Study Title	Phase 2, Double-blind, Randomized, Placebo-controlled Study of NasoVAX in the Prevention of Clinical Worsening in Patients with Early Coronavirus Infectious Disease 2019 (COVID-19)
NCT Number	NCT04442230
Document	Study Protocol
Document Date	04 January 2021

Altimmune, Inc.
910 Clopper Road, Suite 201 S
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USA

Clinical Study Protocol

Study Title:	Phase 2, Double-blind, Randomized, Placebo-controlled Study of NasoVAX in the Prevention of Clinical Worsening in Patients with Early Coronavirus Infectious Disease 2019 (COVID-19)
Study Number:	ALT-601-201
Study Phase:	Phase 2
Test Product:	NasoVAX
Sponsor:	Altimmune, Inc. 910 Clopper Road, Suite 201-S Gaithersburg, MD 20878 USA

[redacted]

Confidentiality Statement

CLINICAL PROTOCOL APPROVAL

Protocol Title: Phase 2, Double-blind, Randomized, Placebo-controlled Study of NasoVAX in the Prevention of Clinical Worsening in Patients with Early Coronavirus Infectious Disease 2019 (COVID-19)

Study No: ALT-601-201

Protocol Version No: 6.0

Protocol Version Date: 04 January 2021 (Amendment 05)

This study protocol was subject to critical review and has been approved by the Sponsor representative.

PROTOCOL ALT-601-201

Phase 2, Double-blind, Randomized, Placebo-controlled Study of NasoVAX in the Prevention of Clinical Worsening in Patients with Early Coronavirus Infectious Disease 2019 (COVID-19)

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to NasoVAX are the confidential and proprietary information of Altimmune, Inc., and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of Altimmune, Inc.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practice (GCP) and International Council for Harmonisation (ICH) guidelines and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by Altimmune, Inc., or specified designees. I will discuss the material with them to ensure that they are fully informed about NasoVAX and the study.

Principal Investigator Name (printed)	Signature
_____	_____
__ __ - __ __ __ - __ __ __ __ Date (dd-mmm-yyyy)	__ __ Site Number

STUDY SUMMARY

Sponsor: Altimmune, Inc.
Study Title: Phase 2, Double-blind, Randomized, Placebo-controlled Study of NasoVAX in the Prevention of Clinical Worsening in Patients with Early Coronavirus Infectious Disease 2019 (COVID-19)
Study Number: ALT-601-201
Study Phase: 2
Study Centers: Up to 12 centers in the United States
Number of Patients Planned: NasoVAX Approximately 96 patients with early COVID-19 will be enrolled and randomized 1:1 to NasoVAX or placebo in 3 successive cohorts defined by age and risk factors for severe COVID-19 (Exclusion Criterion 5) (Cohort 1, ages 18-49 years and risk factors disallowed; Cohort 2, ages 18 and above and risk factors disallowed; and Cohort 3, ages 18 and above and risk factors allowed) of approximately 20, 28, and 48 patients, respectively, with patients randomized 1:1 to NasoVAX or placebo within each cohort. Cohort 2 will be stratified by age groups of 18-64 years and 65 years and above, whereas Cohort 3 will be stratified by age groups (ages 18-64 years, ages 65 and above) and co-morbidity (one or more risk factors present, no risk factors present).
Duration of Patient Participation: Each patient will participate in the study up to approximately 4 weeks (28 days). Patients who remain hospitalized at the end of 28 days will be followed through Day 42 or death, whichever is sooner.
Enrollment Period: Approximately 3 months
[redacted]
Study Objectives: *Efficacy* Primary Objective: To assess the effectiveness of NasoVAX in preventing clinical worsening in patients with early COVID-19 Secondary Objectives: • To assess the effects of NasoVAX on the severity of COVID-19, as indicated by changes in resting peripheral oxygen pulse saturation (SpO_2) and resting pulse rate • To assess the effects of NasoVAX on rates hospital admission, oxygen supplementation and mechanical ventilation

Safety

Primary Objective

- To assess the safety and tolerability of NasoVAX in patients with early COVID-19

Study Design: This is an exploratory Phase 2 clinical study to evaluate the protective effects of NasoVAX in patients with early COVID-19. Approximately 96 ambulatory patients with COVID-19, with one or more symptom(s) of fever, cough, and/or shortness of breath, onset of these symptoms within 72 hours of screening, and a diagnosis by a PCR-based or rapid antigen test diagnostic, will be enrolled in 3 successive cohorts defined by age and risk factors for severe COVID-19 (Exclusion Criterion 5) (Cohort 1, ages 18-49 years and risk factors disallowed; Cohort 2, ages 18 and above and risk factors disallowed; and Cohort 3, ages 18 and above and risk factors allowed) of approximately 20, 28, and 48 patients, respectively. The cohorts will be enrolled in ascending order, with Cohort 1 preceding Cohort 2, and Cohort 2 preceding Cohort 3. Patients in Cohort 2 will be stratified by age groups of 18-64 years and 65 years and above. Cohort 3 will be stratified by age groups (ages 18-64 years, ages 65 and above) and co-morbidity (one or more risk factors present, no risk factors present).

Study conduct will be overseen by a Data Monitoring Committee (DMC), which will monitor the safety of study participants and review safety data real-time during the course of the study. If any of the Stopping Rules (Section 7.2) are met, enrollment and study drug treatment will be temporarily halted pending DMC review.

Once a cohort is fully enrolled, enrollment will be paused until all patients either complete 14 days of home assessments or they are determined to have been hospitalized. The DMC will then review the safety and tolerability data and make a recommendation regarding whether to progress to the next cohort. The DMC may unblind the data in conducting its assessments although treatment allocation will not be revealed to operational study personnel.

Upon signing informed consent, patients will undergo Screening assessments at the study center, as per the Schedule of Events (Table 1). Within each cohort, patients who are determined to be eligible will be randomized that same day (Day 1) in a 1:1 ratio to receive either NasoVAX or placebo with approximately 10 and 14 patients in Cohorts 1 and 2, respectively, receiving NasoVAX and 10 and 14 receiving placebo in Cohorts 1 and 2, respectively. Approximately 24 patients will receive NasoVAX and 24 will receive placebo in Cohort 3.

Study drug will be administered as a single intranasal dose of 0.5 mL (0.25 mL each nostril) in the supine position after which patients must remain in the supine position for 30 minutes. Patients will be observed for at least 2 hours post intranasal administration. Patients who are randomized will be considered enrolled in the study.

No in-person visits are expected during the study after Day 1 unless a participant experiences a change in symptoms or adverse event (AE) that requires a visit for assessment.

Prior to discharge from the study center on Day 1, patients will be provided with:

- A fingertip pulse oximetry device connecting to a tablet that will be supplied to the patient to measure resting SpO_2 and resting pulse rate remotely. Patients will be trained on the use of the device and tablet.
- A digital thermometer for measurement of oral temperature

- Instructions regarding how to take the above measurements and access and complete a web-based electronic diary (eDiary)

After discharge on Day 1, patients will return home for the duration of the study. Patients are to measure resting SpO_2, resting pulse rate, and oral temperature twice daily at 09:00 hours and 16:00 hours, with a 1-hour window around each time point, and at any time they experience worsening symptoms until Day 14 or hospitalization, whichever comes first. Patients are to record COVID-19-related symptoms daily during this same time period. Study center personnel will contact patients daily by telephone during this period to document the patient's clinical status, record concomitant medications and monitor for AEs.

After Day 14, study center personnel will contact patients via telephone approximately every 7±2 days for 14 additional days to determine if they were hospitalized and to follow AEs that were not resolved by Day 14. If the patient is hospitalized at any time, the dates and times of hospital admission/discharge, intensive care unit (ICU) admission/discharge, and ventilation requirement are to be recorded, as applicable. Patients who remain hospitalized at the end of 28 days will be followed through Day 42 or death, whichever is sooner.

Stopping Rules:

Enrollment and study drug treatment will be temporarily halted pending DMC review for any of the following reasons:

a. Any serious adverse event (SAE) considered possibly or probably related to study drug
b. Any Grade 4 or Grade 5 (death) AE considered possibly or probably related to study drug
c. Three or more subjects in the same cohort experience the same Grade 3 AE in the same Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class considered possibly or probably related to study drug
d. Hospitalization rates in either treatment group in individual cohorts exceeding:
    - 15% (Cohort 1 only)
    - 20% (Cohort 2 only)
    - 25% (Cohort 3 only)
e. Mechanical ventilation rates in either treatment group in individual cohorts equal to or exceeding:
    - 2 patients (Cohort 1 only)
    - 3 patients (Cohort 2 only)
    - 4 patients (Cohort 3 only)

The DMC will be advised each time a patient dies or is hospitalized. The DMC may unblind individual patients for the assessment of the relationship of the event to study drug. The DMC may recommend resumption of dosing if subject safety is not considered to be at significant risk following analysis.

Inclusion Criteria:

1. Able and willing to provide informed consent

   Patients themselves must provide written informed consent before the performance of any study-related procedures, and surrogate consent by family members, designated legal representatives or caregivers will not be permitted.
2. Men and women 18 years of age and older
3. Early COVID-19, defined as one or more symptom(s) of fever (oral temperature ≥ 100.4ºF), cough or shortness of breath, onset of these symptoms within 72 hours of screening, and confirmation of SARS-CoV-2 infection by a polymerase chain reaction (PCR)-based or rapid antigen test diagnostic
4. Resting $SpO_2 \geq 96.0\%$ on room air on two successive measurements
5. For women of childbearing potential (women who are not permanently sterile [documented hysterectomy, bilateral tubal ligation, salpingectomy, or oophorectomy] or postmenopausal [12 months with no menses without an alternative medical cause])
   - Negative urine pregnancy test at Screening
   - Willingness to practice a highly effective method of contraception that includes, but is not limited to, abstinence, sex only with persons of the same sex, monogamous relationship with a postmenopausal partner, monogamous relationship with vasectomized partner, vasectomy, licensed hormonal methods, intrauterine device, or consistent use of a barrier method (eg, condom, diaphragm) with spermicide for 28 days after the last dose of study drug
6. For men with sexual partners of childbearing potential, willingness to practice a highly effective method of contraception, as defined above, for 45 days after the last dose of study drug
7. Ability and willingness to comply with all aspects of the study, including reliable internet access, through the entire study period

Exclusion Criteria:

1. Pregnant or lactating women or planning to conceive a child during the next 3 months
2. Resting respiratory rate >20 breaths/min on room air or resting pulse rate ≥ 125 beats per minute
3. A rapidly worsening course that in the opinion of the Investigator or treating medical practitioner would lead to hospitalization within the next 24-48 hours
4. Any chronic pulmonary disease, including chronic obstructive pulmonary disease and asthma, or other respiratory diseases that could exacerbate independent of COVID-19
5. The following risk factors for severe COVID-19 (Cohorts 1 and 2 only):
   a. Severe obesity, defined as body mass index ≥ 40 kg/m^2

b. History of
   i. Severe cardiovascular disease, including but not limited to congestive heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, or pulmonary hypertension
   ii. Diabetes mellitus
   iii. Chronic or current vaping or cigarette smoking
   iv. Chronic kidney disease requiring dialysis
   v. Chronic liver disease, including but not limited to chronic viral hepatitis, non-alcoholic steatohepatitis, or cirrhosis of any cause
   vi. Hemoglobin disorder, including sickle cell disease and thalassemia

   Based on ongoing review of efficacy and safety data, the DMC may remove part or all of these risk factors if preliminary data show no signal for adverse or paradoxical effects.

