Concurrently with determination of NEWS2, severity of participant's COVID-19 (Appendix 4) and subjective 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.

This chart collected variable and scoring system is not intended to guide or modify standard-of-care at the respective investigative sites.

APPENDIX 3 SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE

SOFA score	0	1	2	3	4
Respiration					
PaO_2/FIO_2 (mmHg)	> 400	301–400	201–300	101–200	≤ 100
(kPa)	> 5.3)	(4.1–5.3)	(2.8–4.0)	(1.4–2.7)	≤ 1.3)
Coagulation					
Platelets ($x10^3/mm^3$)	> 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
(µmol/l)	< 20)	(20–32)	(33–101)	(102–204)	≥ 204)
Cardiovascular					
Hypotension	No hypotension	MAP < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose)*	Dopamine > 5	Dopamine > 15
Central nervous system					
Glasgow coma score	15	13–14	10–12	6–9	< 6
Renal					
Creatinine (mg/dl)	< 1.2	1.2–1.9	2.0–3.4	3.5–4.9	> 5.0
(µmol/l)	< 110)	(110–170)	(171–299)	(300–440)	> 440)
or urine output				< 500 ml/day	< 200 ml/day

* adrenergic agents administered for at least 1 h (doses given are in µg/kg/min)

Source: de Mendonça *et al*., 2000
FIO_2=fraction of inspired oxygen; PaO_2=partial pressure of oxygen.

APPENDIX 4 CRITERIA FOR MODERATE, SEVERE, AND CRITICAL COVID-19

Severity	Criteria
Moderate	Development of one of the following: 1. Symptoms suggestive of moderate illness (fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, AND **shortness of breath with exertion**, OR 2. Clinical signs indicative of moderate systemic illness with COVID-19, such as respiratory rate ≥20 breaths per minute, heart rate ≥90 beats per min, SpO_2 >93% on room air, AND No criteria for Severe or Critical Severity
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

Reference: FDA. COVID-19: Developing Drugs and Biological Products for Treatment or Prevention: Guidance for Industry. May 2020.

APPENDIX 5 LABORATORY ASSESSMENTS

Hematology (Local Laboratory Tests)*	**Serum Chemistry (Local Laboratory Tests)***
Hemoglobin	Blood urea nitrogen (BUN)
Hematocrit	Creatinine
Total WBC count with 5-part differential	Sodium
Platelet count	Potassium
	Chloride
	Carbon dioxide
	Glucose
Coagulation (Local Laboratory Tests)*	Total bilirubin
Partial thromboplastin time (aPTT)	Direct Bilirubin
Prothrombin time (PT)	Alkaline phosphatase (ALP)
International normalized ratio (INR)	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
	Additional Tests (Central Laboratory Tests)
	D-dimer
	Cardiac troponin
	Ferritin
	LDH
	CRP
	Exploratory tests (e.g., IL-6, TF, MCP-1, IP-10)

* Denotes laboratory assessment used primarily to generate safety summaries

APPENDIX 6 PK SAMPLE COLLECTION SCHEDULE (STUDY PART 1 ONLY)

	Day 1, 2, 3, or Day 4				
SAMPLING SCHEDULE	Pre-Dose (i.e., within 30 minutes)	1 hour (+/- 30 minutes)	4 hour (+/- 30 minutes)	8 hour (+/- 30 minutes)	Pre-Dose to next study drug (i.e., within 30 minutes) administration

Please refer to the Central Laboratory Manual for primary and back-up sample collection and processing instructions. Remaining blood plasma volume may be used for central laboratory and/or exploratory analyses (e.g., IL-6, tissue factor, MCP-1 and IP-10).