



CLINICAL TRIAL PROTOCOL

Study Title:	Single-ascending-dose Study of the Safety and Immunogenicity of NasoVAX
Study Number:	ALT-103-201
Study Phase:	Phase 2a
Test Product:	Influenza vaccine, intranasal (NasoVAX)
Indication:	Prophylaxis of influenza
Sponsor:	Altimune, Inc. 19 Firstfield Road Gaithersburg, MD 20878 USA

Version	Date
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INVESTIGATOR SIGNATURE PAGE

ALT-103-201: Single-ascending-dose Study of the Safety and Immunogenicity of NasoVAX

I have read the protocol and agree to conduct the trial in compliance with the International Council for Harmonisation Guideline for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this trial of their responsibilities and obligations.

Signed: _____ Date: _____

Print Name: _____

LIST OF ABBREVIATIONS

Abbreviation	Definition
Ad5	adenovirus serotype 5
AdVAV	adenovirus serotype 5-vectored anthrax vaccine
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
CDC	US Centers for Disease Control and Prevention
CI	confidence interval
CSR	Clinical Study Report
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISpot	enzyme-linked immunosorbent spot assay
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMR	geometric mean ratio
GMT	geometric mean titer
HA	hemagglutinin
HAI	hemagglutination inhibition
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IgA	immunoglobulin A
IP	investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
LAIV	live attenuated influenza vaccine
MAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
NCI	new-onset chronic illness

Abbreviation	Definition
NOAEL	no-observed-adverse-effect level
PBMC	peripheral blood mononuclear cell
PP	per-protocol
qPCR	quantitative polymerase chain reaction
RD	replication deficient
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCR	seroconversion rate
SD	standard deviation
SFU	spot-forming unit
SPR	seroprotection rate
SRC	Safety Review Committee
vp	viral particles
WT	wild type

1 PROTOCOL SUMMARY

1.1 Synopsis

Sponsor: Altimmune, Inc.	
Study Title: Single-ascending-dose Study of the Safety and Immunogenicity of NasoVAX	
Study Number: ALT-103-201	Study Phase: 2a
Study Objectives and Endpoints:	
OBJECTIVES	ENDPOINTS
Primary Objective	
<ul style="list-style-type: none"> To describe the safety profile of NasoVAX in healthy adults when administered by intranasal spray at a single dose of 1×10^9, 1×10^{10}, or 1×10^{11} viral particles (vp) 	<ul style="list-style-type: none"> Reactogenicity: counts and percentages of subjects with local events (nasal irritation, sneezing, nasal congestion, cough, sore throat, change in smell, change in taste, change in vision, eye pain) and systemic events (headache, fatigue, muscle ache, nausea, vomiting, diarrhea, chills, fever) for 14 days after vaccination Adverse events (AEs): counts and percentages of subjects with AEs from Day 1 to Day 29; medically attended AEs (MAEs), serious AEs (SAEs), new-onset chronic illnesses (NCIs) from Day 1 to Day 181
Secondary Objective	
<ul style="list-style-type: none"> To evaluate the humoral immune response to NasoVAX when administered by intranasal spray at a single dose of 1×10^9, 1×10^{10}, or 1×10^{11} vp 	<ul style="list-style-type: none"> Antibody level measured by hemagglutination inhibition (HAI) in serum: <ul style="list-style-type: none"> Geometric mean titer (GMT): the antilog of the mean of the log-transformed titers Geometric mean ratio (GMR): the ratio of postvaccination and prevaccination GMTs within the same dose group Seroprotection rate (SPR): the percentage of subjects with a HAI titer $\geq 1:40$ Seroconversion rate (SCR): the percentage of subjects with either a baseline HAI titer $< 1:10$ and a postvaccination titer $\geq 1:40$ (which is 4 times the assay lower limit of quantitation), or a baseline HAI titer $\geq 1:10$ and a 4-fold increase in postvaccination HAI titer relative to baseline Antibody level measured by microneutralization in serum: <ul style="list-style-type: none"> GMT Responder rate: the proportion of subjects with 2-fold and 4-fold rise since baseline

Exploratory Objectives	
<ul style="list-style-type: none"> To evaluate the cellular immune response to NasoVAX when administered by intranasal spray at a single dose of 1×10^9, 1×10^{10}, or 1×10^{11} vp 	<ul style="list-style-type: none"> Spot-forming units (SFUs) to hemagglutinin (HA) peptides measured by enzyme-linked immunosorbent spot assay (ELISpot) in peripheral blood mononuclear cells (PBMCs): <ul style="list-style-type: none"> Geometric mean SFUs Responder rate
<ul style="list-style-type: none"> To evaluate the mucosal immune response NasoVAX when administered by intranasal spray at a single dose of 1×10^9, 1×10^{10}, or 1×10^{11} vp 	<ul style="list-style-type: none"> Immunoglobulin A (IgA) antibody level measured by enzyme-linked immunosorbent assay (ELISA): <ul style="list-style-type: none"> GMT GMR
<ul style="list-style-type: none"> To evaluate the humoral immune response against nonrepresented influenza strains after NasoVAX administration 	<ul style="list-style-type: none"> Humoral immune response to nonrepresented influenza strain antigens (antibody level measured by HAI and microneutralization in serum) against each strain tested: <ul style="list-style-type: none"> GMT GMR Responder rate: the number and percentage of subjects with 2-fold and 4-fold rise since baseline
<ul style="list-style-type: none"> To evaluate the effect of predose Ad5 serum antibody levels on the immunogenicity of NasoVAX 	<ul style="list-style-type: none"> Predose Ad5 antibody GMT measured by microneutralization in serum Day 29 GMR and responder rate from antibody level measured by HAI in serum
<ul style="list-style-type: none"> To compare immunogenicity results to those obtained from banked samples from a previous study of licensed seasonal vaccine in a similar subject population 	<ul style="list-style-type: none"> Antibody level measured by HAI in serum: <ul style="list-style-type: none"> GMT GMR SPR SCR Antibody level measured by microneutralization in serum: <ul style="list-style-type: none"> GMT Responder rate SFUs to hemagglutinin peptides measured by ELISpot in PBMCs: <ul style="list-style-type: none"> Geometric mean SFUs Responder rate IgA antibody level measured by ELISA: <ul style="list-style-type: none"> GMT GMR

Study Design: The Schedule of Events showing time points for all study procedures is provided in Section 1.2.

This is a Phase 2a, randomized, double-blind, placebo-controlled trial to evaluate the safety and immunogenicity of NasoVAX in healthy adults 18 to 49 years of age. Subjects will be screened within 28 days of randomization (Day 1). Approximately 60 subjects who meet all inclusion and no exclusion criteria and provide written informed consent will be enrolled into 3 sequential cohorts of 20 subjects each defined by the viral particle dose (1×10^9 , 1×10^{10} , and 1×10^{11} vp). Within each cohort and its sentinel group, subjects will be randomized in a 3:1 ratio to receive 1 intranasal dose of NasoVAX or placebo (Day 1).

A sentinel cohort of 5 subjects from each cohort will be dosed. Dosing of the remainder of each cohort may proceed after the last sentinel subject completes Day 8 if no events meeting stopping criteria have occurred. The Safety Review Committee (SRC), consisting of the Investigator, the Medical Monitor, and a Sponsor Representative, will review all AE, reactogenicity, and laboratory data through at least Day 8 for all subjects in each cohort before subjects are randomized to the next higher dose. If any event meeting the following criteria occurs, the SRC will review all available safety information before additional patients are dosed:

- Occurrence of any related SAE or Grade 4 AE
- Occurrence of 2 Grade 3 AEs in the same organ system
- Occurrence of the same Grade 3 laboratory abnormality in 2 or more subjects

Each subject will record reactogenicity (local events, systemic events, and oral temperature) and whether any medication or treatment was used for the symptom(s) in a diary daily for 14 days after the NasoVAX/placebo dose. Each subject will be contacted by telephone on Day 2 for safety assessment and review of the diary. Subjects will return to the investigational site on Days 4, 8, 15, 29, 91, and 181 for safety and immunogenicity assessments. At each visit, the subject will also be asked about the interim medical history and use of any medications.

A serum sample will be collected from each subject for evaluation of influenza HAI assay against A/California/04/2009(H1N1) predose on Day 1 and on Days 4, 8, 15, 29, 91, and 181; adenovirus serotype 5 (Ad5) antibody, microneutralization assay against both A/California/04/2009(H1N1) and nonrepresented strains, and HAI against nonrepresented strains will also be evaluated at Days 1 and 29. A whole blood sample will be collected from each subject and processed to isolate PBMCs for evaluation of T-cell responses by ELISpot predose on Day 1 and on Day 8.

A nasopharyngeal swab sample will be collected from each subject at Screening and on Days 4, 8, 15, 29, and 91 to measure concentration of the Ad5 vector for assessment of vaccine vector shedding by quantitative polymerase chain reaction (qPCR) assay. Once a negative result is obtained, later samples may not be tested. ELISA for measurement of IgA will also be performed on the swab samples from Screening and Day 29 for evaluation of mucosal immune response.

Banked samples from a previous study of licensed seasonal vaccine in a similar subject population will be analyzed alongside samples collected in this study.

All AEs and medications will be recorded from signing of the informed consent form to Day 29. Thereafter to the end of the study, only MAEs, NCIs, SAEs, immunosuppressive medications, and vaccines will be recorded. Samples for clinical laboratory tests (hematology, serum chemistry, urinalysis) will be collected at Screening and on Days 8 and Day 29. A complete physical examination and vital signs will be performed at Screening and predose on Day 1, and

targeted and symptom-driven physical examinations will be performed and vital signs measured 2 hours postdose and on Days 4, 8, 15, and 29. An electrocardiogram (ECG) will be performed at Screening and on Day 29. If a subject experiences acute symptoms compatible with adenoviral infection within 28 days after the NasoVAX/placebo dose, a sample will be collected for viral culture as clinically indicated.

One interim analysis of humoral immunogenicity data and safety data (including summaries of AE, reactogenicity, concomitant medications and vaccines, vital signs, ECG, and laboratory data and listing of any viral culture results) will be conducted when all data through the Day 29 visit is available and monitored for all subjects.

Duration of Subject Participation and Study: Each subject will participate in the study for approximately 7 months.

The end of the study is defined as the last visit of the last subject participating in the study. The expected duration of the study is approximately 9 months.

Study Centers: 1 site in the United States

Number of Subjects Planned: 60 subjects

Diagnosis and Main Eligibility Criteria: Healthy adults 18 to 49 years of age

Test Product: NasoVAX (influenza vaccine, intranasal) administered by intranasal spray at a single dose of 1×10^9 , 1×10^{10} , or 1×10^{11} vp

Reference Product: Normal saline administered by intranasal spray at a single dose

Concomitant Products: None

Statistical Methods:

Sample Size and Power: The sample size for this study was selected as adequate and reasonable for an initial review of the safety and immunogenicity profile of the NasoVAX at doses to be well tolerated by young adults, rather than for statistical power. The sample size will permit initial estimates of reactogenicity. Given a total of 45 subjects receiving NasoVAX, the study will have an 80% probability of detecting at least 1 AE which occurs at a rate of 3.6%. If no SAEs are observed among the 45 subjects who receive NasoVAX, an approximation to the 1-sided upper bound of the 90% confidence interval (CI) on the rate of SAE occurrence would be 5%.

