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)
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STATISTICAL ANALYSIS PLAN

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)

Version 0.2
Date: 28 JUL 2020

for

Protocol No. ALT-601-201

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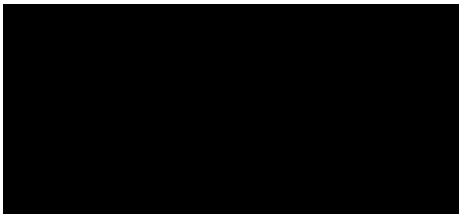

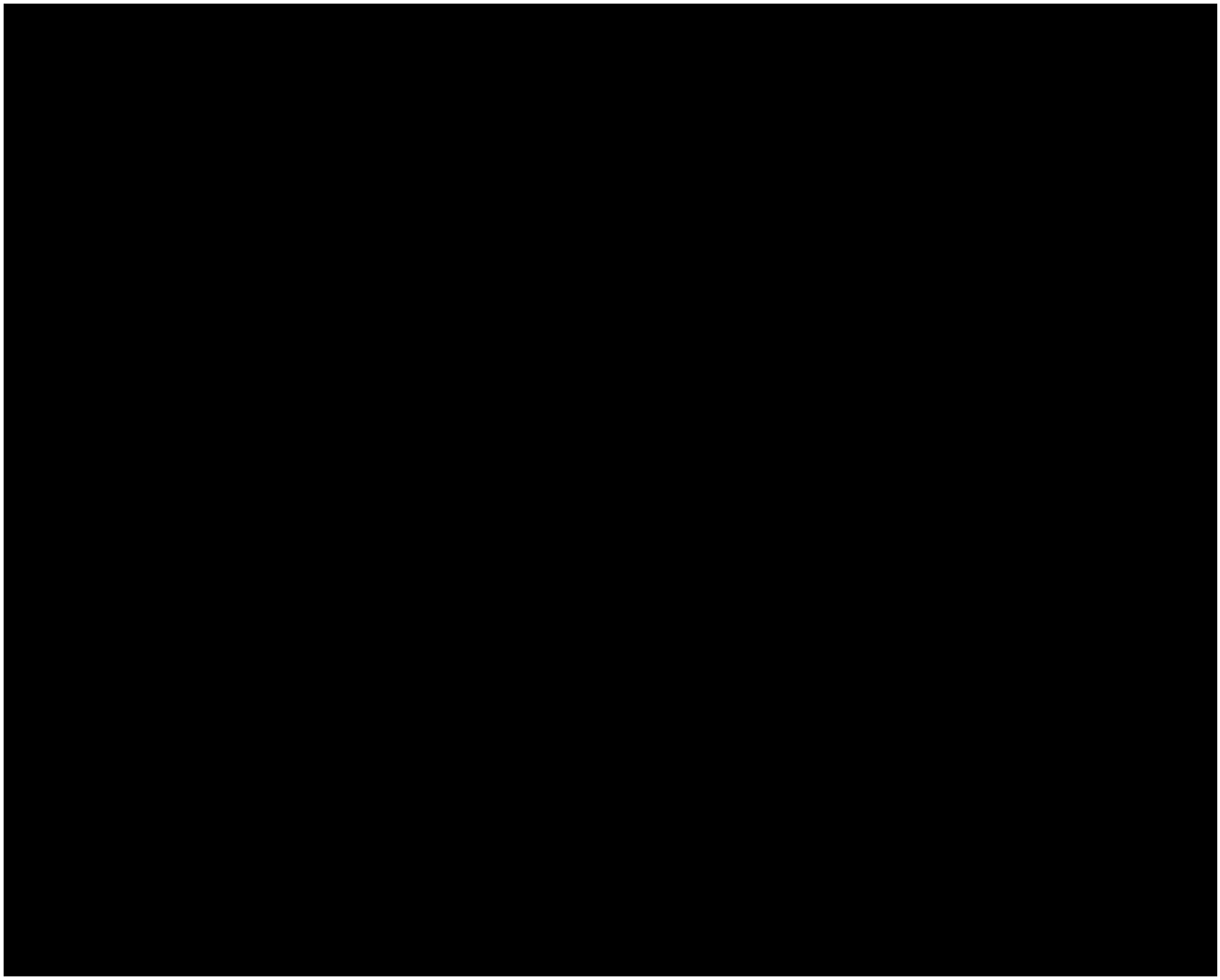

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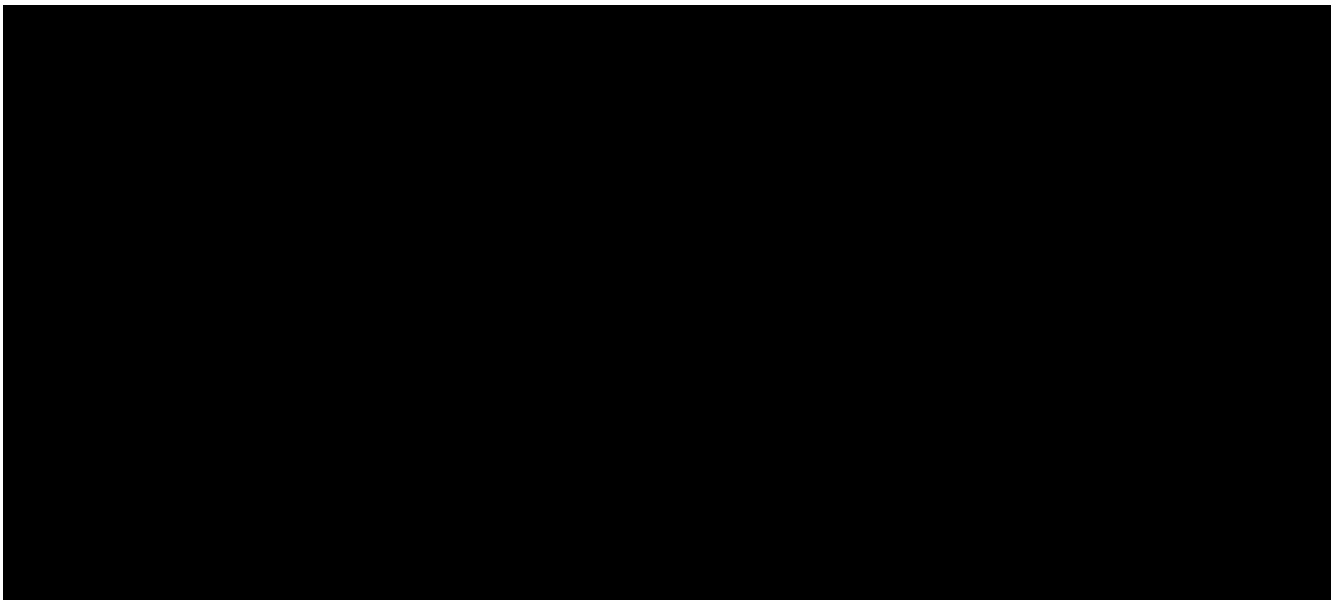

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CI	confidence interval
COVID-19	Coronavirus Infectious Disease 2019
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DMP	Data Management Plan
eCRF	electronic case report form
eDiary	electronic diary
ICH	International Council for Harmonisation
ICU	intensive care unit
IP	investigational product
LOCF	Last Observed Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MMRM	mixed model for repeated measures
PCR	polymerase chain reaction
PP	Per Protocol
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SpO_2	peripheral oxygen pulse saturation
TEAE	treatment-emergent adverse event
vp	viral particles
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) is consistent with the statistical methods section of the final study protocol (Version 4.0, dated 28July 2020) and includes additional details of efficacy and safety summaries to be included in the clinical study report (CSR).