6. History of Bell's Palsy
7. Nasal conditions that might affect the suitability of intranasal medication, such as a history of chronic rhinitis, nasal septal defect, cleft palate, nasal polyps, or nasal surgery other than cosmetic rhinoplasty.
8. Use of hydroxychloroquine within the past 4 months, chloroquine with the past 9 months, or other investigational agents for COVID-19 within the past 30 days
9. History of conditions associated with immunocompromise, including but not limited to poorly controlled HIV, or treatments known to affect the immune system, including but not limited to oral or intravenous corticosteroids, alkylating drugs, antimetabolites, cytotoxic drugs, radiation, immune-modulating biologics (including interleukin [IL]-6, IL-12, Janus kinase inhibitors or antagonists), and cancer treatments, within 30 days of Screening, or anticipated use within 6 months following participation in this study
10. Any medical, psychiatric, or social condition or occupational or other responsibility that in the judgment of the Investigator would interfere with or serve as a contraindication to protocol adherence, assessment of safety (including reactogenicity), or a patient's ability to give informed consent

Efficacy Endpoints:

Primary Efficacy Endpoint:

The primary endpoint is the proportion of patients with clinical worsening, defined as an absolute 4.0% decrease from Baseline in resting SpO_2 by mobile pulse oximetry on two consecutive measurements during home follow-up, or hospitalization.

Secondary Efficacy Endpoints:

1. Maximal severity of COVID-19 after treatment, as assessed by the following:
   - average decrease in resting SpO_2 from Baseline resting SpO_2 at Screening during the 14 days of home follow-up or hospitalization
   - average increase in resting pulse rate from Baseline resting pulse rate at Screening during the 14 days of home follow-up or hospitalization

- proportion of patients requiring hospitalization through Day 42 according to maximal level of oxygen supplementation:
  - No oxygen supplementation
  - Oxygen supplementation with nasal cannula
  - Oxygen supplementation with high flow device or non-invasive ventilation
  - Mechanical ventilation

2. All-cause mortality through Day 42

Safety Endpoints

- Incidence and severity of AEs
- Oral temperatures
- Use of antipyretics and bronchodilators
- Hospital length of stay, and ICU length of stay

Statistical Methods:

Power and Sample Size Assumptions:

The study is considered exploratory to assess the initial safety of NasoVAX in COVID-19 and response to treatment. The sample size chosen for this study was considered adequate to meet the study objectives and was selected without statistical significance considerations.

Statistical Analysis:

Population definitions:

Safety Analysis Set: All patients who receive any study drug.

Modified intent to treat (mITT): All randomized patients who receive any amount of study drug and have a Baseline and at least one post-Baseline resting SpO_2 measurement. Patients will be analyzed according to the treatment that they receive.

Per Protocol (PP): All randomized patients who receive any amount of study drug according to the correct treatment assignment and who have 80% of twice daily results from resting SpO_2 measurements through Day 14 or hospitalization.

General:

Baseline is defined as data collected closest to randomization prior to any study drug dosing. For resting SpO_2 and resting pulse rate, Baseline is defined as the average of the two measurements at Screening. All analyses and summary statistics will be presented by treatment group (NasoVAX, placebo) across cohorts, as well as by treatment group pooled across all cohorts.

Descriptive statistics, including the numbers and percentages for categorical variables and the numbers, means, standard deviations, medians, minimums and maximums for continuous variables will be provided by treatment across cohorts.

Patients will be randomized 1:1 to NasoVAX or placebo and proceed in 3 cohorts defined by age and risk factors for severe COVID-19 (Exclusion Criterion 5) (Cohort 1, ages 18-49 years and risk factors disallowed; Cohort 2, ages 18 and above and risk factors disallowed; and Cohort 3, ages 18 and above and risk factors allowed) of approximately 20, 28, and 48 patients, respectively. The cohorts will be enrolled in ascending order, with Cohort 1 preceding Cohort 2, and Cohort 2 preceding Cohort 3. Cohort 2 will be stratified by

age groups of 18-64 years and 65 years and above, whereas Cohort 3 will be stratified by age groups (ages 18-64 years, ages 65 and above) and co-morbidity (one or more risk factors present, no risk factors present). Patients in Cohorts 2 and 3 will be stratified first, and then randomized 1:1 to NasoVAX or placebo. Enrollment of patients ages 18-49 will not exceed approximately 30% of the randomized population of either treatment arm. In addition, a minimum of 40% of Cohort 3 will either be 65 years or above or have one or more risk factors for severe COVID-19.

Efficacy Analyses:

Descriptive statistics will be used to evaluate differences between Baseline and post-Baseline efficacy endpoints. The study is considered exploratory, and inferential statistics will be employed as appropriate.

For the primary analysis, proportions of patients with clinical worsening, defined as a 4.0% decrease from Baseline in resting SpO_2 on two consecutive measurements during the 14 days of home follow-up, or hospitalization, will be compared between NasoVAX and placebo groups using the Cochrane Mantel Haenszel test, while considering the stratification of age groups and risk factors, at a one-sided significance level of 0.025. The same approach will be applied for secondary or exploratory endpoints that are categorical in nature. Sensitivity analyses will be performed to assess the effect of site on the response to study drug. Linear and logistic regression will be employed to examine the effects of Baseline factors, such as age, sex, medications, and medical co-morbidities on response.

Changes from Baseline in Severity of COVID-19, assessed by maximum decrease in resting SpO_2 or increase in resting pulse rate by outpatient pulse oximetry and COVID-19 symptoms (eDiary) during home follow-up, will be analyzed using a mixed model for repeated measures. The model will include the fixed effects of treatment, week, and treatment-by-visit interaction as well as the continuous, covariate of Baseline level. The model will employ an unstructured within patient covariance matrix and a restricted maximum likelihood estimation method.

A Kaplan-Meier method will be applied to compare changes between treatment groups in resting SpO_2 over time.

For the purpose of study efficacy endpoints, resting SpO_2 and resting pulse rate will be assessed on observed data only; if data is missing, it will not be imputed.

No multiplicity adjustments will be made for secondary or exploratory endpoints.

Safety and Tolerability:

Quantitative safety data, including the frequencies of AEs, oral temperatures, use of antipyretics and bronchodilators, and length of hospital and ICU stay, will be summarized using descriptive statistics and frequency distributions. Qualitative safety data will be summarized by frequencies and percentages. All summaries will be presented by treatment arms. AEs will be coded using MedDRA, and severity will be coded using the Common Terminology Criteria for Adverse Events (CTCAE), v.4.0.3. Concomitant medications will be coded using World Health Organization (WHO) drug dictionary.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
BMI	Body Mass Index
CCL	Chemokine [C-C motif] ligand
COVID-19	Coronavirus Infectious Disease 2019
DMC	Data Monitoring Committee
eCRF	Electronic case report form
eDiary	Electronic diary
GCP	Good Clinical Practice
GMT	Geometric mean titer
HLA	Human leukocyte antigen
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICU	Intensive care unit
IFN	Interferon
IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
PCR	Polymerase chain reaction
RD-Ad5	Replication-deficient adenovirus-5
SAE	Serious adverse event

Abbreviation	**Definition**
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SpO_2	Peripheral oxygen pulse saturation
TEAE	Treatment-emergent adverse event
WHO	World Health Organization
US	United States
vp	Virus particles

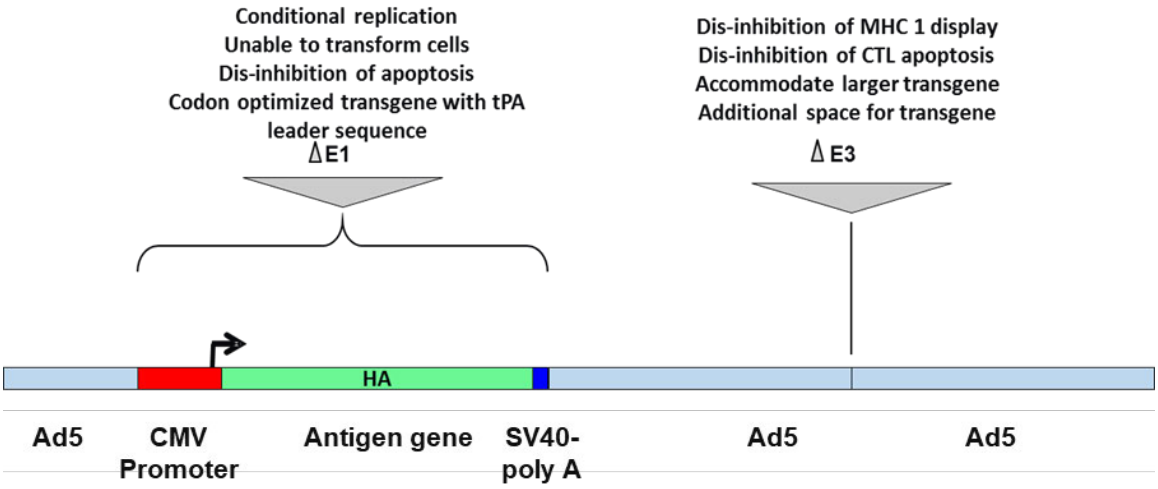
1 INTRODUCTION AND RATIONALE

1.1 Background

NasoVAX is being developed under IND 21210 for the prevention and treatment of Coronavirus Infectious Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The RD-Ad5 vector that forms the basis of NasoVAX has been employed with genetic inserts against other pathogens in other vaccine products conducted under earlier INDs, including different strains of influenza (BB-IND 8888, BB IND13575), tetanus (IND 10852), and anthrax (IND 017832, NasoShield). NasoVAX is also being developed under IND 017626 for the treatment of influenza A and B. Figure 1 provides a schematic diagram of the RD-Ad5 vector and identifies those sequences from the parent Ad5 genome that are retained in the vector.

For the current study, NasoVAX is being developed for the prevention and treatment of clinical worsening in patients with early coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Administration of NasoVAX is by intranasal delivery. The rationale for investigating the use of NasoVAX in COVID-19 is based on observations, as described in Section 1.2, that the RD-Ad5 viral vector itself is protective against respiratory viruses independent of its influenza effects, because protection is afforded in the presence or absence of the influenza HA transgene. The collective safety experience with RD-Ad5 vectors suggests that NasoVAX will be safe in COVID-19 and that the HA transgene insert will not prevent the development of immunogenicity to the SARS-CoV-2 virus or alter the drug's safety profile in patients with COVID-19.