Analyses:

Safety

The primary endpoint for evaluation of the safety profile is the number and percentage (95% CI) of subjects with solicited and unsolicited AEs recorded postvaccination. Safety analyses will be performed using the Safety Population.

The number (percentage, 95% CI) of subjects with local reactions and systemic events will be summarized by dose group and overall. Reactogenicity events will also be summarized by severity.

The number (percentage, 95% CI) of subjects with AEs from Day 1 to Day 29 (including MAEs, NCIs, SAEs) will be summarized for each MedDRA (Medical Dictionary for Regulatory Activities) system organ class and preferred term and by dose group and overall. The number (percentage) of subjects with MAEs, with NCIs, and with SAEs from Day 1 to Day 181 will be summarized in a similar fashion. The number (percentage, 95% CI) of subjects with AEs by severity and by relationship to investigational product (IP) will also be summarized.

Listings of AEs, MAEs, NCIs, and SAEs will be provided.

Summary statistics for continuous parameters (clinical laboratory tests and vital signs) will be presented by dose group as follows: prevaccination, postvaccination, and change from prevaccination to postvaccination assessment.

The number and percentage of subjects with postvaccination clinical laboratory values or vital sign values recorded as newly abnormal (ie, an event with an increase in the toxicity grade relative to the baseline value and with a severity grade of moderate or higher) after study vaccination will be tabulated. Shift tables which cross-tabulate the prevaccination and postvaccination clinical laboratory values of each subject by severity grade will be prepared.

Summaries of the number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant ECG interpretations will be presented.

For shedding of the vector, data will be summarized by count and percent positive by time point, along with median copy number.

Viral culture results for evaluation of adenovirus infection will be listed.

Immunogenicity

Immunology analyses will be conducted using the Intent-to-treat (ITT) and Per-protocol (PP) Populations with primary conclusions drawn from the PP Population. Analyses based on the ITT Population will be undertaken and presented only if >5% of subjects in any 1 dose group were excluded from the PP Population. No imputation for missing data will be performed. Data will be transformed as appropriate prior to analysis.

Baseline is defined as the sample collected prior to IP administration on Day 1.

The primary variable of interest for assessment of humoral immune response to the NasoVAX antigen is homologous HAI antibody titer. The following HAI immunogenicity measures and their 95% CIs will be summarized by dose group:

- GMT at baseline and postvaccination on Days 4, 8, 15, 29, 91, and 181
- GMR on Days 4, 8, 15, 29, 91, and 181 (analysis of GMR will be performed using analysis of covariance [ANCOVA] with baseline titer as a covariate)
- SPR on Days 4, 8, 15, 29, 91, and 181
- SCR on Days 4, 8, 15, 29, 91, and 181

Humoral immune response as measured by microneutralization in serum will be summarized by GMT at baseline and postvaccination on Day 29 and responder rate (the proportion of subjects with 2-fold and 4-fold rise since baseline) (95% CI) on Day 29.

Cellular responses (ELISpot SFUs to influenza HA peptides) will be summarized by geometric mean at baseline and postvaccination on Day 8 and responder rate on Day 8.

Humoral immune response to nonrepresented influenza strain antigens (antibody level measured by HAI and microneutralization in serum) against each strain tested will be summarized by GMT at baseline and postvaccination on Day 29; GMR postvaccination on Day 29; and responder rate (the proportion of subjects with 2-fold and 4-fold rise since baseline) on Day 29.

For the effect of predose Ad5 serum antibody levels on immunogenicity of NasoVAX on Day 29, analysis will be performed using ANCOVA, with baseline Ad5 titer as a covariate.

Immunogenicity results from samples collected in this study will be compared to those from banked samples from a previous study of licensed seasonal vaccine in a similar subject population using a 2-sample comparison of means or nonparametric tests as indicated.

1.2 Schedule of Events

Study Visit Window (days)	Screening Day -28 to Day -1	Dosing Period						Follow-up Period		
		Day 1 Predose	Day 1 Postdose	Day 2 ^a	Day 4 ± 1	Day 8 ± 1	Day 15 ± 1	Day 29 ± 3	Day 91 ± 10	Day 181 ± 10
Informed consent	X									
Demographics	X									
Medical history	X									
Concomitant medication recording	X	X	X	X	X	X	X	X		
Immunosuppressive medication and vaccine recording	X	X		X	X	X	X	X	X	X
Eligibility criteria check	X	X								
Complete PE	X	X								
Targeted and symptom-driven PE			X ^b		X	X	X	X		
Height and weight	X									
ECG	X							X		
Vital signs ^c	X	X	X ^b		X	X	X	X		
Drug and alcohol screen	X	X								
Laboratory samples:										
Hepatitis B and C and HIV tests	X									
Safety laboratory tests	X					X		X		
Serum (S)/urine (U) pregnancy test ^d	S	U						U		
Serum sample for humoral response		X ^e			X	X	X	X ^e	X	X
Whole blood sample for isolation of PBMCs		X				X				
Nasopharyngeal swab	X				X	X	X	X	X	
AE (including MAEs, NCIs, and SAEs) assessment	X	X	X	X	X	X	X	X		
Randomization		X								
NasoVAX/placebo administration			X							
Viral culture		If a subject experiences acute symptoms compatible with adenoviral infection within 28 days after dose, collect a sample as clinically indicated.								
Distribution (D)/review (R) of Diary			D	R	R	R	R			
MAE/NCI/SAE assessment									X	X

AE = adverse event; ECG = electrocardiogram; ET = early termination; HIV = human immunodeficiency virus; MAE = medically attended adverse event; NCI = new-onset chronic illness; PBMC = peripheral blood mononuclear cell; PE = physical examination; SAE = serious adverse event.

^a Telephone call
^b 2 hours postdose
^c Measured before any blood sample collection
^d Required for all women who are not surgically sterilized or have laboratory confirmation of postmenopausal status
^e A larger serum sample will be collected on Days 1 and 29 for additional assays (see Section 7.10.2 and the laboratory manual for details).

2 INTRODUCTION

2.1 Seasonal Influenza

Influenza is one of the most common viral respiratory infections, leading to significant morbidity and mortality. In particular, individuals with chronic medical conditions or who are pregnant or at the extremes of age are vulnerable to developing influenza-related complications [CDC 2016]. The World Health Organization reports 3 to 5 million severe cases and between 250,000 and 500,000 deaths annually [WHO 2016]. The number of deaths associated with seasonal influenza varies from year to year, depending on the severity of circulating strains and the effectiveness of that year's influenza vaccine.

Influenza illness is commonly associated with acute onset of fever, cough, sore throat, and nasal congestion and resolves within a week in most individuals but can be associated with severe respiratory distress, secondary pneumonia, and increased risk of myocardial infarction [CDC 2016; WHO 2016].

It is well established that elderly populations have greater influenza-related morbidity and mortality. The US Centers for Disease Control and Prevention (CDC) estimated that 90% of influenza-associated deaths between 1976 and 2007 occurred among adults 65 years and older [CDC 2010]. Even though usually less severe, the burden of influenza in healthy young adults is also significant with an average of 2.4 million outpatient visits and 32,000 hospitalizations in the US each year [Molinari 2007].

Many influenza strains circulate during a given influenza season and the individual strains are systematically named by (1) the type of influenza virus (either A or B), (2) the geographical location where the strain was isolated, (3) which isolate from that location it represents (starting with the number 01), and (4) the year it was isolated. For example, the isolate termed A/California/04/2009 is the strain associated with the 2009 pandemic. This system of naming virus strains sometimes includes information on the subtype of influenza virus as a suffix at the end of the name, eg, A/California/04/2009(H1N1), where the familiar designation H1N1 reveals the subunit structure of the virus, designating an influenza subtype comprised of hemagglutinin (HA) protein H1 and neuraminidase protein N1.

2.2 Current Vaccines for Seasonal Influenza

The CDC recommends that everyone in the United States over 6 months of age receive an annual influenza vaccination. Most currently licensed vaccines are based on circulating influenza strains adapted to grow in chicken eggs. The viruses are harvested, inactivated, and combined into trivalent (containing A H1N1, A H3N2, and B strains) or quadrivalent formulations (which also contain a second B strain) and administered by injection. Other injectable vaccines currently available include a tissue culture-derived vaccine (Afluria, Seqirus), a recombinant HA protein vaccine (Flublok, Protein Sciences), and an adjuvanted inactivated vaccine (Fluad, Seqirus). In general, these vaccines are well tolerated but provide limited protection to influenza viruses that are not well matched to the vaccine strains.

An intranasal live attenuated influenza vaccine (LAIV) has been licensed since 2003 (FluMist, MedImmune). This product is replication-competent, and its use is limited to older children and adults up to age 49 years because of safety concerns. LAIV does not elicit antibody responses at the levels of other licensed influenza vaccines, but initial studies showed significant cellular immune responses, and protective efficacy was demonstrated in Phase 3 studies. More recently postmarketing studies have shown declining effectiveness, and FluMist was not recommended for use in the 2016-2017 influenza season [Seasonal 2016]. Possible reasons for the decreased effectiveness seen may be instability in viral sequence or poor immunogenicity in the presence of pre-existing antibody.

For all types of influenza vaccines, effectiveness can vary greatly from year to year, and in many years overall protection is poor. According to the CDC, the average overall adjusted vaccine effectiveness for influenza seasons has been approximately 40% from 2005 to 2015 [CDC 2016]. One reason for vaccine ineffectiveness is the constantly changing nature of influenza virus strains. The viral protein HA is an important target of vaccination, and each type of HA protein, such as H1 or H3, has multiple forms which can vary from year to year. Because the process used to produce over 99% of influenza vaccines today requires 6 months of advance planning, regulatory agencies must commit to the strains to be used well in advance of the start of the influenza season. The low estimated 19% overall efficacy of the 2014-2015 influenza vaccine in the United States was attributed to the fact that most of the H3N2 viruses circulating that season were of a different form than the H3N2 strain included in vaccine production [Zimmerman 2016]. Worse still, a more dramatic change in influenza virus makeup occasionally arises when an entirely new HA protein emerges, which can result in a human pandemic. Because humans have never encountered the new HA protein, they are likely to have little or no immunity, leaving them at much greater risk for serious complications or death.