2 STUDY OBJECTIVES

2.1 Efficacy

2.1.1 Primary Objective

- To assess the effectiveness of NasoVAX in preventing clinical worsening in patients with early COVID-19

2.1.2 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

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 a 4.0% decrease from Baseline in resting SpO_2 by mobile pulse oximetry on two consecutive measurements during home follow-up, or hospitalization.

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.

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 according to maximal level of oxygen supplementation:
        - No oxygen supplementation
        - Oxygen supplementation with nasal cannulae
        - 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 adverse events (AEs)
- Oral temperatures
- Use of antipyretics and bronchodilators
- Hospital length of stay, and intensive care unit (ICU) length of stay

4 STUDY DESIGN

4.1 General

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 onset of symptoms (fever, cough, and/or shortness of breath) within 48 hours and a diagnosis within the prior 24 hours, will be enrolled in 3 successive cohorts defined by age and risk factors for severe COVID-19 (Exclusion Criterion 5 in the Protocol) (Table 1) (Cohort 1, ages 35-49 years and risk factors disallowed; Cohort 2, ages 35 and above and risk factors disallowed; and Cohort 3, ages 35 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).

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 5.1.2) 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 2). 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 (Table 1). Approximately 24 patients will receive NasoVAX and 24 will receive placebo in Cohort 3. Randomization in Cohort 2 will be stratified by age groups of 35-64 years and 65 years and above. Randomization in Cohort 3 will be stratified by age groups (ages 35-64 years, ages 65 and above) and co-morbidity (one or more risk factors present, no risk factors present). Enrollment of patients ages 35-49 will not exceed approximately 30% of the randomized population of either treatment arm.

Table 1 Study Design

Cohort	Cohort Description	Number of Doses	NasoVAX Dose (vp)	Number of patients	
				NasoVAX	Placebo
1	Ages 35-49 years and risk factors disallowed	Single	1×10^{11}	10	10
2	Ages 35 and above and risk factors disallowed	Single	1×10^{11}	14	14
3	Ages 35 and above and risk factors allowed	Single	1×10^{11}	24	24
			Group Total	**48**	**48**
			Study Total	**96**	

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 1unless 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 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 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.

4.2 Schedule of Events

The schedule for study activities is presented in Table 2.

Table 2 Schedule of Events – Screening and Treatment Periods

	Study Visit Type / Day			
	Screening	Study Drug Treatment	Diary Completion/ Telephone Contact	Telephone Contact
	Study Center Visit		Remote Visit	
Procedure	**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 of the Protocol.

[h] The script for the Day 21 and Day 28 phone calls is provided in Appendix B of the Protocol. 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.

4.3 Study Population

Approximately 96 ambulatory patients with COVID-19, with onset of fever, cough, or shortness of breath within 48 hours and a confirmation of SARS-CoV-2 infection by a polymerase chain reaction (PCR)-based diagnostic within the prior 24 hours, will be enrolled at up to 5 study centers in the US.

The Inclusion and Exclusion Criteria of patients are provided in Protocol Sections 5.2 and 5.3, respectively.

4.4 Randomization and Treatment Assignments

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 within each cohort. Randomization will proceed in 3 cohorts defined by age and risk factors (Exclusion Criterion 5 in the Protocol) for severe COVID-19. 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 35-64 years and 65 years and above, whereas Cohort 3 will be stratified by age groups (ages 35-64 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 35-49 will not exceed approximate 30% of the randomized population of either treatment arm.

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

4.5 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.

4.6 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.

Since 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.

4.7 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.

4.7.1 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.

5 PREMATURE DISCONTINUATION

5.1.1 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.

5.1.2 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 patients 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 patient safety is not considered to be at significant risk following analysis.

5.1.3 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

6 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.

6.1 Screening Assessments

6.1.1 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 6.2.2) is not completed patient does not respond to telephone calls (Section 6.2.3). The contact information for the patient's personal doctor (s) will also be obtained.

6.1.2 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.