Figure 1 Schematic Illustration of NasoVAX



1.1.1 Nonclinical Data

[redacted]

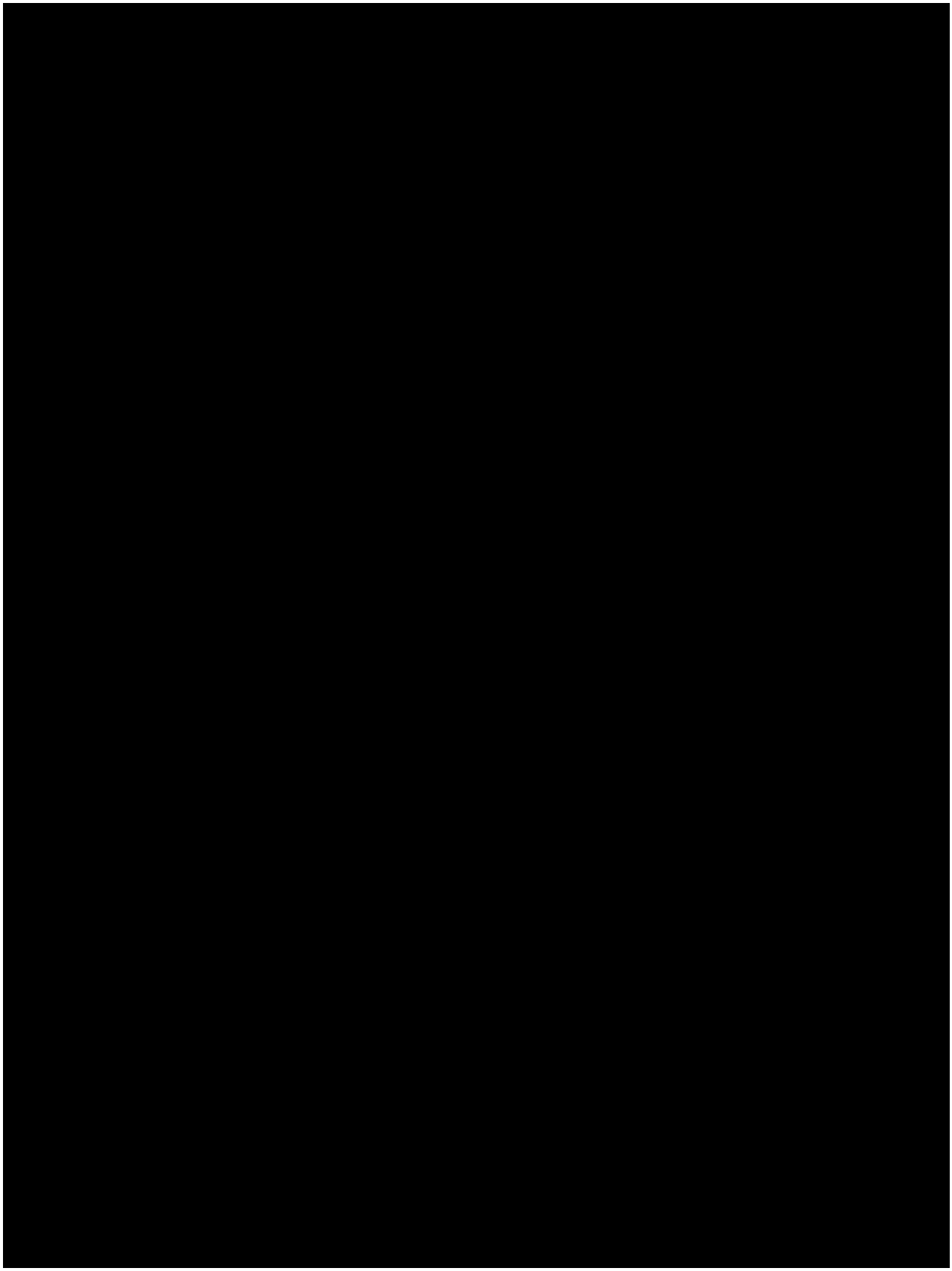
Refer to the Investigator's Brochure for additional information.

1.1.2 Clinical Data

[redacted]

1.2 Rationale for NasoVAX in COVID-19

[redacted]



The current exploratory Phase 2, double-blind, placebo-controlled study is designed to evaluate the potential of NasoVAX to decrease the progression of disease in ambulatory patients in early COVID-19. Nonclinical studies in support of this indication demonstrated a rapid and prolonged effect of intranasal administration of RD-Ad5 vectors, with protection from lethal challenge occurring within 2 days and lasting for as long as 47 days. In the context of the proposed clinical plan where patients with newly conformed COVID-19 will receive NasoVAX treatment, it is important to realize that the kinetics of virally induced death in the murine model (onset around 5-7 days post-challenge) is considerably faster than that observed in COVID-19 (median of 18.5 days) (Zhou 2020). Given the rapid (2 days) and prolonged (at least 47 days) protection treatment with RD-Ad5 vectors provides, the clinical development plan is supported by the nonclinical data.

2 STUDY OBJECTIVES

2.1 Efficacy

2.1.1 Primary

The primary objective is to assess the effectiveness of NasoVAX in preventing clinical worsening in patients with early COVID-19.

2.1.2 Secondary

The secondary objectives of the study are:

- To assess the effects of NasoVAX on the severity of COVID-19, as indicated by changes in resting peripheral oxygen pulse saturation (SpO_2) and resting pulse rate
- To assess the effects of NasoVAX on rates hospital admission, oxygen supplementation and mechanical ventilation

2.2 Safety

- To assess the safety and tolerability of NasoVAX in patients with early COVID-19

3 STUDY ENDPOINTS

3.1 Primary Efficacy Endpoint

The primary endpoint is the proportion of patients with clinical worsening, defined as an absolute 4.0% decrease from Baseline in resting SpO_2 on two consecutive measurements during home follow-up, or hospitalization.

3.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are:

1. Maximal severity of COVID-19 after treatment, as assessed by the following:
    - average decrease in resting SpO_2 from Baseline resting SpO_2 at Screening during the 14 days of home follow-up or hospitalization
    - average increase in resting pulse rate from Baseline resting pulse rate at Screening during the 14 days of home follow-up or hospitalization
    - proportion of patients requiring hospitalization through Day 42 by maximal level of oxygen supplementation:
        - No oxygen supplementation
        - Oxygen supplementation with nasal cannula
        - Oxygen supplementation with high flow device or non-invasive ventilation
        - Mechanical ventilation
2. All-cause mortality through Day 42

3.3 Safety Endpoints

Safety endpoints are:

- Incidence and severity of AEs
- Oral temperatures
- Use of antipyretics and bronchodilators
- Hospital length of stay, and ICU length of stay

4 STUDY PLAN

4.1 Study Design

This is an exploratory Phase 2 clinical study to evaluate the protective effects of NasoVAX in patients with early COVID-19. Approximately 96 ambulatory patients with COVID-19, with one or more symptom(s) of fever, cough, and/or shortness of breath, onset of these symptoms within 72 hours of screening, and a PCR-based or rapid antigen test diagnostic, will be enrolled in 3 successive cohorts defined by age and risk factors for severe COVID-19 (Exclusion Criterion 5) (Cohort 1, ages 18-49 years and risk factors disallowed; Cohort 2, ages 18 and above and risk factors disallowed; and Cohort 3, ages 18 and above and risk factors allowed) of approximately 20, 28, and 48 patients, respectively. The cohorts will be enrolled in ascending order, with Cohort 1 preceding Cohort 2, and Cohort 2 preceding Cohort 3. Cohort 2 will be stratified by age groups of 18-64 years and 65 years and above, whereas Cohort 3 will be stratified by age groups (ages 18-64 years, ages 65 and above) and co-morbidity (one or more risk factors present, no risk factors present).

Study conduct will be overseen by a Data Monitoring Committee (DMC), which will monitor the safety of study participants and review safety data real-time during the course of the study. If any of the Stopping Rules (Section 7.2) are met, enrollment and study drug treatment will be temporarily halted pending DMC review.

Once a cohort is fully enrolled, enrollment will be paused until all patients either complete 14 days of home assessments or they are determined to have been hospitalized. The DMC will then review the safety and tolerability data and make a recommendation regarding whether to progress to the next cohort. The DMC may unblind the data in conducting its assessments although treatment allocation will not be revealed to operational study personnel.

Upon signing informed consent, patients will undergo Screening assessments at the study center, as per the Schedule of Events (Table 1). Within each cohort, patients who are determined to be eligible will be randomized that same day (Day 1) in a 1:1 ratio to receive either NasoVAX or placebo with approximately 10 and 14 patients in Cohorts 1 and 2, respectively, receiving NasoVAX and 10 and 14 receiving placebo in Cohorts 1 and 2, respectively. Approximately 24 patients will receive NasoVAX and 24 will receive placebo in Cohort 3.

Study drug will be administered as a single intranasal dose of 0.5 mL (0.25 mL each nostril) in the supine position after which patients must remain in the supine position for 30 minutes. Patients will be observed for at least 2 hours post intranasal administration. Patients who are randomized will be considered enrolled in the study.

No in-person visits are expected during the study after Day 1 unless a participant experiences a change in symptoms or AE that requires a visit for assessment.

Prior to discharge from the study center on Day 1, patients will be provided with:

- A fingertip pulse oximetry device connecting to a tablet that will be supplied to the patient to measure resting SpO_2 and resting pulse rate remotely. Patients will be trained on the use of the device and tablet
- A digital thermometer for measurement of oral temperature
- Instructions regarding how to take the above measurements and access and complete a web-based electronic diary (eDiary)

After discharge on Day 1, patients will return home for the duration of the study. Patients are to measure resting SpO_2, resting pulse rate and oral temperature twice daily at 09:00 hours and 16:00 hours, with a 1-hour window around each time point, and at any time they experience worsening symptoms until Day 14 or hospitalization, whichever comes first. Patients are to record COVID-19-related symptoms daily during this same time period. Study center personnel will contact patients daily by telephone during this period to document the patient's clinical status, record concomitant medications and monitor for AEs.

After Day 14, study center personnel will contact patients via telephone approximately every 7±2 days for 14 additional days to determine if they were hospitalized and to follow AEs that were not resolved by Day 14. If the patient is hospitalized at any time, the dates and times of hospital admission/discharge, ICU admission/discharge, and ventilation requirement are to be recorded, as applicable. Patients who remain hospitalized at the end of 28 days will be followed through Day 42 or death, whichever is sooner. If a patient is discharged and then readmitted before Day 42, he/she will be followed until Day 42.

4.2 Rationale for Study Design

Several design features are employed in the current study in an effort to minimize bias, including a double-blind design, with patients randomly assigned to NasoVax or placebo on a 1:1 basis. Random assignment of patients avoids bias and helps ensure that both known and unknown risk factors are distributed evenly between treatment groups. The use of placebo control permits prospective comparison between the active treatment group and the control group.

In order to mitigate the risk of exposure to SARS-CoV-2 at the study center and reduce the use of personal protective equipment, all data after administration of study drug will be collected remotely, either electronically or via telephone; no in-person visits post-vaccination are required unless a participant experiences a change in symptoms or AE that requires a visit for assessment. After study drug administration on Day 1, patients will be evaluated remotely.

The study design adheres to the March 2020 FDA Guidance on the conduct of clinical trials during the COVID-19 pandemic (Centers for Disease Control and Prevention, Coronavirus Disease 2019 (COVID-19): Groups at Higher Risk for Severe Illness, Updated May 14,

2020 https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/groups-at-higher-risk.html#serious-heart-conditions (last accessed June 7, 2020)

United States Food and Drug Administration 2020).