Changes in influenza virus formulation and manufacturing are essential to protect the public from the significant morbidity and mortality associated with seasonal influenza infections. The ability to provide cross-protection between different HA protein types is key to addressing the efficacy problems created by ever-mutating influenza viruses. Avoidance of egg-based production, because of supply chain risks, manufacturing timelines, and potential for allergic response in many individuals is another goal for new influenza vaccines. Altimmune, Inc. is developing NasoVAX, an Ad5-vectored, intranasal influenza vaccine, to address these issues.

2.3 NasoVAX

Adenovirus is a naturally occurring respiratory virus that has been used frequently as a vector to introduce genetic material into cells. By incorporating the influenza HA gene into replication-deficient (RD) adenovirus (Ad-HA) and applying the Ad-HA into the nose, the adenoviral vector can transduce the HA gene into cells of the nasal mucosa, leading to transient expression of the encoded HA protein. An immune response to the expressed HA antigen can thus be induced. Thus, RD Ad-HA constructs hold potential as a novel type of influenza virus vaccine that does not require administration by needle injection.

NasoVAX is based on Altimmune's RespirVec platform, an RD-Ad5 vector that expresses the protein of interest within respiratory epithelial cells. In the case of NasoVAX, the vector contains a genetic insert encoding the HA surface protein antigen from influenza type A or B. The

RespirVec platform has the potential to provide a more rapid production system than egg-based vaccines. In previous nonclinical and clinical studies, NasoVAX does not appear impeded by prior existing adenoviral immunity and generates strong antibody and cellular immune responses. In an animal challenge model, NasoVAX protected against highly divergent influenza strains and was protective within days of administration.

2.4 Nonclinical Studies

The Sponsor has conducted nonclinical studies of immunogenicity, lethal challenge, biodistribution, and single-dose and repeat-dose toxicity with Ad5-vectored vaccines incorporating other influenza genetic inserts and with a similar Ad5-vectored vaccine AdVAV (Ad5-vectored anthrax vaccine). Additional details of the studies can be found in the current Investigator Brochure.

Studies of humoral immunogenicity in mice and ferrets demonstrated that Ad5-vectored vaccines encoding an HA surface protein antigen elicit a strong dose-dependent immunogenic response (as measured by HAI antibody titer) to a single intranasal administration at doses ranging from 2.5×10^8 to 2.5×10^{10} vp. A booster dose administered 21 or 28 days later increased the response, indicating that an antivector immune response to the initial dose did not block a booster effect.

Studies in mice and ferrets also showed protection from a lethal influenza virus challenge, even in the absence of a protective level of HAI antibody titers. A single intranasal dose of 2.5×10^9 vp or 2.5×10^{10} vp provided 100% protection from a lethal challenge in mice, and a single intranasal dose of 1×10^{10} vp or 2 intranasal doses of 1×10^8 vp 21 days apart provided 100% protection in ferrets. Furthermore, a study in mice showed protection from lethal challenge from vaccination administered 2 days before the challenge and protection elicited by an empty (no influenza gene insert) Ad5 vector. These findings suggest multiple mechanisms of action—perhaps including mucosal and innate immunity as well as humoral immunity—for this vaccine construct.

Biodistribution studies of Ad5-vectored influenza vaccines in CD-1 mice showed primarily localization to the olfactory bulb, lungs, and nasopharynx. At 3 weeks after vaccination, minimal residual virus was detected, and no evidence of widespread dissemination was seen, indicating that the Ad5 vector DNA was rapidly cleared from all tissues. A GLP (Good Laboratory Practice) study of AdVAV in rabbits showed localization of the vaccine in the trachea and esophagus through 2 days after the last dose, in the olfactory bulb through 14 days after the last dose, and in the nasal epithelium through the end of the study (90 days after the last dose of a 3-dose series). As with the mouse studies, no evidence of widespread dissemination was seen, and the Ad5 vector DNA was rapidly cleared from all tissues except at the site of administration. Taken together, these biodistribution studies indicate that after intranasal delivery of NasoVAX the vector biodistribution is localized to tissues of the upper respiratory tract as opposed to a more widespread or systemic dissemination. Localization to the olfactory bulb was transient, consistent with other intranasally delivered compounds, and not associated with inflammation or clinical observations.

In 4 nonclinical single-dose and repeat-dose toxicity studies of Ad5-vectored vaccines in mice and rabbits, no test article-related changes were observed except for the following effects:

- Inflammatory changes in the lung were observed in mice that received a 1×10^{10} vp dose and in a dose-dependent manner in mice that received 10^6 vp, 10^7 vp, or 10^8 vp doses. Observations of lung inflammation in the mouse studies is not surprising and is probably related to the dose volume used in these studies relative to the volume of the nasal cavity of mice as is evidenced by the greater lung involvement noted in the mouse studies that used a 50 μ L dose volume compared to the mouse study that used a 25 μ L dose volume.
- A nonadverse inflammatory/immune response in the rabbits, ie, increases in fibrinogen and C-reactive protein concentrations, was observed in all groups (including controls), was most pronounced in samples collected 2 days after dosing, and resolved by the recovery sample collection. The inflammatory/immune response was likely related to minimal to mild nonadverse microscopic changes in the lung, which included alveolar histiocytosis, heterophil or mononuclear infiltration, and intra-alveolar subacute/chronic inflammation.

The NOAEL established in New Zealand White rabbits in the GLP repeat-dose toxicity study for AdVAV was 1×10^{11} vp.

2.5 Previous Clinical Experience with Adenoviral Vectors

The ability of RD-Ad5 vectors to adequately express the protein of interest following parenteral administration in the presence of pre-existing immunity to wild-type (WT) Ad5 has been a concern [Yang1994]. However, several lines of evidence, including clinical trials of earlier formulations of NasoVAX, suggest that anti-Ad5 immunologic components may not represent the same barrier to efficacy when the vector is administered using the intranasal route and that administration by this route may overcome pre-existing immunity to the adenovirus vector.

A significant body of evidence supports the general safety of RD-Ad5 vectors, including lack of potential for replication and recombination with WT adenovirus. The Sponsor's previous nonclinical and clinical experience with Ad5-vectored vaccines has shown no evidence suggestive of viral recombination in vaccinated subjects.

2.6 Clinical Trials of NasoVAX

The immunogenicity and safety of Ad-5 vectored influenza vaccines has been evaluated in 2 Phase 1 studies in healthy volunteers. These studies involved doses similar to the lowest dose being delivered in the this study or lower. The vaccines were well tolerated. Immune responses were weak but measurable despite the relatively low doses tested. The trials are summarized below, and additional details are provided in the current Investigator Brochure.

In a 2002 study of an Ad5-vectored vaccine encoding the HA surface protein antigen from the A/Puerto Rico/8/34(H1N1) strain of influenza of 24 male health volunteers aged 20 to 31 years, 6 subjects received 2 intranasal doses of 5×10^8 vp 28 days apart [Van Kampen 2005]. In addition to the intranasal vaccine recipients, 18 other subjects received 2 topical doses of either 4.8×10^9 , 4.8×10^{10} , or 4.8×10^{11} vp. No SAEs or severe AEs were observed. For both administration sites, most (85%) of the side effects were mild in severity, 15% were moderate, and no serious reactions to the vaccine were observed either systemically or at the site of inoculation. The local

AEs reported in the intranasal group were discoloration (1 subject), burning (2 subjects), and bitter taste (1 subject). Systemic events of soreness, headache, nausea/vomiting, and muscle pain were reported for 1 subject each in the intranasal group. Four of the 6 subjects who received the intranasal vaccine had increased HAI antibody titers after the primary dose, and this number increased to 5 after the booster dose. No correlation was observed between prevaccination Ad5 antibody titers and HAI titer fold changes for intranasal administration.

In a 2007 study of an Ad5-vectored vaccine encoding the HA surface protein antigen from the A/Vietnam/1203/2004(H5N1) influenza virus strain, 48 subjects were randomized for intranasal administration in groups of 12 to receive 5.0×10^7 vp, 2.4×10^8 vp, 3.3×10^9 vp, or placebo 28 days apart. A total of 36 women and 12 men aged 25 to 40 (mean 34.0) years were enrolled. No SAEs and no anaphylaxis, hives, or other allergic reactions were reported. The most common local reactogenicity events were headache, runny nose, sore throat, nasal congestion, and nasal irritation and were predominantly mild. Incidence rates of reactogenicity events, unsolicited AEs, and abnormal physical examination findings, and shift rates from normal to abnormal laboratory results were not statistically significantly different between active and placebo groups. Although only 1 subject (8.3%) in the highest dose group seroconverted, 4 of the 12 (33%) had increases in HAI titer. Pre-existing immunity to the adenovirus vector was not associated with influenza antibody response.

2.7 Study Rationale

This study is designed to evaluate safety and immunogenicity of a monovalent A/California/04/2009(H1N1)-like strain version of NasoVAX, testing doses similar to and higher than those tested in previous Phase 1 studies. Exploratory endpoints will evaluate the breadth of antibody response and the ability of NasoVAX to induce cellular and mucosal immune responses.

2.8 Benefit/Risk Assessment

On the basis of nonclinical and clinical study results to date, the efficacy issues associated with existing influenza vaccines, and the potential morbidity and mortality associated with influenza, NasoVAX is considered to have a positive benefit-risk profile for healthy adults aged 18 to 49.

3 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary Objective	
<ul style="list-style-type: none"> • To describe the safety profile of NasoVAX in healthy adults when administered by intranasal spray at a single dose of 1×10^9, 1×10^{10}, or 1×10^{11} vp 	<ul style="list-style-type: none"> • Reactogenicity: counts and percentages of subjects with local events (nasal irritation, sneezing, nasal congestion, cough, sore throat, change in smell, change in taste, change in vision, eye pain) and systemic events (headache, fatigue, muscle ache, nausea, vomiting, diarrhea, chills, fever) for 14 days after vaccination • AEs: counts and percentages of subjects with AEs from Day 1 to Day 29; MAEs, SAEs, NCIs from Day 1 to Day 181
Secondary Objective	
<ul style="list-style-type: none"> • To evaluate the humoral immune response to NasoVAX when administered by intranasal spray at a single dose of 1×10^9, 1×10^{10}, or 1×10^{11} vp 	<ul style="list-style-type: none"> • Antibody level measured by HAI in serum: <ul style="list-style-type: none"> ○ GMT: the antilog of the mean of the log-transformed titers ○ GMR: the ratio of postvaccination and prevaccination GMTs within the same dose group ○ SPR: the percentage of subjects with a HAI titer $\geq 1:40$ ○ SCR: the percentage of subjects with either a baseline HAI titer $< 1:10$ and a postvaccination titer $\geq 1:40$ (which is 4 times the assay lower limit of quantitation), or a baseline HAI titer $\geq 1:10$ and a 4-fold increase in postvaccination HAI titer relative to baseline • Antibody level measured by microneutralization in serum: <ul style="list-style-type: none"> ○ GMT ○ Responder rate: the proportion of subjects with 2-fold and 4-fold rise since baseline