6.1.3 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.

6.1.4 Concomitant Medications

Concomitant medications will be documented as described in Protocol Section 6.7.

6.2 Efficacy Assessments

6.2.1 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.

6.2.1.1 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 in the second minute of each measurement will be used to determine study eligibility. Resting pulse rate will also be determined during this time. To be eligible for the study, patients will be required to have an average resting $SpO_2 \geq 96.0\%$ on both measurements. Average resting pulse rate will also be determined from these measurements. Oral temperature will also be recorded.

6.2.1.2 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 6.2.2).

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.

6.2.2 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.

6.2.3 Telephone calls

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

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

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

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

The criteria in Appendix C of the Protocol 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.

6.2.5 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.

6.2.6 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 SpO2 or resting pulse rate or COVID-19 symptoms that are reported at Screening (Protocol 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.

6.3 Safety Assessments

6.3.1 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.

6.3.2 Physical Examination

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

6.3.3 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 Protocol Section 8.2.1.

6.3.4 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 7.

6.3.5 Use of Antipyretics and Bronchodilators

The use of antipyretics and bronchodilators will be considered study safety endpoints and should be collected with concomitant medications as describe in Protocol Section 6.7.1.

6.4 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.

7 ADVERSE EVENTS

7.1 Definitions

7.1.1 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 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.

7.1.2 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 SAEs considered possibly or probably related to study medication by the Sponsor and unexpected SAEs (see SAEs Protocol Section 9.1.3) will be considered IND-Safety Reports.

7.1.3 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.

7.2 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 or, 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 Protocol 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 at Baseline will not be considered an SAE.

7.3 Assessment of Adverse Events

7.3.1 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 latest version of Common Terminology Criteria for Adverse Events (CTCAE).

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 Protocol Section 9.1.3.

7.3.2 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

7.4 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product (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 Protocol 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.

7.5 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.

7.6 Procedures for Recording and Reporting Adverse Events

7.6.1 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.

7.6.2 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 Protocol Section 9.2 and Section 8.2.6, hospitalizations and deaths related to worsening fever, cough, shortness of breath, resting SpO2 or resting pulse rate or symptoms of COVID-19 at Screening 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.

8 QUALITY CONTROL AND QUALITY ASSURANCE METHODS FOR DATA ANALYSIS

[redacted]

9 STATISTICAL METHODS

9.1 General

The statistical analysis will be conducted following the principles specified in the International Council for Harmonisation (ICH) Topic E9 Statistical Principles for Clinical Trials (CPMP/ICH/363/96).

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.

All statistical tabulations and analyses will be done using the SAS Version 9.4 or higher. Unless otherwise noted, continuous variables will be presented by summary statistics (eg, mean, standard deviation [SD], median, minimum, and maximum). The continuous efficacy endpoints

will be presented by means and 95% confidence intervals (CIs). Categorical variables will be presented by frequency counts and percentages. The categorical endpoints will be by frequency distributions (percentages and 95% CIs calculated according to Clopper-Pearson method). 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.

Most of the 95% CIs will be produced using standard methods, but in some instances the Clopper-Pearson method will be used, and in these latter situations the method will be footnoted.

In the data listings, for each patient the time point will be presented as study day defined relative to the first dose of investigational product. Study day will be calculated as: event date – first date +1 (when event date ≥ first dose date), and as event date – first date (when event date is prior to date of first investigational product). The day of first investigational product intake is Day 1, the day prior to first investigational product intake is Day -1, there is no Day 0.

Unless otherwise specified, baseline will be the last available measurement prior to the first dose of investigational product.

For all summary tables, the values from unscheduled visits will not be considered and the repeated values will only be used if the preceding value was hemolyzed or if the specimen was lost or the quantity was insufficient to run the assay. However, in individual data listings, both repeated measurements and those from unscheduled visits will be included.

All investigational product dosing will be listed and summarized by cohorts.