To ensure further the safety of participating patients, a DMC will review safety data after each cohort is enrolled and throughout the study. If any safety concerns are identified, the DMC will make a determination regarding continuation of the study; the DMC may be unblinded for this review. The DMC will oversee all aspects of the study to optimize the safety of study participants. Stopping Rules have also been developed for the further protection of patients.

4.3 Rationale for Study Population

The model of lethal influenza challenge in mice recapitulates the key sequela associated with human infection with COVID-19 disease, including severe disease and death associated with massive lung inflammation and significant elevation in lung inflammatory cytokines. The ability of RD-Ad5 vectors to significantly decrease inflammatory cytokines, lung inflammation and morbidity following viral challenge in mice may be directly relevant to the treatment of COVID-19.

Preclinical data show that intranasal administration of RD-Ad5 vectors, either harboring a transgene or not, can protect mice from lethal challenge with a respiratory pathogen when administered as a single intranasal dose within 2 days and up to 47 days before a lethal challenge with a respiratory pathogen. These observations support the use of NasoVAX or RD-Ad5 vectors in patients with recent or early COVID-19.

To enhance the safety of study participants, the study will be enrolled in cohorts of increasing age and increasing risk for complications of COVID-19. Patients with risk factors for severe COVID-19 will be excluded from Cohort 1. Based on ongoing review of efficacy and safety data, the DMC may remove part or all of these risk factors if preliminary data show no signal for adverse or paradoxical effects.

Because the cooperation of the patients is essential for the proper conduct of the study, patients themselves must provide written informed consent before the performance of any study-related procedures, and surrogate consent by family members, designated legal representatives, or caregivers will not be permitted.

Hydroxychloroquine and chloroquine are excluded because these medications are known to acidify vesicles that may prohibit the entry of viruses like RD-Ad5 into respiratory mucosal cells. The half-lives of these agents are 22 and 55 days, respectively, and the periods of exclusion are based on 5 half-lives. The use of these agents is only permitted by the United States (US) Food and Drug Administration under Emergency Use Authorization in the hospital setting, so they are also not allowed in this study as rescue medications for patients with progressive symptoms in the outpatient setting.

While remdesivir use is not prohibited, it is not expected to interfere with study conduct, since it is an intravenous medication, the use of which would be restricted to hospitalized patients with severe forms of COVID-19.

4.4 Dose Rationale

4.5 Schedule of Events

The schedule for study activities is presented in Table 1.

Table 1 Schedule of Events – Screening and Treatment Periods

Procedure	Study Visit Type / Day			
	Screening	Study Drug Treatment	Diary Completion/ Telephone Contact	Telephone Contact
	Study Center Visit		Remote Visit	
	Day 1 Pre-Dose	Day 1	Daily Days 1 to 14	Days 21 and 28 ±2 days
Informed consent	X			
Eligibility criteria check	X			
Demographics	X			
Medical history	X			
Focused cardiovascular and respiratory physical examination	X			
Height and weight	X			
Blood pressure and respiratory rate	X			
Urine pregnancy test[a]	X			
Randomization	X			
Study drug administration[b]		X		
Resting SpO_2[c]	X		X[d]	
Resting pulse rate[c]	X		X[d]	
Oral temperature[c]	X		X[d]	
Baseline/Concomitant medications	X		X	X
AEs			X	X
eDiary completion for COVID-19 symptoms[e]	X		X	
Criteria for the Assessment of Severity of Illness in Patients with COVID-19 [f]	X			X
Daily telephone contact to document concomitant medications, clinical and hospitalization status and AEs[g]			X	
Follow-up contact for hospitalization status, COVID-19 outcomes, and AEs[h]				X

[a] For women of child-bearing potential only. Results must be available and confirmed to be negative before study drug administration.

[b] Study drug is to be administered with the patient in the supine position. The patient is to remain in the supine position for 30 minutes thereafter and be observed for at least 2 hours post intranasal administration.

[c] To be measured remotely daily at 09:00 and 16:00 hours or at any time the patient experiences worsening symptoms using the study-supplied devices and recorded in the eDiary. Resting SpO_2 and pulse are to be measured at rest for 2 minutes. A ±1 hour window will be allowed. On Day 1, only the afternoon (16:00 hours) measurement is required and may be measured at the study center or remotely.

[d] If the Screening visit occurs in the morning, the patient will be responsible for recording the 16:00 measurements at home later that day; if the visit occurs after 16:00, measurements will commence at home the following morning.

[e] The following symptoms will be recorded: fatigue, chills, headache, cough (with or without sputum production), myalgia, sore throat, shortness of breath, nasal congestion, diarrhea, and nausea or vomiting.
[f] After Screening, the patient will be assessed at different timepoints over the course of the trial. The final determination will be made on Day 28 in patients who are not hospitalized and Day 42 in patients who are hospitalized.
[g] Telephone calls to the patient will commence on Day 2. The script for these calls is provided in Appendix A.
[h] The script for the Day 21 and Day 28 phone calls is provided in Appendix B. For hospitalized patients, the dates and times of hospital admission/discharge, date and time of intensive care unit admission/discharge, and ventilation requirement are to be recorded, as applicable. Patients who remain hospitalized at the end of 28 days will be followed through Day 42 or death, whichever is sooner.

5 POPULATION

5.1 Number of Patients

Approximately 96 ambulatory patients with COVID-19, with one or more symptom(s) of fever, cough, or shortness of breath, onset of these symptoms within 72 hours of screening, and a confirmation of SARS-CoV-2 infection by a polymerase chain reaction (PCR)-based or rapid antigen test diagnostic, will be enrolled at up to 12 study centers in the US.

5.2 Inclusion Criteria

Patients who meet all of the following criteria are eligible for participation in the study.

1. Able and willing to provide informed consent

   Patients themselves must provide written informed consent before the performance of any study-related procedures, and surrogate consent by family members, designated legal representatives, or caregivers will not be permitted.

2. Men and women 18 years of age and older

3. Early COVID-19, defined as one or more symptom(s) of fever (oral temperature $\geq 100.4^{o}F$), cough or shortness of breath, onset of these symptoms within 72 hours of screening, and confirmation of SARS-CoV-2 infection by a PCR-based or rapid antigen test diagnostic

4. Resting $SpO_2 \geq 96.0\%$ on room air on two successive measurements

5. For women of childbearing potential (women who are not permanently sterile [documented hysterectomy, bilateral tubal ligation, salpingectomy, or oophorectomy], postmenopausal [12 months with no menses without an alternative medical cause] or in monogamous same-sex relationships)

   - Negative urine pregnancy test at Screening

   - Willingness to practice a highly effective method of contraception that includes, but is not limited to, abstinence, sex only with persons of the same sex, monogamous relationship with a postmenopausal partner, monogamous relationship with vasectomized partner, vasectomy, licensed hormonal methods, intrauterine device, or consistent use of a barrier method (eg, condom, diaphragm) with spermicide for 28 days after the last dose of study drug

6. For men with sexual partners of childbearing potential, willingness to practice a highly effective method of contraception, as defined above, for 45 days after the last dose of study drug

7. Ability and willingness to comply with all aspects of the study, including reliable internet access, through the entire study period

5.3 Exclusion Criteria

Patients meeting any of the following criteria are not eligible for participation in the study:

1. Pregnant or lactating women or planning to conceive a child during the next 3 months

2. Resting respiratory rate >20 breaths/min on room air or resting pulse rate ≥ 125 beats per minute

3. A rapidly worsening course that in the opinion of the Investigator of treating medical practitioner would lead to hospitalization within the next 24-48 hours

4. Any chronic pulmonary disease, including chronic obstructive pulmonary disease and asthma, or other respiratory diseases that could exacerbate independent of COVID-19

5. The following risk factors for severe COVID-19 (Cohorts 1 and 2 only) (Centers for Disease Control 2020):

    a. Severe obesity, defined as body mass index ≥ 40 kg/m^2

    b. History of

        i. Severe cardiovascular disease, including but not limited to congestive heart failure, coronary artery disease, congenital heart disease, cardiomyopathies, or pulmonary hypertension

        ii. Diabetes mellitus

        iii. Chronic or current vaping or cigarette smoking

        iv. Chronic kidney disease requiring dialysis

        v. Chronic liver disease, including but not limited to chronic viral hepatitis, non-alcoholic steatohepatitis, or cirrhosis of any cause

        vi. Hemoglobin disorder, including sickle cell disease and thalassemia

    Based on ongoing review of efficacy and safety data, the DMC may remove part or all of these risk factors if preliminary data show no signal for adverse or paradoxical effects.

6. History of Bell's Palsy

7. Nasal conditions that might affect the suitability of intranasal medication, such as a history of chronic rhinitis, nasal septal defect, cleft palate, nasal polyps, or nasal surgery other than cosmetic rhinoplasty.

8. Use of hydroxychloroquine within the past 4 months, chloroquine with the past 9 months, or other investigational agents for COVID-19 within the past 30 days

9. History of conditions associated with immunocompromise, including but not limited to poorly controlled HIV, or treatments known to affect the immune system, including but not limited to oral or intravenous corticosteroids, alkylating drugs, antimetabolites, cytotoxic drugs, radiation, immune-modulating biologics (including IL-6, IL-12, Janus kinase inhibitors or antagonists), and cancer treatments, within 30 days of Screening or anticipated use within 6 months following participation in this study

10. Any medical, psychiatric, or social condition or occupational or other responsibility that in the judgment of the Investigator would interfere with or serve as a contraindication to protocol adherence, assessment of safety (including reactogenicity), or a patient's ability to give informed consent

6 STUDY DRUG

6.1 Description

6.1.1 NasoVAX

[redacted]

6.1.2 Placebo

Commercially available 0.9% Sodium Chloride injectable solution for intranasal administration will be supplied to the site pharmacy. The placebo will be prepared in syringes identical to those used for the NasoVAX dose.

6.1.3 Packaging, Storage, and Handling

[redacted]

[redacted]

Full preparation instructions are detailed in a separate pharmacy manual.

6.2 Randomization

Following completion of the Screening activities, patients who meet all the inclusion and none of the exclusion criteria will be registered by the Interactive Web Response System (IWRS). Eligible patients will be randomly assigned in a 1:1 ratio to the NasoVAX or placebo group. Randomization will proceed in 3 cohorts defined by age and risk factors for severe COVID-19 (Exclusion Criterion 5) (Cohort 1, ages 18-49 years and risk factors disallowed; Cohort 2, ages 18 and above and risk factors disallowed; and Cohort 3, ages 18 and above and risk factors allowed) of approximately 20, 28, and 48 patients, respectively. The cohorts will be enrolled in ascending order, with Cohort 1 preceding Cohort 2, and Cohort 2 preceding Cohort 3. Cohort 2 will be stratified by age groups of 18-64 years and 65 years and above, whereas Cohort 3 will be stratified by age groups (ages 18-64 years, ages 65 and above) and co-morbidity (one or more risk factors present, no risk factors present). Patients in Cohorts 2 and 3 will be stratified first, and then randomized 1:1 to NasoVAX or placebo. Enrollment of patients ages 18-49 years will not exceed approximately 30% of the randomized population of either treatment arm. In addition, a minimum of 40% of Cohort 3 will either be 65 years or above or have one or more risk factors for severe COVID-19.