OBJECTIVES	ENDPOINTS
Exploratory Objectives	
<ul style="list-style-type: none"> To evaluate the cellular immune response to NasoVAX when administered by intranasal spray at a single dose of 1×10^9, 1×10^{10}, or 1×10^{11} vp 	<ul style="list-style-type: none"> SFUs to HA peptides measured by enzyme-linked ELISpot in PBMCs: <ul style="list-style-type: none"> Geometric mean SFUs Responder rate
<ul style="list-style-type: none"> To evaluate the mucosal immune response NasoVAX when administered by intranasal spray at a single dose of 1×10^9, 1×10^{10}, or 1×10^{11} vp 	<ul style="list-style-type: none"> IgA antibody level measured by ELISA: <ul style="list-style-type: none"> GMT GMR
<ul style="list-style-type: none"> To evaluate the humoral immune response against nonrepresented influenza strains after NasoVAX administration 	<ul style="list-style-type: none"> Antibody level measured by HAI and microneutralization in serum against each strain tested: <ul style="list-style-type: none"> GMT GMR Responder rate: the number and percentage of subjects with 2-fold and 4-fold rise since baseline
<ul style="list-style-type: none"> To evaluate the effect of predose Ad5 serum antibody levels on the immunogenicity of NasoVAX 	<ul style="list-style-type: none"> Predose Ad5 antibody GMT measured by microneutralization in serum Day 29 GMR and responder rate from antibody level measured by HAI in serum
<ul style="list-style-type: none"> To compare immunogenicity results to those obtained from banked samples from a previous study of licensed seasonal vaccine in a similar subject population 	<ul style="list-style-type: none"> Antibody level measured by HAI in serum: <ul style="list-style-type: none"> GMT GMR SPR SCR Antibody level measured by microneutralization in serum: <ul style="list-style-type: none"> GMT Responder rate SFUs to hemagglutinin peptides measured by ELISpot in PBMCs: <ul style="list-style-type: none"> Geometric mean SFUs Responder rate IgA antibody level measured by ELISA: <ul style="list-style-type: none"> GMT GMR

4 STUDY DESIGN

4.1 Overall Study Design

The Schedule of Events showing time points for all study procedures is provided in Section 1.2.

This is a Phase 2a, randomized, double-blind, placebo-controlled trial to evaluate the safety, and immunogenicity of NasoVAX in healthy adults 18 to 49 years of age. Subjects will be screened within 28 days of randomization (Day 1). Approximately 60 subjects who meet all inclusion and no exclusion criteria and provide written informed consent will be enrolled into 3 sequential cohorts of 20 subjects each defined by the viral particle dose (1×10^9 , 1×10^{10} , and 1×10^{11} vp). Within each cohort and its sentinel group, subjects will be randomized in a 3:1 ratio to receive 1 intranasal dose of NasoVAX or placebo (Day 1) as shown in Table 1.

Table 1 NasoVax Study Design

Cohort	Dose (vp)	Number of Subjects	
		NasoVAX	Placebo
1	1×10^9	15	5
2	1×10^{10}	15	5
3	1×10^{11}	15	5
Study Total Target		45	15
Total		60	

A sentinel group of 5 subjects from each cohort will be dosed. Dosing of the remainder of each cohort may proceed after the last sentinel subject completes Day 8 if no events meeting stopping criteria have occurred. The SRC, consisting of the Investigator, the Medical Monitor, and a Sponsor Representative, will review AE, reactogenicity, and laboratory data through at least Day 8 for all subjects in each cohort before subjects are randomized to the next higher dose. If any event meeting stopping criteria occur, the SRC will review all available safety information before additional patients are dosed. Stopping criteria are as follows:

- Occurrence of any related SAE or Grade 4 AE
- Occurrence of 2 Grade 3 AEs in the same organ system
- Occurrence of the same Grade 3 laboratory abnormality in 2 or more subjects

Each subject will record reactogenicity (local events, systemic events, and oral temperature) and whether any medication or treatment was used for the symptom(s) in a diary daily for 14 days after the NasoVAX/placebo dose. Each subject will be contacted by telephone on Day 2 for safety assessment and review of the diary. Subjects will return to the investigational site on Days 4, 8, 15, 29, 91, and 181 for safety and immunogenicity assessments. At each visit, the subject will also be asked about the interim medical history and use of any medications.

A serum sample will be collected from each subject for evaluation of influenza HAI assay against A/California/04/2009 predose on Day 1 on Days 4, 8, 15, 29, 91, and 181; Ad5 antibody, microneutralization assay against both A/California/04/2009(H1N1) and nonrepresented strains,

and HAI against nonrepresented strains will also be evaluated at Days 1 and 29. A whole blood sample will be collected from each subject and processed to isolate PBMCs for evaluation of T-cell responses by ELISpot predose on Day 1 and on Day 8.

A nasopharyngeal swab sample will be collected from each subject at Screening and on Days 4, 8, 15, 29, and 91 to measure concentration of the Ad5 vector for assessment of vaccine vector shedding by quantitative polymerase chain reaction (qPCR) assay. Once a negative result is obtained, later samples may not be tested. ELISA for measurement of IgA will also be performed on the swab samples from Screening and Day 29 for evaluation of mucosal immune response.

Banked samples from a previous study of licensed seasonal vaccine in a similar subject population will be analyzed alongside samples collected in this study.

All AEs and medications will be recorded from signing of the ICF to Day 29. Thereafter to the end of the study, only MAEs, NCIs, SAEs, immunosuppressive medications (see list in [Appendix 3](#)), and vaccines will be recorded. Samples for clinical laboratory tests (hematology, serum chemistry, urinalysis) will be collected at Screening and on Days 8 and 29. A complete physical examination and vital signs will be performed at Screening and predose on Day 1, and targeted and symptom-driven physical examinations will be performed and vital signs measured 2 hours postdose and on Days 4, 8, 15, and 29. An ECG will be performed at Screening and on Day 29. If a subject experiences acute symptoms compatible with adenoviral infection within 28 days after the NasoVAX/placebo dose, a sample will be collected for viral culture as clinically indicated.

One interim analysis of humoral immunogenicity data and safety data (including summaries of AE, reactogenicity, concomitant medications and vaccines, vital signs, ECG, and laboratory data and listing of any viral culture results) will be conducted when all data through the Day 29 visit is available and monitored for all subjects.

4.2 Study Design Rationale

4.2.1 Population

Healthy, immunocompetent adults aged 18 to 49 years were selected as the population for this study to minimize risk to subjects and to maximize the potential to produce an immune response.

4.2.2 Dose

The initial dose to be tested in this study (1×10^9 vp) is in the range of intranasal doses that were shown to be safe and modestly immunogenic in earlier clinical trials of NasoVAX (Section 2.6). Escalation is planned to the NOAEL (1×10^{11} vp) established in the GLP repeat-dose toxicology study of AdVAV in New Zealand White rabbits (Section 2.4).

4.2.3 Assessments

Safety

An evaluation of safety is the primary objective for this study of NasoVAX that will evaluate doses higher than tested in the previous Phase 1 studies of this adenoviral vector. Safety assessments are standard for early-phase clinical trials and are in accordance with the US Food and Drug Administration's (FDA's) guidance on preventive vaccine clinical trials [FDA 2007b]. Reactogenicity events were requested by the FDA for intranasal administration.

Although NasoVAX is constructed from an RD adenoviral vector, there is a theoretical risk of recombination with WT adenovirus. Clinical illness caused by adenovirus can present as a wide variety of syndromes, including upper respiratory infection, pneumonia, conjunctivitis, and gastroenteritis [Adenoviruses 2015]. Subjects presenting with a potentially compatible clinical syndrome after vaccination will have appropriate specimens obtained for viral culture.

On the basis of animal biodistribution studies, it is expected that carriage of the vaccine vector will be transient and limited to the upper respiratory tract. Swab samples will be obtained for adenovirus qPCR to determine how long the vector persists at the site of administration.

Immunogenicity

Humoral immune response to the influenza HA protein as measured by HAI is a recognized surrogate of protection [FDA 2007a] and will be important in selecting the optimum dose for further clinical development.

4.3 Number of Sites and Subjects

The study will be conducted at 1 site in the United States.

Sixty subjects will be enrolled.

4.4 Duration of Subject Participation and Study

Each subject will participate in the study for approximately 7 months.

The end of the study is defined as the last visit of the last subject participating in the study. The expected duration of the study is approximately 9 months.

5 SUBJECT POPULATION

The Investigator must keep a record (ie, a subject screening log) of subjects who are screened for this study.

5.1 Inclusion Criteria

Subjects who meet all of the following criteria may be included in the study:

1. Men and women 18 to 49 years of age, inclusive
2. Good general health status as determined by the Investigator
3. Adequate venous access for repeated phlebotomies
4. Screening laboratory results within institutional normal range or Grade 1 elevation if the Investigator documents clinical insignificance. Creatine kinase or bilirubin may be Grade 2 if associated with normal alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and the Investigator considers the result not to be clinically significant due to vigorous exercise or Gilbert's syndrome
5. Negative drug and alcohol screen at Screening and predose on Day 1
6. For women who have not been surgically sterilized or have laboratory confirmation of postmenopausal status, negative pregnancy test
7. Willingness to practice a highly effective method of contraception that may include, 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, surgical sterilization (hysterectomy, or bilateral tubal ligation, salpingectomy, or oophorectomy), licensed hormonal methods, intrauterine device (IUD), or consistent use of a barrier method (eg, condom, diaphragm) with spermicide for 28 days after the NasoVAX/placebo dose
8. Willingness to participate and comply with all aspects of the study through the entire study period, including nasopharyngeal swabs and blood and urine samples
9. Provision of written informed consent

5.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. Pregnant, possibly pregnant, or lactating women
2. Household contacts of pregnant women, children <5 years of age, or immunocompromised individuals for the period up through 2 weeks postvaccination
3. Persons who care for pregnant women, children <5 years of age, or immunocompromised individuals for the period up through 2 weeks postvaccination
4. Body mass index >35.0 kg/m²
5. Positive results for HIV, hepatitis B virus, or hepatitis C virus at Screening
6. Asthma or other chronic lung disease that is greater than mild in severity. Specifically excluded are participants with the any of the following events in the past year:
 - Daily symptoms
 - Daily use of short acting beta 2 agonists
 - Use of inhaled steroids or theophylline
 - Use of pulse systemic steroids
 - Emergency care or hospitalization related to asthma or other chronic lung disease
 - Systemic steroids for asthma exacerbation
7. History of diabetes mellitus (gestational diabetes is allowed if treatment was not required postpartum and serum glucose is currently in the normal range)
8. History of coronary artery disease, arrhythmia, or congestive heart failure
9. Clinically significant ECG abnormality as determined by the Investigator
10. Poorly controlled hypertension (systolic blood pressure >150 mmHg or diastolic blood pressure >95 mmHg) at Screening or predose on Day 1
11. History of anaphylaxis or angioedema
12. Known allergy to any of the ingredients in the vaccine formulation
13. History of chronic rhinitis, nasal septal defect, cleft palate, nasal polyps, or other nasal abnormality that might affect vaccine administration
14. Previous nasal surgery or nasal cauterization
15. Any symptoms of upper respiratory infection or temperature >38°C within 3 days before Day 1
16. Any symptoms within 24 hours before Day 1 of upper respiratory illness of allergy flare-up that, in the opinion of the Investigator, presents as nasal congestion or rhinorrhea that could inhibit the proper administration of the IP