9.2 Multicenter Studies

This is a multi-center study which makes use of up to 6 clinical sites in the United States.

9.3 Examination of Subgroups

No subgroup analyses are planned.

9.4 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.

9.5 Analysis Populations

Consented Population: All patients who signed the informed consent.

Randomized Population: All patients who were randomized to receive any study medication.

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 (mITT) 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.

All important protocol deviations documented during study will be collected and finally assessed as major or minor protocol deviation after data base lock and prior to unblinding.

9.6 Summary of Study Data

For all summaries described in the SAP, the patients enrolled in the ALT-601-201 and randomized to an active dose will be summarized/listed under the heading "NasoVAX", while patients enrolled in Placebo will be summarized/listed under the heading "Placebo".

9.7 Subject Accountability

The screening outcomes will be listed and summarized based on the Consented Population. Consented population in the study will be included in the summary of pre-randomized patient status. The summary will include all patients consented, patients who completed screening, and patients who were screening failure. The reasons for screening failure will also be summarized.

Summaries of analysis populations and patient disposition will be presented by NasoVAX cohort, all NasoVAX cohorts combined, placebo pooled from all cohorts, and overall (all NasoVAX cohorts and pooled placebo) based on the Safety Population and will contain the following information:

- Number of patients who were randomized
- Number and percentage of patients who were dosed (Safety Population)
- Number and percentage of patients who did not receive all doses
- Number and percentage of patients in safety population who completed the study
- Number and percentage of patients who discontinued early and reason for early discontinuation of study

The number and percent of patients in each analysis population will also be tabulated.

A listing will present dates of completion or early withdrawal and the reason for early discontinuation of investigational product treatment and discontinuation of study, respectively, if applicable, for each patient.

The randomization allocation and exclusion from each population will also be listed.

9.8 Subject Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized based on the Safety, mITT, and PP populations. Individual patient demographics and baseline characteristics will be presented in listings. Demographic characteristics such as age, sex, race, ethnicity, and BMI, COVID-19 symptoms (Protocol Section 8.2.2), risk factors (Protocol Section 5.3, Exclusion Criterion 5) and baseline resting SpO2 and pulse rates will be summarized and tabulated by overall NasoVAX cohorts, NasoVAX cohort, and pooled placebo groups. Descriptive statistics will be presented for age and BMI. Frequency counts and percentages will be presented for gender, race, and ethnicity.

ALT-601-201 patient demographic data and baseline characteristics will be summarized descriptively by treatment group and overall for all ALT-601-201 patients (ie, patients on NasoVAX cohort and pooled placebo groups).

A listing of the medical and surgical history will be provided for all randomized patients. Medical and surgery history will be summarized by system organ class (SOC) and preferred term (PT) for each treatment group. Within each level of summarization, patients will be counted only once if they had more than one event reported. Medical and surgery history will be summarized for the Safety Population.

9.9 Analysis of Efficacy Data

Efficacy analyses will be conducted using the mITT and PP Populations with the primary conclusions drawn from the mITT Population. Placebo will be the collective (pooled) across cohorts.

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 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.

The p-values from significance tests will be obtained at a one-sided significance level of 0.025.

No multiplicity adjustments will be made for the efficacy endpoints.

9.9.1 Analysis of Response Data Endpoints

Response data endpoints – the primary endpoint of the proportion of patients with clinical worsening, defined as a 4.0% decrease from Baseline in resting SpO_2 by mobile pulse oximetry on two consecutive measurements during home follow-up, or hospitalization and the secondary endpoint of the proportions of patients requiring hospitalization through Day 42 according to maximal level of oxygen supplementation – will be tabulated by counts, percentages, and the 95% Clopper-Pearson exact CI of the percentage by overall NasoVAX, NasoVAX cohort, and pooled placebo groups. Differences of 95% CIs will also be presented to compare the proportion of patients of each NasoVAX cohort group to the pooled placebo group. CIs will be calculated in PROC FREQ procedure in SAS using the EXACT binomial-option for the individual dose groups and by the METHOD=SCORE riskdiff-option for the differences in treatment groups. In addition, comparisons of proportions of patients in each NasoVAX group against pooled placebo will be conducted using Fisher's exact test.