The randomization list will be generated by an independent unblinded statistician.

6.3 Dose and Administration

NasoVAX or normal saline placebo will be administered as a single intranasal dose of 0.5 mL (0.25 mL in each nostril) on Day 1 in the supine position followed by remaining in supine position for 30 minutes, according to the patient's treatment assignment. Patients will be observed for at least 2 hours post intranasal administration.

6.4 Dosing Modifications

As this is a single-dose study, no dose adjustments will be made on an individual patient basis.

6.5 Blinding and Unblinding

The Pharmacy staff will be unblinded for the purpose of final drug preparation. The pharmacist will consult the unblinded study statistician for dose allocation and the Pharmacy staff will prepare each dose in compliance with the randomization list.

Due to the fact that formulations cannot be made to look identical, a blinded syringe will be used for administration. Study staff either preparing the syringes and/or administering the study drug will be independent and will not take part in any other activity of the study (eg, telephone contact).

Knowledge of the randomization list will be limited to the persons responsible for creation of the randomization list, pharmacy staff who prepare the study drugs, and any unblinded study monitors or auditors, until all data collection and verification activities and assignment of patients to the analysis populations has been completed, the database has been locked, and the study formally unblinded.

Data provided to the DMC may be unblinded, as required, for the assessment of safety.

If unblinding is required in the interest of the safety of a patient, an Investigator will discuss the matter with the Sponsor before unblinding. In a medical emergency, the Investigator or delegate may unblind via the IWRS for that patient without prior consultation with the Sponsor. In that event, the Investigator or delegate will notify the Sponsor as soon as possible that the randomization code has been broken for the patient. If the blind is broken, the date, time, and reason must be recorded.

Patients may also be unblinded for the assessment of Stopping Rules, DMC evaluations, expedited safety reports, and the emergency unblinding of individual patients, as detailed in a separate Safety Management Plan.

6.6 Accountability

The Investigator (or designee) will maintain an accurate record of the receipt of each IP as shipped by the Sponsor (or designee), including the date received. In addition, an accurate IP disposition record will be kept, specifying the amount dispensed for each patient and the dates of dispensation and any returns.

Sponsor approval is required for on-site destruction of all used IP and shipment of all unused IP back to the Sponsor at the completion of the study once all reconciliation has occurred.

6.7 Prior and Concomitant Therapy

In the interests of patient safety and acceptable standards of medical care, both the Investigator and patient personal physician(s) will be permitted to prescribe additional treatment(s) at his/her discretion.

Any medications that are ongoing at Screening are to be documented in the electronic case report form (eCRF). Thereafter, all concomitant medications, including supplemental oxygen, through 30 days after study drug administration are to be documented in the eCRF.

Concomitant medications, including supplemental oxygen, are to be recorded in the source documents and in the eCRF.

6.7.1 Prohibited Prior and Concomitant Medications

Prohibited prior and concomitant medications are as follows:

- Hydroxychloroquine within 4 months or chloroquine within 9 months of Screening
- Any treatment known to affect the immune system, including but not limited to oral or intravenous corticosteroids, alkylating drugs, antimetabolites, cytotoxic drugs, radiation, immune-modulating biologics, within 30 days of Screening
- Live vaccines (such as live influenza vaccinations or live travel vaccinations) within 30 days of Screening and through Day 14 post study drug administration
- Receipt of any investigational drug or treatment within 30 days of Screening.

The above medications are prohibited through Day 14 or hospitalization, and all other concomitant medications are permitted. If a patient is hospitalized due to COVID-19, there are no restrictions regarding concomitant medications. However, all medications administered, including antipyretics, bronchodilators, and supplemental oxygen requirements, are to be documented in the eCRF.

6.8 Contraception

All female patients of childbearing potential must practice a highly effective method of contraception for 28 days after study drug administration. Male patients with partners of childbearing potential must practice a highly effective method of contraception for 45 days after study drug administration.

Highly effective methods of contraception include, but are not limited to, abstinence, sex only with persons of the same sex, monogamous relationship with a postmenopausal partner, monogamous relationship with vasectomized partner, vasectomy, licensed hormonal methods, intrauterine device, or consistent use of a barrier method (eg, condom, diaphragm) with spermicide.

6.9 Compliance

A single dose of study drug will be administered by study personnel and therefore compliance with study drug dosing is not a concern. The study personnel will be appropriately trained on study drug administration procedures and documentation requirements prior to study start.

Non-compliance with study procedures will be reported to the Sponsor who will decide if persistent non-compliant patients should be withdrawn from continued study participation.

7 PREMATURE DISCONTINUATION

7.1 Individual Patients

Patients can choose to discontinue study participation at any time, for any reason, without prejudice to their future medical care. Patients could be discontinued for any of the following reasons:

- Patient request/withdrawal of consent
- Noncompliance with study requirements
- Loss to follow-up
- Investigator discretion
- Sponsor request, including termination of the study by the Sponsor

For all patients who discontinue for reasons other than withdrawal of consent, a final telephone contact will be made by study center personnel to document final outcome and AEs. Serious adverse event (SAEs), hospital, and ICU lengths of stays, and mortality in hospitalized patients also will be documented.

Eligible patients who are randomized and withdrawn before study drug administration will be replaced. Patients who receive study drug who are subsequently withdrawn from the study will not be replaced.

To optimize the safety of study participants, once patients receive study drug, all efforts will be made to monitor their clinical courses according to study procedures.

7.2 Stopping Rules

Enrollment and study drug treatment will be temporarily halted pending DMC review for any of the following reasons:

- Any SAE considered possibly or probably related to study drug
- Any Grade 4 or Grade 5 (death) AE considered possibly or probably related to study drug
- Three or more subjects in the same cohort experience the same Grade 3 AE in the same Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class considered possibly or probably related to study drug

- Hospitalization rates in either treatment group in individual cohorts exceeding:
  - 15% (Cohort 1 only)
  - 20% (Cohort 2 only)
  - 25% (Cohort 3 only)
- Mechanical ventilation rates in either treatment group in individual cohorts equal to or exceeding:
  - 2 patients (Cohort 1 only)
  - 3 patients (Cohort 2 only)
  - 4 patients (Cohort 3 only)

The DMC will be advised each time a patient dies or is hospitalized. The DMC may unblind individual patients for the assessment of the relationship of the event to study drug. The DMC may recommend resumption of dosing if subject safety is not considered to be at significant risk following analysis.

7.3 Study as a Whole

Both the Sponsor and the Investigator reserve the right to terminate the study at the Investigator's site at any time. Should this be necessary, the Sponsor or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Investigator will inform the IRB of the same. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the patients' interests.

Possible reasons for termination are:

- Safety reasons –the incidence of AEs in this or any other study using the same investigational product(s) indicates a potential health risk for the patients
- New scientific knowledge becomes known that makes the objectives of the study no longer feasible/valid
- Unsatisfactory enrollment of patients

8 DESCRIPTION OF STUDY PROCEDURES

Patients will be solicited from medical office, clinics, or hospitals where they seek care for COVID-19 symptoms and where COVID-19 test positivity is documented. All recruitment materials will be reviewed by the Institutional Review Board overseeing the study. Patients need not have a personal doctor to participate in the study. Patients themselves must provide written informed consent before the performance of any study-related procedures, and surrogate consent by family members, designated legal representatives, or caregivers will not be permitted. In the event that the patient progresses to hospitalization or is unable to complete the eDiary or telephone calls, designated legal representatives, family members or caregivers will be contacted, as provided by informed consent, for this information.

8.1 Screening Assessments

8.1.1 Demographics

Demographic data (age, sex, race, ethnicity) will be recorded during Screening. The name and contact information for the patient's family member(s) or caregiver(s) will also be obtained in the event that the eDiary (Section 8.2.2) is not completed patient does not respond to telephone calls (Section 8.2.3). The contact information for the patient's personal doctor (s) will also be obtained.

8.1.2 Medical History

A complete medical history, including diabetes, hypertension, and respiratory history, is to be documented during Screening. Smoking history of use of any inhalation products (eg, nicotine-containing products including e-cigarettes or e-vaporizers) is to be documented.

The patient's COVID-19 symptom history, including fever (temperature >100.4ºF [38.0ºC]), fatigue, chills, headache, cough (with or without sputum production), myalgia, sore throat, shortness of breath, nasal congestion, diarrhea, and nausea or vomiting is to be documented, including date of onset of symptoms, and any laboratory or radiological test results obtained.

The date of initial SARS-CoV-2 positivity also is to be documented.

8.1.3 Pregnancy Testing (Females of Childbearing Potential Only)

A urine pregnancy test is to be performed for female patients of childbearing potential at Screening. Results must be available and confirmed to be negative before study drug administration.

8.1.4 Concomitant Medications

Concomitant medications will be documented, per Section 6.7.

8.2 Efficacy Assessments

8.2.1 Pulse Oximetry, Pulse Rate, and Temperature

After signing informed consent, patients will be provided with a fingertip pulse oximetry device that connects to a mobile device connecting to a tablet that will be supplied to the patient to measure resting SpO_2 and resting pulse rate. Patients will be trained on the use of the device and tablet. This device will be used to determine study eligibility at Screening, and if the patient is eligible, he/she will return home with the device for remote monitoring of resting SpO_2 and resting pulse rate for the duration of the study.

8.2.1.1 Screening

Resting SpO_2 and resting pulse rate will be measured twice at Screening, with each measurement being of 2 minutes duration. For the first measurement, the patient will be sitting and breathing room air for at least 5 minutes before the measurement is made. A 3- to 5-minute interval will transpire before the second measurement is commenced. The patient should continue to sit and breath room air through the time that the second measurement is completed. To ensure stabilization of resting SpO_2, only the average of resting SpO_2 and resting pulse rate in the second minute of each measurement will be used to determine study eligibility. To be eligible for the study, patients will be required to have an average resting $SpO_2 \geq 96.0\%$ and average resting pulse rate < 125 beats per minute on both measurements. Baseline for resting SpO_2 and resting pulse rate will be defined as the mean of the two measurements. Oral temperature will also be recorded.

8.2.1.2 Home Monitoring

Resting SpO_2 and resting pulse rate will be measured remotely twice daily at 09:00 hours and 16:00 hours for 14 days, with each measurement being of 2 minutes duration and with a 1-hour window around each time point. They will also record resting SpO_2 and resting pulse rate at any time they experience worsening symptoms. The patient will be sitting at rest and breathing room air for at least 5 minutes before these measurements are made and should continue to sit and breath room air through the time that the measurement is completed. To ensure stabilization of resting SpO_2 and resting pulse measurements, only the averages of these parameters in the second minute of measurement will be analyzed.

Similarly, patients will be provided with a digital thermometer to measure oral temperature at 09:00 hours and 16:00 hours twice daily, with a 1-hour window around each time point, and at any time they experience worsening symptoms through Day 14, with results recorded in the eDiary.

Resting SpO_2 and resting pulse rate measurements will automatically be captured in the mobile device, while oral temperature will be captured in the eDiary (Section 8.2.2).

The Screening visit is defined as Day 1. If the visit occurs in the morning, the patient will be responsible for recording the 16:00-hour measurements at home later that day; if the

visit occurs after 16:00 hours, measurements will commence at home the following morning.