17. Known or suspected malignancy, excluding non-melanoma skin cancers and other early stage surgically excised malignancies that the Investigator considers to be exceedingly unlikely to recur
18. Immunocompromised individuals, including those who have used corticosteroids (including intranasal steroids), alkylating drugs, antimetabolites, radiation, immune-modulating biologics, or other immunomodulating therapies within 90 days before Day 1 or those who plan use during the study period
19. Use of statin medication within 30 days before Day 1 (see list in Section 6.8.1)
20. Receipt of intranasal medications (including over-the-counter medications) within 30 days before Day 1
21. Receipt of any IP within 30 days before Day 1
22. Receipt of any vaccine within 30 days before Day 1
23. Receipt of intranasal vaccine within 90 days before Day 1
24. Receipt of any influenza vaccine within 6 months before Day 1
25. Any change in medication for a chronic medical condition within 30 days before Day 1
26. Past regular use or current use of intranasal illicit drugs
27. Smokers, including smoking of any type (eg, cigarettes, electronic cigarettes, marijuana). Prior smokers must have quit smoking at least 30 days before Day 1.
28. 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 subject's ability to give informed consent

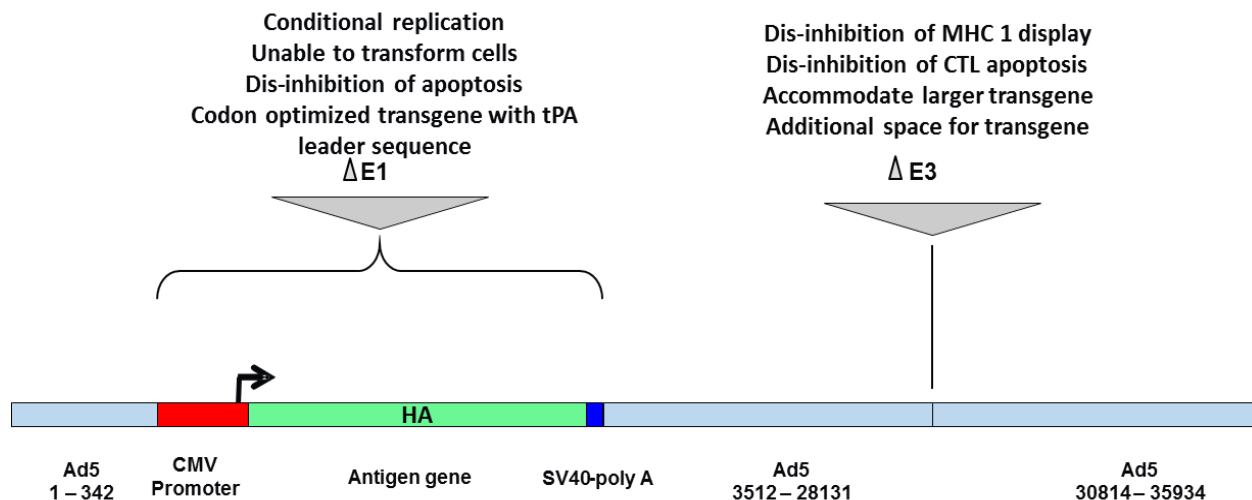
6 INVESTIGATIONAL PRODUCTS

6.1 Formulation, Packaging, and Administration

6.1.1 NasoVAX

NasoVAX uses the RespirVec platform developed by Altimmune for intranasally administered vaccines, an E1/E3-deleted, RD-Ad5 vector that expresses the protein of interest within respiratory epithelial cells. In the case of NasoVAX, the vector contains a genetic insert encoding the HA surface protein antigen from influenza type A or B. The recombinant Ad5 vector lacks the E1 region of the viral genome (nucleotides 343 to 3511), which renders the virus RD and incapable of producing infectious virus particles upon entry into a host cell. An additional deletion of nucleotides 28132 to 30813 in the E3 region of the vector removes genes that are involved in evading the host immune response and are dispensable for virus replication. An expression cassette consisting of a cytomegalovirus transcriptional enhancer/promoter to drive the expression of the HA gene, a bioengineered HA gene, and a Simian Virus 40 polyadenylation signal has been inserted in place of the E1 gene sequences. Figure 1 provides a schematic diagram of the RD-Ad5 vector and identifies those sequences from the parent adenovirus genome that are retained in the vector.

Figure 1 Schematic Diagram of the Adenovirus Vector



Numbers refer to base pair# in wild-type Ad5 sequence, GenBank ID AY339865.1.

In this trial, the vector will contain a genetic insert encoding the HA surface protein antigen from an A/California/04/2009(H1N1)-like strain of influenza (AdcoCA09.HA).

NasoVAX is manufactured by propagation of the RD-Ad5 vector in replication-permissive PER.C6 cells, followed by purification of the virus from the infected cell harvest, and the final product includes the following excipients: Tris HCl (pH 7.4), histidine, sucrose, sodium chloride, magnesium chloride, polysorbate 80, ethylenediaminetetraacetic acid, and ethanol.

NasoVAX will be supplied in single-use glass vials each containing a nominal volume of 0.7 mL of a sterile, frozen suspension of vaccine formulated to deliver the nominal doses of 1×10^9 , 1×10^{10} , or 1×10^{11} vp. According to the release specifications for NasoVAX, the actual dose to be administered may be up to approximately 3-fold lower or higher than the nominal dose. The 0.5 mL NasoVAX doses will be administered as an intranasal spray using a 1 mL syringe fitted with a Teleflex LMA MAD Nasal Intranasal Mucosal Atomization Device. Further information on dose preparation and administration is provided in the pharmacy manual.

6.1.2 Placebo

The placebo is normal saline provided by the investigational site.

The 0.5 mL placebo doses will be administered as an intranasal spray using a 1 mL syringe fitted with a Teleflex LMA MAD Nasal Intranasal Mucosal Atomization Device and will be identical in appearance to NasoVAX doses. Further information on dose preparation and administration is provided in the pharmacy manual.

6.2 Labelling

All IPs will be labelled in accordance with applicable regulatory guidelines.

6.3 Storage

NasoVAX will be stored in a secure place under appropriate storage conditions at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$. Normal saline will be stored in a secure place in accordance with storage conditions on the product label.

6.4 Blinding and Unblinding

Investigators, subjects, and all study staff with direct subject contact will be blinded to assignment to NasoVAX or placebo. A designated unblinded pharmacist (or otherwise qualified person) at the site will assign the NasoVAX or placebo based on the block randomization table provided by the unblinded statistician and prepare the blinded syringe for dispensing to the subject. The individual performing these tasks will have no contact with the subjects and minimize contact with other site study personnel.

Unblinding of vaccine assignment is discouraged. In the event of a medical emergency, for which the identity of the assignment is critical to the care of a subject, the Investigator will call the Medical Monitor to discuss. In the event that unblinding is deemed necessary, a designated unblinded study team member will provide the assignment to the Medical Monitor who will provide the information to the Investigator.

Sponsor personnel and other members of the study team will have no access to data aggregated by treatment arm until after the interim analysis (see Section 12.10). Sponsor personnel and other members of the study team will have no access to any individual treatment assignment except as needed to satisfy requirements for prompt reporting of SAEs to Regulatory Authorities. In this case, unblinded data from an individual subject will be provided immediately to the Medical Monitor.

6.5 Randomization and Timing of NasoVAX/Placebo

Subjects will be enrolled into 3 sequential cohorts of 20 subjects each defined by the viral particle dose (1×10^9 , 1×10^{10} , or 1×10^{11} vp). Within each sentinel group and cohort, subjects will be randomized at a ratio of 3:1 ratio to receive 1 intranasal dose of NasoVAX or placebo on Day 1.

A sentinel cohort of 5 subjects from each cohort will be dosed. Dosing of the remainder of each cohort may proceed after the last sentinel subject completes Day 8 if no events meeting stopping criteria (Section 6.6) have occurred. The SRC, consisting of the Investigator, the Medical Monitor, and a Sponsor Representative, will review all AE, reactogenicity, and laboratory data through Day 8 for all subjects in each cohort before subjects are randomized to the next higher dose.

6.6 Stopping Criteria

If any event meeting the following criteria occurs, the SRC will review all available safety information before additional patients are dosed:

- Occurrence of any related SAE or Grade 4 AE
- Occurrence of 2 Grade 3 AEs in the same organ system
- Occurrence of the same Grade 3 laboratory abnormality in 2 or more subjects

6.7 Accountability, Dispensing, and Destruction

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 subject 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 and once all reconciliation has occurred.

6.8 Prior and Concomitant Treatments

All concomitant treatments, including over-the-counter medicines, will be recorded from 30 days before the NasoVAX/placebo dose through 28 days after the NasoVAX/placebo dose and coded using the WHO Drug Dictionary. Only immunosuppressive medication (see list in [Appendix 3](#)) and vaccines will be recorded from Day 29 to the end of the study.

6.8.1 Prohibited Prior Medications and Vaccines

Subjects who received any of the following medications and vaccines may not be enrolled:

- Corticosteroids, alkylating drugs, antimetabolites, radiation, immune-modulating biologics, or other immunosuppressive therapies within 90 days before Day 1 (see list in [Appendix 3](#))

- Immunomodulating medications, including intranasal steroids, within 30 days before Day 1
- Statin medication within 30 days before Day 1 (including atorvastatin [Lipitor], fluvastatin [Lescol, Lescol XL], lovastatin [Mevacor, Altoprev], pravastatin [Pravachol], rosuvastatin [Crestor], simvastatin [Zocor], pitavastatin [Livalo])
- Intranasal medications, including over-the-counter medications within 30 days before Day 1
- IP within 30 days before Day 1
- Any vaccine within 30 days before Day 1
- Intranasal vaccine within 90 days before Day 1
- Influenza vaccine within 6 months before Day 1

6.8.2 Prohibited Concomitant Medications and Vaccines

The following medications and vaccines are prohibited during the study:

- Statin medication from Day 1 to Day 29 (see list in Section [6.8.1](#))
- Corticosteroids, alkylating drugs, antimetabolites, radiation, immune-modulating biologics, or other immunosuppressive therapies at any time during the study (see list in [Appendix 3](#))
- Any vaccine from Day 1 to Day 29
- Any influenza vaccine other than NasoVAX within 90 days after NasoVAX/placebo dose (receipt of influenza vaccine other than NasoVAX is discouraged through the end of the study)

6.9 Contraception

All subjects must practice a highly effective method of contraception that may include, 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, surgical sterilization (hysterectomy, bilateral tubal ligation, salpingectomy, or oophorectomy), licensed hormonal methods, IUD, or consistent use of a barrier method (eg, condom, diaphragm) with spermicide through Day 29.