The Cochran-Mantel-Haenszel (CMH) test will also be used to compare the proportion of patients with clinical worsening and the proportion of patients requiring hospitalization through Day 42 between NasoVAX cohort and pooled placebo groups, while considering the stratification of age groups and risk factors.

9.9.2 Analysis of Continuous Data Endpoints

The continuous data endpoints – the secondary endpoints of average decrease in resting SpO_2 from Baseline and average increase in resting pulse rate from Baseline during the 14 days of home follow-up or hospitalization – will be tabulated by mean changes on each post-treatment day from baseline and their 95% CIs by NasoVAX cohort, pooled placebo, and overall NasoVAX groups. The p-values from parametric (ie, Pearson's t-test) or nonparametric (ie, Mann-Whitney test) tests will be calculated to see significant differences in continuous endpoints between each NasoVAX cohort and pooled placebo groups and between overall NasoVAX and pooled placebo groups.

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 also be analyzed using mixed model for repeated measures (MMRM). The MMRM model will include the fixed effects of treatment, days, and treatment-by-visit interaction, and the stratification factors (ages 35-64 years vs. ages 65 years and above, one or more risk factors present vs. no risk factors present). The model will also include the baseline characteristics (gender, race) and the corresponding baseline measures (resting SpO_2 at Baseline, resting pulse rate at Baseline). The model will employ an unstructured within patient covariance matrix and a restricted maximum likelihood estimation method.

9.9.3 Analysis of Time to Event Data Endpoints

Time to event data endpoints – the primary endpoint of the first 4.0% decrease or greater from Baseline in resting SpO_2 on two consecutive measurements during the 14 days of home follow-

up, or hospitalization; the secondary endpoints of the first incidence of resting pulse rate ≥ 125 beats per minute during the 14 days of home follow-up, or hospitalization; and all-cause mortality through Day 42 – will be analyzed by the Kaplan-Meier method. The summary statistics will be tabulated by treatment arms over visits and will include number of patients without event, number patients censored, 25^{th}, 50^{th}, and 75^{th} percentiles with 95% CIs, the event rates across all visits with 95% CIs. Kaplan-Meier estimates are calculated with the PROC LIFETEST procedure in SAS. The CIs of the event rates will be calculated via log-log transformation method (default option CONFTYPE=LOGLOG in SAS) based on standard errors computed using the Greenwood's formula. Time to event data comparisons will be made by treatment group and may include comparisons for cohort or stratification factors (ages 35-64 years vs. ages 65 years and above, one or more risk factors present vs. no risk factors present). The summary statistics may also have the p-values from log-rank test to compare changes in events between NasoVAX cohorts and pooled placebo and overall NasoVAX and pooled placebo groups. The log-rank test stratified by age groups and risk factors will also be performed. The Kaplan-Meier curves will also be plotted for each NasoVAX cohort and pooled placebo groups.

Non-informative censoring is assumed, as censored patients the same probability of experiencing an event as patients that remain in the study. Patients who do not meet the event or loss to follow-up before the study-end are censored at the last day during the 14 days of home follow-up or hospitalization in resting SpO_2 and resting pulse or at Day 42 for all-cause mortality.

9.9.4 Analysis for Covariates

Analysis of covariance (ANCOVA) will be used in the analysis of the secondary efficacy endpoints at each post-baseline visit, with the average decrease in resting SpO_2 from Baseline or the average increase in resting pulse rate from Baseline as a dependent variable, treatment arm as a factor, the stratification factors (ages 35-64 years vs. ages 65 years and above, one or more risk factors present vs. no risk factors present) and the corresponding baseline characteristics and measures (gender, race, resting SpO_2 at Baseline or resting pulse rate at Baseline) as covariates. This model will be generated using SAS PROC MIXED with treatment arm in the CLASS statement and visit/day in the BY statement. Comparisons of post-baseline average decrease in resting SpO_2 and average increase in resting pulse rate will be conducted for each NasoVAX dose group against the pooled placebo group. Least square (LS) means and 95% CIs of the LS means of treatment arm, difference of LS means and 95% CIs of the difference in LS means will be obtained from the model via ESTIMATE statements.