8.2.2 eDiary

The eDiary will be completed by patient each day through Day 14. The following symptoms will be collected:

- Fatigue
- Chills
- Headache
- Cough (with or without sputum production)
- Myalgia
- Sore throat
- Shortness of breath
- Nasal congestion
- Diarrhea
- Nausea or vomiting

For each of these symptoms, the patient will be asked to grade them by the following scale:

- Not at all
- A little bit
- Somewhat
- Quite a bit
- Very much

The patient will also record all temperatures in the eDiary.

In the event that the patient progresses to hospitalization or is unable to complete the eDiary, family members, designated legal representatives or caregivers will be contacted, as provided by informed consent, to determine the status of the patient.

8.2.3 Telephone calls

The patient will be called each day, Day 2 through Day 14. The telephone script is provided in Appendix A.

After the completion of Day 14, the patient will be called weekly through Day 28. The telephone script is provided in Appendix B.

Based on the findings of telephone calls, an Unscheduled Visit with the Investigator or personal doctor may be scheduled (Section 8.4).

In the event that the patient progresses to hospitalization or is unable to complete the telephone calls, family members or caregivers will be contacted, as provided by informed consent, to determine the status of the patient.

8.2.4 Criteria for the Assessment of Severity of Illness in Patients with COVID-19

The criteria in Appendix C will be used to assess changes in the severity of COVID-19 in patients at different timepoints over the course of the trial. The final determination will be made on Day 28 in patients who are not hospitalized and Day 42 in patients who are hospitalized.

8.2.5 Additional Data Collection in Hospitalized Patients

Additional data to be collected for patients hospitalized due to COVID-19 through Day 42 to include the following:

- Date and time of hospital admission and discharge
- If transferred to ICU, date and time of ICU admission and discharge
- Requirement for oxygen (yes/no), and if yes, method of oxygenation (mask/nasal prongs, non-invasive ventilation, or high-flow oxygen; intubation and mechanical ventilation
  - If required ventilation, start date and time of ventilation, method of ventilation including whether intubated (yes/no)
- Change in ambulatory status
- Death

It is anticipated that most of this information will be obtained from the medical record. When necessary, a family member, designated legal representative or caregiver, as permitted by informed consent, will be contacted if the patient has expired or is too ill or otherwise unable to provide this information.

The rate (liters/min) of oxygen administered is to be captured as a concomitant medication. If, in the Investigator's opinion, a patient required a higher level of oxygenation, but did not receive due to resource availability, this should be documented.

Furthermore, if, in the Investigator's opinion, the patient required a higher level of care (ie, admittance to the ICU) but did not receive due to resource availability, this should be documented.

8.2.6 Vital Status

Vital status is to be documented at each study contact. If the patient died due to a reason other than COVID-19, the primary cause of death is to be recorded and reported as an SAE. Death due to worsening fever, cough, shortness of breath, resting SpO_2, or resting pulse rate or COVID-19 symptoms that are reported at Screening (Section 8.1.2) is not considered to be an SAE in the context of this study although cause of death will be reviewed by the DMC in real time.

8.3 Safety Assessments

8.3.1 Height, Weight and Body Mass Index (BMI)

Height (cm) and weight (kg) will be measured and recorded at Screening. BMI will be subsequently be calculated from these measurements.

8.3.2 Physical Examination

A cardiovascular and respiratory-focused physical examination will be performed by trained medical personnel during Screening.

8.3.3 Screening Vital Signs

Blood pressure and respiratory rate obtained after sitting at rest for at least 5 minutes will be recorded at Screening. The procedures for recording resting pulse rate and oral temperature are detailed in Section 8.2.1.

8.3.4 Adverse Events

The AE reporting period is from the start of study drug administration on Day 1 through Day 14 or until time of hospitalization. AEs will be assessed by direct observation on Day 1 and then by web-based questionnaire and patient interview during daily telephone contact through Day 14 after study drug administration and then through telephone contact thereafter until resolved, stabilized, or transitioned to the patient's main healthcare provider for follow up.

Details on the definitions, reporting, and management of AEs are provided in Section 9.

8.3.5 Use of Antipyretics and Bronchodilators

The use of antipyretics and bronchodilators will be considered study safety endpoints and should be collected with concomitant medications, per Section 6.7.1.

8.4 Concomitant Care and Unscheduled Visits

No study center visits are scheduled other than Screening. Patients will continue to follow with their personal doctors during the study and receive medications at their direction after Screening. The prescription and use of any prohibited medications through Day 14 will be recorded but will not result in the discontinuation of any study procedures. If it determined that the patient is in the need of an unscheduled clinic visit for further evaluation, an unscheduled visit with the personal doctor, or hospitalization, these arrangements will be made. The Investigator will assist in making these arrangements whenever possible. The decision to seek this unscheduled care will be at the discretion of the patient, the personal doctor, or Investigator.

9 ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the investigational product whether or not related to the investigational product. An AE can be any sign, symptom, or diagnosis that appears or changes in intensity during the course of the study.

Unchanged chronic conditions are not AEs and should not be recorded on the AE pages of the eCRF. These medical conditions should be adequately documented on the appropriate page of the eCRF (medical history or physical examination). However, medical conditions present on the first day of treatment that worsen in intensity or frequency during the treatment or post-treatment periods in a manner not consistent with natural disease progression should be reported and recorded as AEs. The Investigator will actively solicit this information and assess the event in terms of severity and relationship to the study treatment regimen.

The objective of this study is to assess the effective and safety of NasoVAX in preventing clinical worsening of early COVID-19. The worsening of fever, cough, shortness of breath, resting SpO_2 or resting pulse rate and symptoms of COVID-19 that are reported in the eDiary during Screening (Section 8.1.2) will be captured in aggregate in the eCRF and will not be reported as AEs.

The term AE is used to include any AE whether serious or not serious.

9.1.2 Unexpected Adverse Drug Experience

An unexpected adverse drug experience is defined as an adverse experience, the nature or severity of which is not consistent with the reference safety information in the Investigator's Brochure.

For the purpose of expedited reporting of IND-Safety Reports, only unexpected serious adverse events considered possibly or probably related to study medication by the Sponsor and unexpected serious AEs (SAEs [Section 9.1.3]) will be considered IND-Safety Reports.

9.1.3 Serious Adverse Event

An AE or suspected adverse reaction is considered serious (an SAE) if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening (An AE is considered life-threatening if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE 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

Life-threatening means that the patient or subject was at immediate risk of death at the time of the SAE; it does not refer to a serious AE that hypothetically might have caused death if it were more severe. Hospitalization does not include same day surgery, elective surgery, optional admission not associated with a precipitating AE (ie, elective cosmetic surgery), or hospitalization planned before the start of the study for a pre-existing condition that has not worsened. Persistent or significant disability or incapacity means that there is a substantial disruption of a person's ability to carry out normal life functions.

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 subject 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.

9.2 Reporting Responsibilities and Periods

It is the responsibility of the Investigator to perform periodic assessment for AEs. AEs spontaneously reported by the patient or reported in response to an open question from the study personnel (eg, 'Have you had any health problems since the previous visit/you were last asked?') or revealed by observation will be recorded.

AEs and concomitant medications will be recorded from the start of study drug administration on Day 1 through 14 or until the time of hospitalization. The AE term, date of AE onset, date of AE resolution (if applicable), severity, causality, action taken for the AE, outcome and whether or not the AE was serious will be recorded.

AEs must be monitored until they are resolved, stabilized or transferred to the patient's main healthcare provider for follow up, are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es), the patient is hospitalized, or follow-up is no longer possible. Data describing AEs will be recorded in the patient's medical record and as appropriate, an SAE report form. SAEs will be reported to the Sponsor as described in Section 9.6.

Any SAE that the Investigator considers to be related to study drug and occurs at any time after completion of the study must be reported to the Sponsor or designee. If at the time the Investigator initially reports an SAE, the event has not resolved, the Investigator must provide a follow-up report as soon as it resolves (or upon receipt of significant information if the event is still ongoing).

Note that for the purposes of this study, hospitalization due to worsening fever, cough or shortness of breath, resting SpO_2 or resting pulse rate or symptoms of COVID-19 that are reported prior to treatment (Section 8.1.2) will not be considered an SAE.

9.3 Assessment of Adverse Events

9.3.1 Severity

The Investigator should assess the severity of each AE. The AE will be recorded at its initial severity level. The initial AE will be considered ended and a new AE will be recorded if the event changes in severity.

The severity of all AEs, both serious and non-serious, will be assessed by assigning a Grade of 1, 2, 3, 4, or 5 according to the CTCAE, v 4.03 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

When an AE cannot be graded by CTCAE, the following severity grading may be used:

- Grade 1 (Mild): awareness of sign or symptom, but easily tolerated
- Grade 2 (Moderate): discomfort enough to cause interference with usual activity
- Grade 3 (Severe): incapacitating with inability to work or do usual activity
- Grade 4 (Life-Threatening): refers to an event in which the patient was, in the view of the Investigator, at risk of death at the time of the event. (This category is not to be used for an event that hypothetically might have caused death if it were more severe.)
- Grade 5 (Fatal): death related to AE

An AE that is assessed as severe should not be confused with an SAE. Severity is a category for rating the intensity of an event, and both non-serious AEs and SAEs can be

assessed as severe. An event will be defined as serious when it meets one of the criteria described in Section 9.1.3.

9.3.2 Relatedness (Causality) to Study Drug

The assessment of causality will be based on the information available and may be changed upon receipt of additional information.

Causality should be assessed using the following categories:

- Unrelated/Unlikely Related: clinical event with an incompatible time relationship to investigational agent administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the investigational agent
- Possibly related: clinical event with a reasonable time relationship to investigational agent administration, and that is unlikely to be attributed to concurrent disease or other drugs or chemicals
- Probably related: clinical event with plausible time relationship to investigational agent administration, and that cannot be explained by concurrent disease or other drugs or chemicals

9.4 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP may have interfered with the effectiveness of a contraceptive medication. Pregnancy in a patient's partner is not considered an AE. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of a pregnancy will be followed-up and documented even if the patient was withdrawn from the study. See Section 9.6.4 for further information on reporting of pregnancy.

An induced elective abortion to terminate a pregnancy without medical reason is not regarded as an AE. However, an induced therapeutic abortion to terminate a pregnancy because of complications or medical reasons must be reported as an SAE. The underlying medical diagnosis for this procedure should be reported as the SAE term. A spontaneous abortion in a study patient is always considered an SAE.

9.5 Overdose

Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved study drug must be communicated to the Sponsor or a specified designee within 24 hours and be fully documented as an SAE. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

An overdose of study drug is not expected to occur in this study, as a single dose is being administered intranasally. Should patients receive a higher dose than the allocated dose, this should be reported in the eCRF and the Sponsor should be informed. Any deviations from the assigned dose will be handled as a protocol deviation.

9.6 Procedures for Recording and Reporting Adverse Events

9.6.1 Recording Adverse Events

To improve the quality and precision of AE data, Investigators should observe the following guidelines:

- Whenever possible, use recognized medical terms when recording AEs on the AE page of the eCRF. Do not use colloquialisms, jargon, or abbreviations.