6.10 Compliance

All IPs will be administered by trained personnel at the investigational site.

7 STUDY ASSESSMENTS AND DATA COLLECTION

Refer to Section 1.2. for the Schedule of Events.

7.1 Demographics

Demographic data and other baseline characteristics will be obtained and recorded at Screening.

7.2 Medical History

A standard medical, medication, and surgical history will be obtained and recorded at Screening.

7.3 Reactogenicity (Diary)

Each subject will be provided with a diary and a thermometer after each dose. The subjects will record and provide severity grade (except for temperature) for the following items in a diary (sample provided in Appendix 2) and whether any medication or treatment was used for the symptom(s) daily for the first 14 days after dosing.

- Local events: nasal irritation, sneezing, nasal congestion, cough, sore throat, change in smell, change in taste, change in vision, eye pain
- Systemic events: headache, fatigue, muscle ache, nausea, vomiting, diarrhea, chills
- Oral temperature

If there are any events ongoing after the diary reporting period, these events will be followed until resolution and the stop date recorded. The Investigator (or Subinvestigator) will review the diary with the subject. Any changes or comments to the subject's diary by the Investigator (or Subinvestigator) must be made on the diary and initialed and dated by the Investigator (or Subinvestigator).

A reactogenicity event recorded on the diary will not be recorded as an AE unless it meets the criteria of an SAE.

7.4 Adverse Events (Including Medically Attended Events, Serious Adverse Events, and New-onset Chronic Illnesses)

See Section 9.

7.5 Height and Weight

Height and weight will be measured and recorded at Screening.

7.6 Complete Physical Examination

Examination of the following systems will be performed at the time points specified in the Schedule of Events and as clinically indicated: cardiovascular; dermatological; head, eyes, ear,

nose, and throat; extremities; gastrointestinal; musculoskeletal; neurological ophthalmological; neurological; respiratory.

Any clinically significant change in physical examination finding will be recorded as an AE (see Section 9.5).

7.7 Targeted and Symptom-driven Physical Examination

Examination of the respiratory and head, eyes, ear, nose, and throat systems and any additional systems as indicated by signs or symptoms reported by the subject will be performed at the time points specified in the Schedule of Events and as clinically indicated. An otorhinoscopic examination and visual examination of the nasopharynx will be conducted with findings recorded on a structured evaluation form.

Any clinically significant change in physical examination finding will be recorded as an AE (see Section 9.5).

7.8 Vital Signs

At the time points specified in the Schedule of Events and before any blood sample collection, systolic and diastolic blood pressure and pulse will be measured and recorded using a semiautomatic recording device with an appropriate cuff size after the subject has been in a supine position for at least 5 minutes. Oral temperature will also be measured. Any clinically significant abnormal vital sign value will be recorded as an AE (see Section 9.5).

7.9 Electrocardiogram

At the time points specified in the Schedule of Events and before any blood sample collection, a 12-lead ECG will be performed after the subject has been in a supine position for at least 5 minutes. Interpretation (normal, abnormal not clinically significant, abnormal clinically significant) will be recorded. Any clinically significant change in ECG interpretation will be recorded as an AE (see Section 9.5).

7.10 Blood Samples

7.10.1 Safety Laboratory Tests

Samples for the following tests will be collected, processed, and shipped to the laboratory in accordance with instructions in the laboratory manual at the time points specified in the Schedule of Events:

- Hematology: hemoglobin, platelet count, white blood cell count with differential (absolute or percent counts of neutrophils, lymphocytes, monocytes, basophils, eosinophils)
- Serum chemistry: alkaline phosphatase, ALT, AST, bicarbonate, bilirubin, chloride, creatine kinase, creatinine, glucose, potassium, sodium, urea nitrogen
- Urinalysis: glucose, protein

Any laboratory abnormality deemed clinically significant by the Investigator should be recorded as an AE (see Section 9.5).

7.10.2 Serum Samples (Immunogenicity)

Serum samples will be collected and processed at the time points specified in the Schedule of Events. Collection, processing, labelling, storage and shipping instructions for these samples are provided in the laboratory manual.

Influenza virus HAI assay against A/California/04/2009(H1N1) will be performed on all samples collected.

Ad5 microneutralization, influenza microneutralization against all strains, and HAI against nonrepresented strains will be performed on samples collected on Days 1 and 29 only. A larger serum sample will be collected on Days 1 and 29 for these assays.

7.10.3 Peripheral Blood Mononuclear Cells (Immunogenicity)

Whole blood samples will be collected and processed to isolate PBMCs at the time points specified in the Schedule of Events. Collection, processing, labelling, storage, and shipping instructions for these samples are provided in the laboratory manual.

ELISpot will be performed on all samples for measurement of T-cell activity.

7.11 Pregnancy Tests

A serum or urine sample will be collected from all women who have not been surgically sterilized or have laboratory confirmation of postmenopausal status and tested at the time points specified in the Schedule of Events.

7.12 Nasopharyngeal Swabs

A nasopharyngeal swab sample will be collected and processed at the time points specified in the Schedule of Events. Collection, processing, labelling, storage, and shipping instructions for these samples are provided in the laboratory manual. Nasopharyngeal swabs are not obtained on the day of dosing in order not to disturb the nasal mucosa. A qPCR assay for detection of the RD vector will be performed on swab samples to measure concentration of the RD vector. Once a negative result is obtained, later samples may not be tested. Screening and Day 29 samples will also be tested for influenza IgA by ELISA.

7.13 Viral Culture

A sample (as clinically indicated) for viral culture will be collected from any subject who experiences acute symptoms compatible with possible adenoviral infection within 28 days after the NasoVAX/placebo dose. The sample will be collected, processed, and shipped to the laboratory in accordance with instructions in the laboratory manual.

8 STUDY VISITS

8.1 Screening (Within 28 Days Before Day 1)

The subject will be screened to assess eligibility criteria. The following assessments and procedures will be performed:

- Written informed consent
- Demographics
- Medical history
- Concomitant medications (including vaccines) recording
- Complete physical examination
- Height and weight
- ECG
- Vital signs
- Drug and alcohol screen
- Collection of laboratory samples:
 - Hepatitis B and C and HIV tests
 - Clinical laboratory tests (hematology, serum chemistry, urinalysis)
 - Serum pregnancy test
 - Nasopharyngeal swab

8.2 Dosing Period

If at any time in the Dosing Period (Days 1 to 29) the subject experiences acute symptoms compatible with adenoviral infection, a sample for viral culture will be collected.

8.2.1 Day 1

The following procedures will be performed before NasoVAX/placebo administration:

- Concomitant medications (including vaccines) recording
- AE assessment
- Complete physical examination
- Vital signs
- Drug and alcohol screen
- Urine pregnancy test

- Sample collection:
 - Serum for humoral response (including serum for additional assays [see Section 7.10.2 and the laboratory manual for details])
 - Whole blood sample for isolation of PBMCs for cellular response
- Eligibility criteria check

Upon determination that a subject meets all eligibility criteria, the subject will be **randomized** to treatment assignment (as described in Section 6.5) and NasoVAX/placebo administered. The subject will be instructed not to blow his/her nose for 30 minutes after dosing.

The following procedures will be performed 2 hours after NasoVAX/placebo administration:

- Targeted and symptom-driven physical examination
- Vitals signs

Before discharge from the unit, the subject will be given a diary and instructed to record temperature, local events, and systemic events at the same time today and each day and whether any medication or treatment was used for the symptom(s) for the next 14 days. The subject will also be instructed that, if any event is ongoing for more than 14 days after the dose, to follow the event until resolution and report the stop date. The subject will be instructed to bring the diary back to the unit at the next visit.

Before discharge from the unit, the following procedures will also be performed.

- Concomitant medications recording
- AE assessment

8.2.2 Day 2 (Telephone Contact)

The following procedures will be performed:

- Review of diary
- Concomitant medications (including vaccines) recording
- AE assessment

8.2.3 Day 4 (\pm 1 Day)

The following procedures will be performed:

- Review of diary
- Targeted and symptom-driven physical examination
- Vitals signs
- Concomitant medications (including vaccines) recording
- AE assessment

- Sample collection:
 - Serum for humoral response
 - Nasopharyngeal swab

8.2.4 Day 8 (± 1 Day)

The following procedures will be performed:

- Review of diary
- Targeted and symptom-driven physical examination
- Vitals signs
- Concomitant medications (including vaccines) recording
- AE assessment
- Sample collection:
 - Clinical laboratory tests (hematology, serum chemistry, urinalysis)
 - Serum for humoral response
 - Whole blood sample for isolation of PBMCs for cellular response
 - Nasopharyngeal swab

8.2.5 Day 15 (± 1 Day)

The following procedures will be performed:

- Review of diary
- Targeted and symptom-driven physical examination
- Vitals signs
- Concomitant medications (including vaccines) recording
- AE assessment
- Sample collection:
 - Serum for humoral response
 - Nasopharyngeal swab

8.2.6 Day 29 (± 3 Days)

The following procedures will be performed:

- Targeted and symptom-driven physical examination
- Vitals signs
- Concomitant medications (including vaccines) recording

- AE assessment
- Urine pregnancy test
- ECG
- Sample collection:
 - Clinical laboratory tests (hematology, serum chemistry, urinalysis)
 - Serum for humoral response (including serum for additional assays [see Section 7.10.2 and the laboratory manual for details])
 - Nasopharyngeal swab

8.3 Follow-up Period

8.3.1 Day 91 (± 10 Days)

The following procedures will be performed:

- Recording of immunosuppressive medications (see list in [Appendix 3](#)) and vaccines
- Assessment of SAEs, MAEs, and NCIs
- Sample collection:
 - Serum for humoral response
 - Nasopharyngeal swab

8.3.2 Day 181 (± 10 Days)

The following procedures will be performed:

- Recording of immunosuppressive medications (see list in [Appendix 3](#)) and vaccines
- Assessment of SAEs, MAEs, and NCIs
- Sample collection:
 - Serum for humoral response

9 ADVERSE EVENTS

9.1 Definitions

9.1.1 *Adverse Event*

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, whether or not related to the IP.

The term AE is used to include any AE whether serious or nonserious.

9.1.2 *Medically Attended Adverse Event*

An MAE is an AE resulting in hospitalization, emergency room visit, or visit to or from medical personnel (other than routine health care visits).

9.1.3 *New-onset Chronic Illness*

An NCI is an AE that is new (ie, not present at baseline) and typically chronic. The eCRF will provide a field in which the Investigator will indicate whether or not the AE recorded is an NCI. Because of the significance of this designation for the subject's health and for evaluation of vaccine safety, NCIs are expected to be diagnoses, not symptoms, and the Investigator should record sufficient data in the source document to support the diagnosis.