9.9.5 Sensitivity and Post-Hoc Exploratory Analyses

Sensitivity analyses may be performed to assess the effect of site on the response to study drug. Exploratory analyses of the efficacy data that are not identified in this SAP may also be conducted.

9.9.6 Handling of Missing Data

Efficacy analyses will be conducted based on observed data only. In sensitivity analyses, missing data due to death or hospitalization may also be imputed using the Last Observed Carried Forward (LOCF) or the multiple imputation methods. These analyses will be clearly identified as such in the Clinical Study Report.

9.10 Analysis of Safety Data

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 overall NasoVAX, NasoVAX cohort, and pooled placebo groups. AEs will be coded using the latest version of MedDRA, and severity will be coded using the latest version of the CTCAE, v.4.0.3. Concomitant medications will be coded using the latest version of the World Health Organization (WHO) drug dictionary. Safety comparisons will be made by treatment group and be include comparisons for cohort or stratification factors (ages 35-64 years vs. ages 65 years and above, one or more risk factors present vs. no risk factors present).

9.10.1 Adverse Events

All AEs recorded on the AE eCRF during the study will be coded to SOC and PT using the most current version of MedDRA, currently MedDRA 20.1.

A treatment-emergent AE (TEAE) is defined as an AE that was not present prior to treatment with IP, but appeared following treatment or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated). Programmatically, an AE will be classified as a TEAE if the start date and time occurs on or after the start date and time of first IP dosing.

All reported AEs will be listed, but only TEAEs will be summarized.

The overall incidence of TEAEs (number and percentage of patients, 95% CI) as well as the number of events will be summarized by treatment group, intensity as assessed by the latest version of National Cancer Institute's Common Terminology Criteria for AEs, SAE, related TEAE, TEAEs leading to study or investigational product discontinuation, and SAEs resulting in death.

The number (percentage, 95% CI) of patients with AEs from Day 1 to Day 42 (including SAEs) will be summarized for each MedDRA system organ class and PT and by treatment group. The number (percentage) of patients with SAEs from Day 1 to Day 210 will be summarized in a similar fashion. The number (percentage, 95% CI) of patients with AEs by severity and by relationship to IP will also be summarized.

The TEAEs will be summarized and tabulated at both the patient (n [%] of patients) and event (number of events) level for each treatment group and overall as follows:

- SOC and PT
- SOC, PT, and maximum reported severity
- SOC, PT, and maximum relationship to investigational product

Subjects with SAEs will also be summarized by SOC and PT for each treatment group and overall.

For the incidence at the patient level by SOC and PT, if a patient experiences more than 1 event within the same SOC and PT, only one occurrence will be included in the incidence.

For the incidence at the patient level by SOC, PT, and severity, if a patient experiences more than 1 event within the same SOC and PT, only the most severe occurrence will be included in the incidence.

For the incidence at the patient level by SOC, PT and relationship to investigational product; if a patient experiences more than 1 event within the same SOC and PT, only the most closely related occurrence will be included in the incidence.

Listings of AEs and SAEs will be provided.

9.10.2 COVID-19 Symptoms

Each patient will record the following COVID-19 symptoms daily in the eDiary with the study-supplied devices (ie, tabloid, digital thermometer) through Day 14. For patients who are unable to complete the eDiary, the records of symptoms will be collected over the telephone.

- fatigue, chills, headache, cough (with or without sputum production), myalgia, sore throat, shortness of breath, nasal congestion, diarrhea, nausea or vomiting, and oral temperature.