- If known, record the diagnosis (ie, disease or syndrome) rather than component signs and symptoms on AE pages of the eCRF (eg, record "congestive heart failure" rather than "dyspnea", "rales", and "cyanosis"). However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs on the eCRF page. For example, if congestive heart failure and severe headache are observed at the same time, each event should be recorded as an individual AE.

- Adverse events occurring secondary to other events (ie, sequelae) should be identified by the primary cause. A primary AE, if clearly identifiable, generally represents the most accurate clinical term to record on the AE page of the eCRF. If a primary SAE is recorded on an AE eCRF page, events occurring secondary to the primary event should be described in the narrative description of the event.

- Any laboratory abnormalities that are identified by the Investigator as clinically significant, as applicable, are to be considered AEs and recorded on the AE eCRF page.

9.6.2 Reporting of Serious Adverse Events

Serious AEs require reporting to the Sponsor or designee within 24 hours, regardless of the relationship of the event to the study treatment regimen. Refer to Section 9.1.3 for the definition of an SAE. Procedures for recording and reporting SAEs will be detailed in a separate Safety Management Plan for processing SAEs, expedited safety reports, and the emergency unblinding of patients.

Within 24 hours of the Investigator's observation or learning of an SAE, the Investigator should notify [redacted] by completing the SAE forms as thoroughly as possible with all available details of the event, including a determination of causality (even if preliminary), and signing them. The Investigator should communicate with Pivotal Pharmacovigilance if input is needed to complete the SAE assessment. Investigator

causality determination and signature MUST be included for all SAEs. The completed SAE form and cover sheet should be sent by email or fax to [redacted]

[redacted]

If not all information regarding an SAE is initially available, the Investigator should not wait to receive additional information before completing the AE eCRF and SAE forms. For initial SAE reports, the Investigator should record all case details that can be garnered on the SAE form and the AE eCRF page. Relevant follow-up information is to be submitted on updated SAE forms as soon as it becomes available.

If there are questions regarding reporting an SAE or if information needs to be transmitted that cannot be recorded on the SAE forms (eg, discharge summaries, laboratory reports), the Investigator should contact [redacted]

For unexpected serious adverse drug reactions (SUSARs), blinded reports will be disseminated and provided to Investigators at each study site.

When required and according to local law and regulations, unblinded SUSARs or other SAEs will be reported by an unblinded designee to the IRB and regulatory authorities.

9.6.3 Special Reporting Situations

Hospitalization or Death

Hospitalization and death are outcomes of an event. The event that resulted in hospitalization or death should be recorded and reported on the SAE form and the AE eCRF page.

As noted in Section 9.2 and Section 8.2.6, hospitalizations and deaths related to worsening fever, cough, shortness of breath, resting SpO_2 or resting pulse rate or symptoms of COVID-19 at Screening (Section 8.1.2) will not be considered SAE, although narratives of the hospitalizations and causes of death will be reported to and reviewed by the DMC in real time.

Surgical or Diagnostic Procedures

The illness leading to a surgical or diagnostic procedure is to be recorded as an AE/SAE, not the procedure itself. The procedure is to be captured in the case narrative as part of the action taken in response to the illness.

9.6.4 Reporting Pregnancies

Pregnancy itself is not considered an AE. If a **patient becomes pregnant** during the study or **within 1 month of discontinuing** study drug or the **partner of a patient** participating in the study becomes pregnant during the study or **within 3 months of discontinuing** study drug, the Investigator should report the pregnancy on a separate pregnancy report form provided to the sites. Only pregnancies occurring from the time of first study drug dose administered to the patient will be reported and documented.

The patient/partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy.

This pregnancy report form must be completed and submitted, either by e-mail or fax, immediately but no later than 24 hours of the Investigator's learning of the event to:

[redacted]

However, any pregnancy complication, spontaneous or elective abortion, still birth, neonatal death, or congenital anomaly will be recorded as an AE or SAE, and reported, as applicable.

9.7 Data Monitoring Committee

This study will be overseen by an independent DMC, which will have access to unblinded data, as needed, for the assessment of the efficacy, safety, and tolerability of study drug and make a recommendation regarding whether to progress to the next cohort. Real-time data on patient status, including hospitalization and death, will be provided for review. The DMC may unblind the data in conducting its assessments.

To enhance the safety of study participants, patients with risk factors for severe COVID-19 will be excluded from Cohort 1 (Exclusion Criterion 5). Following DMC review of the efficacy and safety data of each cohort, some or all of these may be removed if preliminary data show no signal for adverse or paradoxical effects.

A charter describing the roles, responsibilities, and operating procedures of the DMC will be implemented prior to study initiation.

9.8 Medical Monitor

A Medical Monitor will provide 24-hour/7-day coverage for medical issues pertaining to this study. The contact information for the Medical Monitor is provided below:

[redacted]

10 STATISTICS

10.1 Sample Size

The study is considered exploratory to assess the initial safety of NasoVAX in COVID-19 and response to treatment. The sample size chosen for this study was considered adequate to meet the study objectives and was selected without statistical significance considerations.

10.2 Analysis Sets

Safety Analysis Set: All patients who receive any study drug. Patients will be analyzed according to the treatment that they receive.

Modified intent to treat (ITT) Analysis Set: All randomized patients who receive any amount of study drug, have a Baseline and at least one post-Baseline resting SpO_2 measurement. Patients will be analyzed according to the treatment that they receive. Patients will be analyzed according to the treatment that they receive. This analysis set will be used for primary and secondary analyses.

Per Protocol (PP) Set: All randomized patients who receive any amount of study drug according to the correct treatment assignment and who have 80% of twice daily results from resting SpO_2 measurements through Day 14 or hospitalization.

10.3 Statistical Methods

10.3.1 General Methods

Baseline is defined as data collected closest to randomization prior to any study drug dosing. For resting SpO_2 and resting pulse rate, Baseline is defined as the average of the two measurements at Screening. All analyses and summary statistics will be presented by treatment group (NasoVAX, placebo) across cohorts, as well as by treatment group pooled across all cohorts, for each analysis set separately.

Descriptive statistics, including the numbers and percentages for categorical variables and the numbers, means, standard deviations, medians, minimums and maximums for continuous variables will be provided by treatment. The study is considered exploratory, and inferential statistics will be employed as appropriate across cohorts, as well as by treatment group pooled across all cohorts.

Patients will be randomized 1:1 to NasoVAX or placebo and proceed in 3 cohorts defined by age and risk factors (Exclusion Criterion 5) for severe COVID-19 (Cohort 1, ages 18-49 years and risk factors disallowed; Cohort 2, ages 18 and above and risk factors disallowed; and Cohort 3, ages 18 and above and risk factors allowed) of approximately 20, 28 and 48 patients, respectively. The cohorts will be enrolled in ascending order, with Cohort 1 preceding Cohort 2, and Cohort 2 preceding Cohort 3. Cohort 2 will be stratified

by age groups of 18-64 years and 65 years and above, whereas Cohort 3 will be stratified by age groups (ages 18-64 years, ages 65 and above) and co-morbidity (one or more risk factors present, no risk factors present). Patients in Cohorts 2 and 3 will be stratified first, and then randomized 1:1 to NasoVAX or placebo. Enrollment of patients ages 18-49 years will not exceed approximately 30% of the randomized population of either treatment arm. In addition, a minimum of 40% of Cohort 3 will either be 65 years or above or have one or more risk factors for severe COVID-19.

All descriptive and statistical analyses will be performed using SAS statistical software Version 9.2 or higher, unless otherwise noted.

10.3.2 Analysis of Efficacy

For the primary analysis, the proportion of patients with clinical worsening, defined as a 4.0% decrease from Baseline in resting SpO_2 on two successive measurements during home follow-up or hospitalization, will be compared between NasoVAX and placebo groups using the Cochran-Mantel-Haenszel test, while considering the stratification of age groups and risk factors, at a one-sided significance level of 0.025. The same approach will be applied for secondary endpoints that are categorical in nature. Sensitivity analyses will be performed to assess the effect of site on the response to study drug. Linear and logistic regression will be employed to examine the effects of Baseline factors, such as age, sex, medications, and medical co-morbidities on response.

Changes from Baseline in Severity of COVID-19, assessed by average decrease in resting SpO_2, average increase in resting pulse rate by outpatient pulse oximetry and COVID-19 symptoms (eDiary) during home follow-up, will be analyzed using a mixed model for repeated measures. The model will include the fixed effects of treatment, week, and treatment-by-visit interaction as well as the continuous, covariate of Baseline level. The model will employ an unstructured within patient covariance matrix and a restricted maximum likelihood estimation method.

A Kaplan-Meier method will be applied to compare changes between treatment groups in resting SpO_2 over time.

For the purpose of study efficacy endpoints, resting SpO_2 and resting pulse rate will be assessed on observed data only; if data is missing, it will not be imputed.

No multiplicity adjustments will be made for secondary endpoints.

10.3.3 Analysis of Safety

Quantitative safety data, including the frequencies of AEs, oral temperatures, use of antipyretics and bronchodilators, and length of hospital and ICU stay, will be summarized using descriptive statistics and frequency distributions. Qualitative safety data will be summarized by frequencies and percentages. All summaries will be presented by treatment

arms. AEs will be coded using MedDRA, Concomitant medications will be coded using World Health Organization (WHO) drug dictionary.

10.3.4 Demographic and Baseline Characteristics

Demographic and Baseline characteristics (age, gender, race, ethnicity, body mass index) will be summarized by treatment group across cohorts and by treatment group pooled across all cohorts for each analysis set separately.

10.4 Statistical Analysis Plan (SAP)

The SAP will be developed and finalized prior to the database lock and unblinding of treatment assignment. This plan will confirm the analysis sets used in the analysis, outline all data handling conventions, and specify all statistical methods to be used for all safety and efficacy analyses. The SAP will supersede the protocol with respect to analyses specified, although the primary analysis will remain the same. It is only anticipated that additional analyses may be desired to be pre-specified in the SAP.

11 DATA QUALITY ASSURANCE

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures. These are described in the following sections.

11.1 Data Handling

Data will be entered into an electronic database and reviewed by the Clinical Research Associate (CRA) remotely. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the eCRF system. The eCRFs will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

11.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

11.3 Data Entry

Data must be recorded using the eCRF system as the study is in progress. All study site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with 21 CFR Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

11.4 Medical Information Coding

The latest version of the WHO Drug Dictionary and MedDRA will be used for coding of concomitant medications and AEs.

11.5 Data Validation

Validation checks programmed within the eCRF system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator who signed the protocol.

11.6 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, Declaration of Helsinki, ICH GCP guidelines, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence

are satisfactory. Monitoring will include review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. All monitoring activities will be reported and archived. In addition, monitoring visits will be documented by CRA signature and date on the study-specific monitoring log and the completion of a detailed monitoring report.

The CRA will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications with the investigational site (monitoring visits, letter, telephone, email, and fax).

All unused study drug and other study materials are to be returned to the Sponsor or designee after the clinical phase of the study has been completed.

Regulatory authorities, the IRB, and/or the Sponsor's clinical quality assurance group may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

11.7 Source Document and Case Report Form Completion

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (ie, original records or certified copies). Source documents and the eCRFs will be completed for each study patient. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's source document/eCRF. The source document/eCRF should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

The Investigator, or designated representative, should complete the source document/eCRF as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must sign and date the Investigator's Statement at the end of the source document/eCRF to endorse the recorded data.