9.1.4 *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 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.

If it is not certain that an event meets the above definitions of an SAE, contact the Medical Monitor to discuss.

9.2 Reporting Responsibilities and Periods

It is the responsibility of the Investigator or Subinvestigator(s) to perform periodic assessment of AEs. AEs spontaneously reported by the subject 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.

All AEs (including MAEs, NCIs, and SAEs) with onset after signing of the ICF until Day 29 will be recorded. Thereafter to the end of study, only MAEs, NCIs, and SAEs will be recorded. Data describing AEs will be recorded in the subject's medical and as appropriate, an SAE report form. SAEs will be reported to the Sponsor as described in Section 9.7.

9.3 Recording of Adverse Events

An AE should be recorded individually in the study subject's own words (verbatim) unless, in the opinion of the Investigator, clarification of the subject's verbatim language is necessary or the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease or syndrome should be named rather than each individual symptom. The AE term will subsequently be coded using MedDRA.

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 is an MAE, NCI, and or SAE will be recorded.

9.4 Assessment of Adverse Events

9.4.1 Severity

The Investigator will grade severity of AEs in accordance with Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials ([Appendix 1](#)). If an appropriate listing is not present in this table for an AE, the AE will be graded as follows:

- **Grade 1 (Mild)** – No interference with daily activity
- **Grade 2 (Moderate)** – Some interference with daily activity but medical intervention not required (eg, doctor visit and/or prescription medicine); over-the-counter medicine permitted
- **Grade 3 (Severe)** – Prevents daily activity and requires medical intervention (eg, doctor visit and/or prescription medicine)
- **Grade 4 (Potentially Life-threatening)** – Emergency room visit or hospitalization

9.4.2 Relatedness (Causality)

The Investigator will assess causality (relationship to NasoVAX/placebo) of AEs as follows:

- **Related** – Reasons to consider an AE related to treatment may include, but are not limited, to the following:
 - Timing of the event relative to the administration of the IP
 - Location of the AE relative to the site of IP administration
 - Likelihood based on experience with similar products
 - A biologically plausible explanation based on the mechanism of action or mode of delivery of the treatment
 - The AE is repeated on subsequent treatments.
 - No other explanation is likely.
- **Unrelated** – An AE with no temporal association with the IP but rather related to other etiologies such as concomitant medications or conditions or subject's known clinical state

9.5 Clinical Laboratory, Physical Examination, Electrocardiogram and Vital Sign Abnormalities

Any abnormal laboratory result, physical examination finding, ECG interpretation, or vital sign measurement considered clinically significant by the Investigator will be recorded as an AE. A clinically significant laboratory abnormality is a confirmed abnormality (by repeat test) that is changed sufficiently from screening/baseline so that in the judgment of the Investigator a change in management is warranted. This alteration may include monitoring the laboratory test further, initiating other diagnostic tests or procedures, changing ongoing treatment, or administering new treatment.

Whenever possible, the underlying medical diagnosis (eg, anemia) will be recorded as the AE term. Repeated additional assessments required to establish the significance and etiology of an abnormal result should be obtained when clinically indicated.

A reactogenicity event recorded on the diary will not be recorded as an AE unless it meets the criteria of an SAE.

9.6 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 subject'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 subject is withdrawn from the study. See Section 10 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 subject is always considered an SAE.

9.7 Reporting of Serious Adverse Events

SAEs must be reported to the Sponsor or designee within 1 business day of becoming aware of the event. 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).

After review of an SAE report, the Medical Monitor may request additional documentation (eg, clinic or hospital records or procedure reports).

9.8 Follow-Up of Adverse Events

A subject who experiences any AE, whether serious or not serious, will be monitored at appropriate intervals and receive appropriate treatment and medical supervision as clinically indicated. All AEs must be followed until resolution/stabilization or until a time that is mutually agreed upon between the Medical Monitor and the Investigator. Clinically significant laboratory abnormalities should be confirmed within 48 hours or as soon as clinically indicated and then followed weekly or as clinically indicated until resolution.

10 PREGNANCY

The ICF will include information regarding reporting of pregnancy to the Sponsor and collection of information through the end of pregnancy that occurs in either a female subject or in a female partner of a male subject. If a female partner becomes pregnant, the Investigator will request consent from the partner to collect this information.

Any pregnancy in a subject or in a subject's partner and the subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) will be reported to the Sponsor.

If a subject becomes pregnant during the study, she should be encouraged to complete all scheduled follow-up unless there is a medical contraindication.

11 SUBJECT AND STUDY DISCONTINUATION

11.1 Subject Withdrawal from the Study

Subjects may be withdrawn from the study at any time for the following reasons:

- Withdrawal of consent
- Noncompliance with study requirements
- Loss to follow-up
- Death
- Investigator discretion
- Sponsor request
- Termination of the study by the Sponsor (see Section 11.3).

Subjects that are withdrawn from the study will not be replaced.

11.2 Procedures for Subjects Who Terminate the Study Early

Any subject who prematurely discontinues the study should be followed-up for at least 28 days after the last dose of any IP.

If a subject prematurely discontinues the study on or before Day 29, then the procedures listed for Day 29 visit (Section 8.2.6) should be performed at the Early Termination Visit. If the subject is unwilling to return to the site for a visit, site staff will contact the subject by telephone to collect information about any AEs that have occurred since the last visit.

If a subject prematurely discontinues the study after Day 29, site staff will contact the subject once by telephone to collect information about any MAEs, NCIs, or SAEs, that have occurred since the last visit.

11.3 Study Discontinuation

The entire study may be discontinued by the Sponsor for reasons including, but not limited to, the following:

- An unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- Lack of evaluable or complete data
- Decision to modify the NasoVAX development plan or to suspend or discontinue NasoVAX development
- Medical or ethical reasons affecting the continued performance of the study
- Difficulty in recruitment of subjects

12 STATISTICAL METHODS

This section includes a brief description of the statistical analyses that will be performed in this study. A detailed statistical analysis plan (SAP) will be written and finalized before database snapshot for the interim analysis. Any deviation from the SAP will be described in the Clinical Study Report (CSR). All descriptive statistical analyses will be performed using SAS statistical software Version 9.2 or higher, unless otherwise noted.

12.1 Analysis Populations

The following analysis populations will be used:

- Safety Population: All subjects who provide informed consent, are randomized, and receive at least 1 dose of IP. The Safety Population will be used for all safety analyses and will be analyzed according to the treatment received.
- ITT Population: All subjects in the Safety Population who have HAI assay results on Day 1 and any postvaccination time point. The ITT Population is the secondary population for immunogenicity analyses and will be analyzed according to treatment as randomized.
- PP Population: All subjects in the Safety Population that received the assigned dose of the test article in accordance with the protocol; have HAI assay results on Days 1, 15, and 29; and had no major protocol deviations affecting the primary immunogenicity outcomes as determined by the Sponsor prior to database lock. The PP Population is the primary population for immunogenicity analyses and will be analyzed as randomized.

12.2 Analysis Conventions

For all data analyses and summary tabulations, categories for analysis and presentation are the NasoVAX and placebo groups.

Baseline is defined as the last nonmissing measurement prior to the administration of IP.

Continuous variables will be presented by geometric means and 95% CIs for the immunogenicity endpoints and by summary statistics (eg, mean, and standard deviation [SD]) for other endpoints. Categorical variables will be presented by frequency distributions (percentages and 95% CIs) for the immunogenicity endpoints and frequency counts and percentages for other endpoints.

12.3 Subject Disposition

The number and percentage of subjects enrolled in the study, completing the study, and discontinuing the study will be presented in a tabular format. Reasons for discontinuation will also be summarized.

Listings of randomized subjects who did not receive the IP and of subjects with other important protocol deviations (to be defined in the SAP, will be provided).

All analysis populations will be defined, and full descriptions of each population will be provided.

12.4 Demographic and Baseline Characteristics

Demographic parameters and other baseline characteristics (age, gender, race, ethnicity, body mass index) will be summarized by dose group for all subjects in the Safety Population.

12.5 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by WHO Drug Dictionary anatomical therapeutic chemical level 3 and preferred term.

12.6 Exposure

All IP doses will be summarized.

12.7 Safety Analyses

The primary endpoint for evaluation of the safety profile is the number and percentage (95% CI) of subjects with solicited and unsolicited AEs recorded postvaccination. Safety analyses will be performed using the Safety Population.

12.7.1 Primary Endpoints

Reactogenicity

The number (percentage, 95% CI) of subjects with local reactions and systemic events will be summarized by dose group and overall. Reactogenicity events will also be summarized by severity.

Adverse Events

The number (percentage, 95% CI) of subjects with AEs from Day 1 to Day 29 (including MAEs, NCIs, SAEs) will be summarized for each MedDRA system organ class and preferred term and by dose group and overall. The number (percentage) of subjects with MAEs, with NCIs, and with SAEs from Day 1 to Day 181 will be summarized in a similar fashion. The number (percentage, 95% CI) of subjects with AEs by severity and by relationship to IP will also be summarized.

Listings of AEs, MAEs, NCIs, and SAEs will be provided.

12.7.2 Clinical Laboratory Tests and Vital Signs

Summary statistics for continuous parameters will be presented by dose group as follows: prevaccination, postvaccination, and change from prevaccination to postvaccination assessment.

The number and percentage of subjects with postvaccination clinical laboratory values or vital sign values recorded as newly abnormal (ie, an event with an increase in the toxicity grade

relative to the baseline value and with a severity grade of moderate or higher) after study vaccination will be tabulated. Shift tables which cross-tabulate the prevaccination and postvaccination clinical laboratory values of each subject by severity grade will be prepared.

12.7.3 Electrocardiograms

Summaries of the number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant interpretations will be presented.

12.7.4 Shedding of Replication-deficient Vector

Data will be summarized by count and percent positive by time point, along with median copy number.

12.7.5 Laboratory-confirmed Adenovirus Infection

Viral culture results will be listed.

12.8 Immunogenicity Analyses

Immunology analyses will be conducted using the ITT and PP Populations with primary conclusions drawn from the PP Population. Analyses based on the ITT Population will be undertaken and presented only if >5% of subjects in any 1 dose group were excluded from the PP Population. No imputation for missing data will be performed. Data will be transformed as appropriate prior to analysis.

Baseline is defined as the sample collected prior to IP administration on Day 1.

12.8.1 Secondary Endpoints (Humoral Immune Response)

The primary variable of interest for assessment of humoral immune response to the NasoVAX antigen is homologous HAI antibody titer. The following HAI immunogenicity measures and their 95% CIs will be summarized by dose group:

- GMT at baseline and postvaccination on Days 4, 8, 15, 29, 91, and 181
- GMR on Days 4, 8, 15, 29, 91, and 181 (analysis of GMR will be performed using analysis of covariance [ANCOVA] with baseline titer as a covariate)
- SPR on Days 4, 8, 15, 29, 91, and 181
- SCR on Days 4, 8, 15, 29, 91, and 181

12.8.2 Exploratory Endpoints

Humoral Immune Response

Humoral immune response (antibody level measured by microneutralization in serum) will be summarized by GMT at baseline and postvaccination on Day 29 and responder rate (the proportion of subjects with 2-fold and 4-fold rise since baseline) (95% CI) on Day 29.