The patient will be asked to grade the symptoms in scale of “not at all”, “a little bit”, “somewhat”, “quite a bit”, and “very much”.

A cumulative summary of the number and percentage of patients experiencing at least one symptom (as local, systemic, and overall) through Day 14 will be tabulated by maximum severity and treatment group. Differences between each NasoVAX cohort and pooled placebo for cumulative events (local, systemic, and overall) will be tested using Kruskal-Wallis tests. The number and percentage of subjects experiencing at least one grade of “quite a bit” and “very much” symptom through Day 14 days for each symptom type, as well as 95% Clopper Pearson exact CIs, will be presented by treatment group.

A summary of the number and percentage of subjects experiencing at least one event through Day 14 will also be tabulated by event type, maximum severity, and treatment group. In addition, a descriptive summary of the duration of events (regardless of severity) will be tabulated by event and dose group.

Generally, symptoms recorded in the eDiary and (unsolicited) AEs recorded in the AE log will be summarized separately. A change in symptoms from baseline will not be recorded as an (unsolicited) AE unless it meets the criteria of an SAE. Any event found in the AE log that is also captured in the eDiary will not be counted as an AE to avoid duplication.

9.10.3 Safety Laboratory Tests and Vital Signs

Clinical laboratory results will be listed for urinalysis. Presentations will use SI Units.

Observed and change from baseline of continuous clinical laboratory values will be summarized descriptively by each treatment group and visit. Summary statistics for continuous parameters will be presented by treatment group as follows: pre-treatment, post-treatment, and change from pre-treatment to post-treatment assessment.

The number and percentage of patients with post-treatment clinical laboratory values recorded as new abnormal (ie, an event with an increase in toxicity grade relative to the baseline value and with a severity grade of moderate [Grade 2]) or higher) after study treatment will be tabulated. Shift tables that cross-tabulate the pre-treatment and post-treatment clinical laboratory values of each patient by toxicity grades defined in Appendix 1 of protocol will be prepared.

Observed values and change from baseline of vital signs will be summarized descriptively at each time point by treatment group. The number and percentage of patients with post-treatment vital sign values recorded as newly abnormal (ie, an event with an increase in the toxicity grades [defined in Appendix 1 of the Protocol] relative to the baseline value) after study treatment will be tabulated. Individual vital signs data will be listed.

9.11 Basic Analyses

9.11.1 Physical Examinations

Physical exam results will be listed including specification of any abnormalities observed.

9.11.2 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by the latest version of WHO Drug Dictionary Anatomical Therapeutic Chemical (ATC) level 3 and PT. If a medication has no ATC Level 3 code, then ATC Level 2 will be used instead. The total number of concomitant medications and the number and percentages of patients with at least 1 concomitant medication will be summarized by treatment group/cohort for the Safety Population. Placebo will be the collective (pooled) across treatment groups.

Concomitant medications that were started prior to study treatment will be summarized similarly. Prior medications that are not concomitant will be listed but not tabulated.

9.12 General Conventions for Tables, Listings and Figures

For summary tables, unless otherwise specified, the number of decimal places provided in the SAS output will be based on the accuracy of the least accurate value in the raw data as follows:

n	integer
Arithmetic mean	1 decimal place more than the least accurate number in the raw data
SD	2 decimal places more than the least accurate number in the raw data
Geometric mean	1 decimal place more than the least accurate number in the raw data
Median	1 decimal place more than the least accurate number in the raw data
Minimum	same number of decimal places as raw data
Maximum	same number of decimal places as raw data
Confidence interval	same number of decimals as the associated statistic
Geometric mean ratio	2 decimal places

9.13 Conflicts and Deviations

In the event of a conflict between the SAP and study protocol, the SAP will supersede.

Any deviation from the original statistical analysis plan will be described and justified in the final clinical study report.

10 REFERENCES

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