The Investigator will retain all completed source documents. A site-specific eCRF archive and audit trail will be provided at the close of the study to each Investigator. The Sponsor or designee will retain the eCRF archive and audit trail for all investigative sites.

11.8 Record Retention

Records of patients, source documents, monitoring visit logs, eCRFs, inventories of study product, regulatory documents, and other correspondence pertaining to the study must be kept in the appropriate study files at the site. The Investigator will maintain all study records according to ICH GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

12 ETHICS

12.1 Good Clinical Practice

The study will be conducted in accordance with the protocol, GCP, the relevant ICH guidelines, the applicable regulatory requirements, and the ethical principles that have their origins in the Declaration of Helsinki. As required by US FDA (21 CFR 56) and the Declaration of Helsinki, the study protocol, amendments, and informed consent form will be reviewed and approved, according to 21 CFR Parts 50 and 56 (or similar local requirements, such as ICH E6, for ex-US sites), respectively, by each study center's IRB or EC.

12.2 Institutional Review Board

The IRB will review all appropriate study documentation in order to safeguard the rights, safety, and wellbeing of patients. Federal/local regulations and ICH GCP guidelines require that approval be obtained from an IRB prior to participation of patients in research studies. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, informed consent form, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

No study drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

12.3 Patient Information and Consent

The informed consent form and any changes to the informed consent form made during the course of the study must be agreed to by the Sponsor or their designee and the IRB/EC prior to its use and must be in compliance with FDA Regulations in 21 CFR Part 50, Department of Health & Human Service in 45 CFR Part 46 (if applicable), ICH GCP guidelines, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study patient or proxy is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the patient has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each patient or the patient's legally authorized representative before any study-specific activity is performed and will document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the informed consent form must be maintained by the Investigator and is subject to inspection by the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies. A copy of the signed informed consent form will be given to the study patient or proxy. Whenever possible, patients who participate based on proxy consent will be re-consented once deemed capable by the Investigator of providing consent on their own.

If significant new findings are developed during the course of research which may affect the willingness of patients to continue study participation, the Sponsor will notify each Investigator of the findings via letter or telephone.

12.4 Patient Confidentiality

In order to maintain patient privacy, all eCRFs, study drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

12.5 Protocol Compliance

The Investigator will conduct the study in compliance with the protocol provided by the Sponsor, the approval/favorable opinion of the IRB and the appropriate regulatory authority(ies). Modifications to the protocol should not be made without agreement of both the Investigator and the Sponsor. Changes to the protocol will require written IRB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB may provide, if applicable regulatory authority(ies) permits, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB. The Sponsor will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the Sponsor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the eCRF and source documentation and reported to the appropriate study monitor or staff in a timely fashion.

13 COMPENSATION, INSURANCE AND INDEMNITY

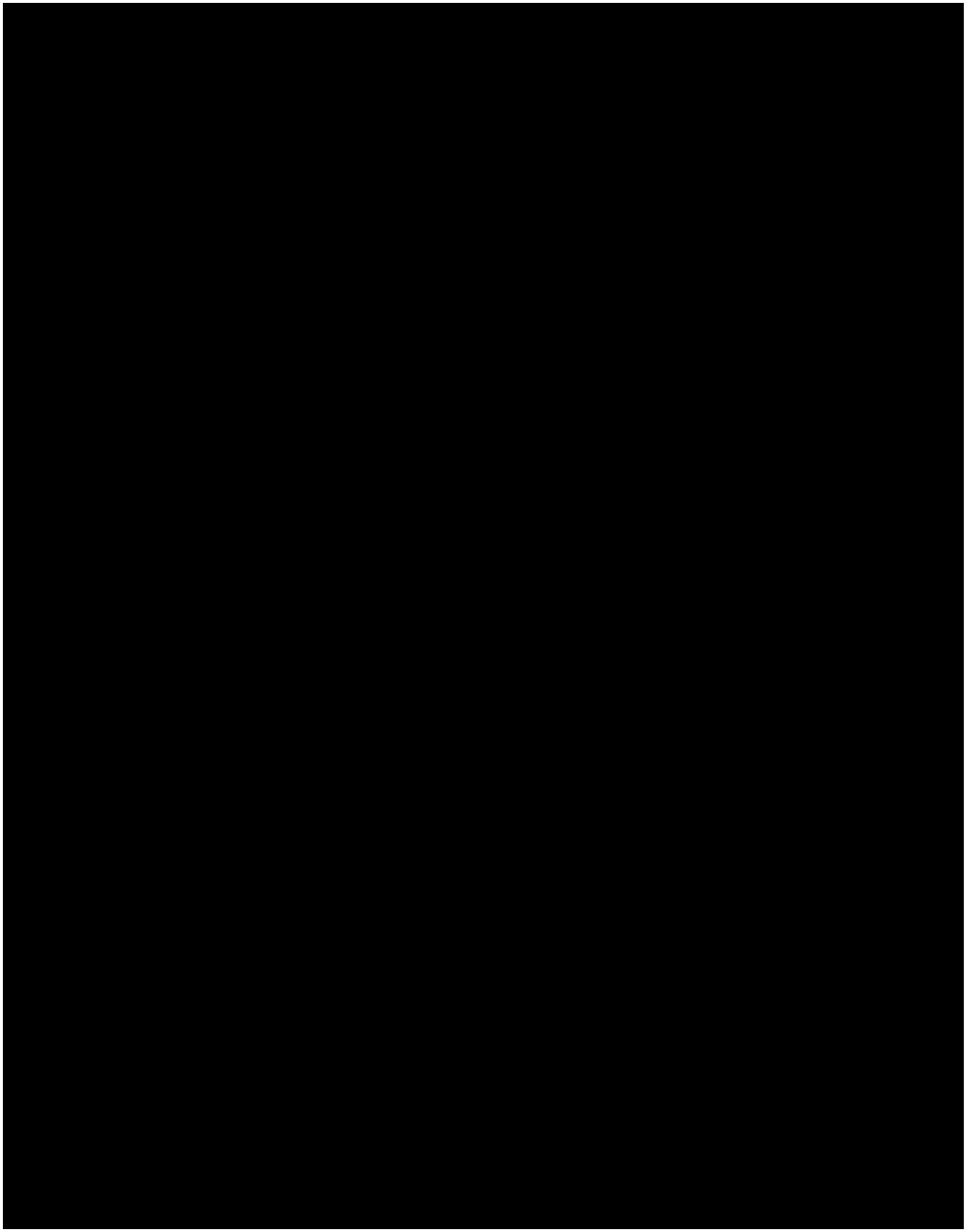
The Sponsor has retained an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards. The patient will be appropriately treated or compensated, or both, for any health or other problems arising from participation in this study.

14 PUBLICATION POLICY

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Investigator agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, either in part or in total, including articles in journals or newspapers, oral presentations, or abstracts, by the Investigator(s) or their representative(s), shall require prior approval, notification, and review within a reasonable time frame by the Sponsor and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee, comprising the Investigators participating in the study and representatives from the Sponsor, as appropriate, will be formed to oversee the publication of the study results, which will reflect the experience of all participating study centers. Subsequently, individual Investigators may publish results from the study in compliance with their agreement with the Sponsor. A pre-publication manuscript is to be provided to the Sponsor at least 60 days prior to the submission of the manuscript to a publisher. Similarly, the Sponsor will provide any company prepared manuscript to the Investigators for review at least 30 days prior to submission to a publisher.



16 REFERENCES

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United States Food and Drug Administration, FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic, March 2020.

Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395:1054-62.

Appendix A: Telephone Script, Days 2 through 14

Greeting

Question about general health and adverse events experienced by the patient.

> "Have you had any changes in your health since our last phone call? If so, please describe."
>
> "If you have a personal doctor, have you been in contact with your doctor about these changes in your health, and what did your doctor recommend to you?"

Question about symptoms *[only for patients who are unable to complete the eDiary]*:

> "Have you had any of the following symptoms? If so, were they mild, moderate, or severe?"
>
> - Fatigue
> - Chills
> - Headache
> - Cough (with or without sputum production)
> - Myalgia
> - Sore throat
> - Shortness of breath
> - Nasal congestion
> - Diarrhea
> - Nausea or vomiting
>
> For each of these symptoms, the patient will be asked to grade them by the following scale:
>
> - Not at all
> - A little bit
> - Somewhat
> - Quite a bit
> - Very much

Question about concomitant medications:

- "Have you taken any medications, including any new medications, changed the dose of any medications, or stopped any medications since our last phone call?"

Question about the need for a clinic or hospital visit:

- Do you feel that you will need to make a visit to see us, your personal doctor, or the hospital? If so, I will call your doctor or the hospital and let them know you will be arriving soon [or time provided by patient]."

- If the Investigator (or delegate) feels that the patient should have a clinic or hospital visit, he/she will make that recommendation.

If the patient cannot be reached, the designated family member or caregiver will be contacted for a determination of the patient's status. The patient's doctor may also be contacted for additional information identified during the telephone call.

Appendix B: Telephone Script, Day 21 and Day 28

Greeting

Question on current health:

- "I am calling to check on the status of your health since you completed the first 14 days in the study. Were you admitted to the hospital at any time? If so, please provide the details of the hospital and dates."

- Have you had any changes to your health that have required a doctor's visit?

If the answer to either of these questions is yes, the doctor or hospital will be contacted for further details.

If the patient cannot be reached, the designated family member or caregiver will be contacted for this information.

Appendix C: Criteria for the Assessment of Severity of Illness in Patients with COVID-19

SARS-CoV-2 infection without symptoms

- Positive testing by standard reverse transcription polymerase chain reaction (RTPCR) assay or equivalent test
- No symptoms

Mild COVID-19

- Positive testing by standard RT-PCR assay or equivalent test
- Symptoms of mild illness that could include fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms
- No clinical signs indicative of Moderate, Severe, or Critical Severity

Moderate COVID-19

- Positive testing by standard RT-PCR assay or equivalent testing
- Symptoms of moderate illness with COVID-19, which could include any symptom of mild illness or shortness of breath with exertion
- Clinical signs suggestive of moderate illness with COVID-19, such as RR ≥ 20, HR ≥ 90, or requires ≤2L oxygen by nasal cannula in order maintain SaO_2 ≥93%
- No clinical signs indicative of Severe or Critical Illness Severity

Severe COVID-19

- Positive testing by standard RT-PCR assay or an equivalent test
- Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress
- Clinical signs indicative of severe systemic illness with COVID-19, such as RR ≥ 30, HR ≥ 125, requires > 2L oxygen by nasal cannula in order maintain SaO_2 ≥93%, or PaO_2/FiO_2 <300
- No criteria for Critical Severity

Critical COVID-19

- Positive testing by standard RT-PCR assay or equivalent test
- Evidence of critical illness, defined by at least one of the following:
  - Respiratory failure defined based on resource utilization requiring at least one of the following:

- 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), noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (ie, clinical need for one of the preceding therapies, but preceding therapies not able to be administered in setting of resource limitation)

– Shock (defined by SBP < 90 mm Hg, or Diastolic BP < 60 mm Hg or requiring vasopressors)

– Multi-organ dysfunction/failure