Cellular Immune Response

Cellular responses (ELISpot SFUs to influenza HA peptides) will be summarized by geometric mean at baseline and postvaccination on Day 8 and responder rate on Day 8.

Mucosal Immune Response

Mucosal responses (IgA to influenza HA peptides by ELISA) will be summarized by geometric mean at baseline and postvaccination on Day 29 and responder rate on Day 29.

Humoral Immune Response to Nonrepresented Influenza Strains

Humoral immune response to nonrepresented influenza strain antigens (antibody level measured by HAI and microneutralization in serum) against each strain tested will be summarized by GMT at baseline and postvaccination on Day 29; GMR postvaccination on Day 29; and responder rate (the proportion of subjects with 2-fold and 4-fold rise since baseline) on Day 29.

Effect of Predose Adenovirus Serotype 5 Serum Antibody Levels on Immunogenicity

For the effect of predose Ad5 serum antibody levels on immunogenicity of NasoVAX on Day 29, analysis will be performed using ANCOVA, with baseline Ad5 titer as a covariate.

Comparison to Licensed Seasonal Influenza Vaccine

Immunogenicity results from samples collected in this study will be compared to those from banked samples from a previous study of licensed seasonal vaccine in a similar subject population using a 2-sample comparison of means or nonparametric tests as indicated.

12.9 Sample Size and Power

The sample size for this study was selected as adequate and reasonable for an initial review of the safety and immunogenicity profile of the NasoVAX at doses to be well tolerated by young adults, rather than for statistical power. The sample size will permit initial estimates of reactogenicity. Given a total of 45 subjects receiving NasoVAX, the study will have an 80% probability of detecting at least 1 AE which occurs at a rate of 3.6%. If no SAEs are observed among the 45 subjects who receive NasoVAX, an approximation to the 1-sided upper bound of the 90% CI on the rate of SAE occurrence would be 5%.

12.10 Interim and Final Analyses

One interim analysis of humoral immunogenicity data and safety data (including summaries of AE, reactogenicity, concomitant medications and vaccines, vital signs, ECG, and laboratory data and listing of any viral culture results) will be conducted when all data through the Day 29 visit are available, monitored, and confirmed by the Investigator for all subjects. The purpose of this review is to plan future studies and adjust the clinical development plan accordingly.

An unblinded team composed only of members not otherwise involved in the study, will perform the interim analysis. All other study personnel including Investigators and investigational site staff and Sponsor staff and contractors will remain blinded to individual treatment assignments until database lock for final analysis.

Safety and immunogenicity analyses from the interim review may be presented in an interim statistical report drafted by the Sponsor. Data therein will be used to support development and planning of future studies, and may be submitted to the Center for Biologics Evaluation and Research and other Regulatory Authorities as needed.

The final CSR will include all study data through the end of study.

13 ETHICAL, LEGAL, AND ADMINISTRATIVE ISSUES

The procedures set out in this study protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and the Investigator abide by Good Clinical Practice (GCP) as described in International Council for Harmonisation (ICH) Guideline E6 and with all relevant laws. Compliance with these regulations also constitutes compliance with the ethical principles that have their origins in the Declaration of Helsinki.

13.1 Institutional Review Board Approval

The protocol, the ICF, any advertisement, or any other written information provided to the subject will be reviewed and approved by the Institutional Review Board (IRB). The Sponsor will supply relevant material for the Investigator to submit to the IRB for the study's review and approval.

The IRB will be informed of amendments to the study protocol, ICF, advertisement, or written information provided to the subject. Such amendments may not be implemented until approval by the IRB except when necessary to eliminate immediate hazards to the subjects.

The IRB will be provided with reports at the interval required (not to exceed 1 year) and a report after the completion or discontinuation of the Investigator's participation in the study.

13.2 Informed Consent

The Investigator (or designee) will explain the nature of the study to each subject. The subjects will be informed that participation is voluntary and that they can withdraw from the study at any time. After the study has been fully explained, each subject will provide written informed consent to study participation. The informed consent process will be documented by the use of a written ICF approved by the IRB and signed by the subject before protocol-specific procedures are performed.

A copy of the ICF will be given to the subject, and the original ICF will be maintained with the subject's study records.

13.3 Biological Samples

Biological samples collected for this study will become the property of the Sponsor and may be used for future research conducted by or on behalf of the Sponsor or its affiliates, partners, or collaborators. No identifiable personal information will be associated with these blood samples. Any samples remaining 15 years after the end of the study will be destroyed.

Subjects who provide informed consent for the study will be informed that any residual samples may be retained for as yet undetermined additional testing. These tests may include human leukocyte antigen typing of the PBMC samples. Subjects will be asked explicitly to consent for such sample retention and potential future genetic research on their blood samples.

A subject who is unwilling to have blood samples stored for future use can consent to participate in this study without having blood samples stored for future testing. In this case, the subject's blood samples will be destroyed after all the tests specified for this study have been concluded.

A subject can withdraw consent for sample retention at any time, in which case the samples will be destroyed and no further testing will take place. To initiate the sample destruction process, the Investigator must notify the Sponsor about the withdrawal of consent for the storage of samples for future use and request sample destruction.

13.4 Confidentiality

Personal study subject data collected and processed for the purposes of this study will be managed by the Investigator and the investigational site staff with adequate precautions to ensure the confidentiality of these data, and in accordance with applicable laws and regulations on personal data protection. Each subject's identity and personal data will remain confidential in the CSR, any presentation of the results of this study at meetings, or any publication.

13.5 Protocol Compliance

The Investigator should conduct the trial in compliance with the approved protocol. The Investigator must not make any changes to the study without Sponsor and IRB approval except when necessary to eliminate apparent immediate hazards to the subjects. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, but the change must then be documented in an amendment, reported to the IRB within 3 working days, and submitted to the appropriate Regulatory Authority in the required time frame. The Investigator is responsible for abiding by the IRB's rules and regulations for reporting protocol deviations. A Protocol Deviation Log will be created by the Investigator, and the Investigator will document and explain any deviation from the approved protocol on this log. The Protocol Deviation Log will be maintained in the study file.

13.6 Protocol Amendments

Any significant change in the study requires a protocol amendment. All protocol amendments must be reviewed and approved by the Sponsor, the Investigator, and the IRB before implementation.

13.7 Publication and Disclosure Policy

All information provided regarding the study, as well as all information collected or 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.

The publication and disclosure policy will be addressed in a separate clinical trial agreement.

13.8 Clinical Study Report

A final CSR will be prepared in accordance with the ICH guideline on structure and contents of CSRs and any applicable regulatory and legal requirements.

13.9 Financing and Insurance

Financing and insurance will be addressed in a separate clinical trial agreement.

14 STUDY DATA AND RECORDS

14.1 Direct Access

The Investigator will grant direct access to the monitors, auditors, and other authorized representatives of the Sponsor; the IRB approving this research; and any applicable Regulatory Authorities to the study subjects' original medical records for verification of clinical trial conduct and data.

14.2 Source Documents

Source documents are defined as the original documents (or certified copies) of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. All source documents produced in this study will be maintained by the Investigator and made available to the Sponsor's representatives, the IRB, and any applicable Regulatory Authorities.

14.3 Case Report Forms

An electronic case report form (eCRF) will be used to record all subject data specified by this protocol into an electronic data capture (EDC) system. It is the responsibility of the Investigator to ensure the subject data are entered in an accurate and timely manner.

14.4 Study Monitoring

Before the start of the study, the Sponsor's monitor will meet with the Investigator and appropriate investigational site staff for training on the protocol requirements and procedures.

Throughout the course of the study, the Sponsor's monitor will conduct site visits to verify that the rights and well-being of the subjects are protected; the reported trial data are accurate, complete, and verifiable from source documents; and that the conduct of the trial is in compliance with the currently approved protocol, GCP, and applicable regulatory and legal requirements. An unblinded monitor will also visit the site to review IP accountability.

14.5 Data Management

The study data will be using an EDC system. The Investigator and study site staff will receive system training and support. All protocol-required information collected during the study must be entered by the Investigator or designated representative in the eCRF. All data entries, modifications, or deletions will be recorded automatically in an electronic audit trail indicating the individual subject, original value, new value, reason for change, who made the change, and when the change was made. All data changes will be clearly indicated with a means to locate prior values. The system will be secured to prevent unauthorized access to the data or the system. This security will include the requirement for a user ID and password to enter or change data. The Investigator will maintain a list of individuals who are authorized to enter or correct data and their user IDs.

All electronic data entered by the site (including an electronic audit trail) as well as computer software (for accessing the data) will be maintained or made available at the site in compliance with applicable record retention regulations. The computerized system will be able to generate accurate and complete copies of records in both human-readable and electronic form for inspection, review, and copying by Regulatory Authorities, the IRB, or an auditor authorized by the Sponsor. Site documentation will identify the software systems used to create, modify, maintain, archive, retrieve, or transmit data.

After review of the data in the eCRF, the Investigator or designated Subinvestigator will confirm the validity of each subject's data.

14.6 Retention of Records

ICH-GCP requires that documents be retained until at least 2 years after the last approval of a marketing application in an ICH region and there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. Study records will be maintained in accordance with these requirements and any applicable laws.

No study records will be destroyed without prior authorization from the Sponsor.

15 REFERENCES

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16 APPENDICES

Appendix 1 Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Vital Signs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Fever (°C) (°F)	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 - 3 loose stools or < 400 gms/24 hours	4 - 5 stools or 400 - 800 gms/24 hours	6 or more watery stools or > 800 gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Systemic Illness	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

Serum Laboratory Abnormalities	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Sodium – hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – hyperglycemia				Insulin requirements or hyperosmolar coma
Fasting – mg/dL	100 – 110	111 – 125	>125	
Random – mg/dL	110 – 125	126 – 200	>200	
Blood urea nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorus – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Albumin – hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in liver function test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when liver function test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

Hematology Laboratory Abnormalities	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Hemoglobin (female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC increase - cell/mm ³	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	> 25,000
WBC decrease - cell/mm ³	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes decrease - cell/mm ³	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils decrease - cell/mm ³	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm ³	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets decreased - cell/mm ³	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

Urine Laboratory Abnormalities	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) - red blood cells per high power field (rbc/hpf)	1 - 10	11 - 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

Appendix 2 Sample Subject Diary



PROTOCOL NUMBER: ALT-103-201

**Single-ascending-dose Study of the Safety and Immunogenicity of
NasoVAX**

SUBJECT DIARY

Dispensed Date _____

Influenza Vaccine, Intranasal (NasoVAX)

SITE NUMBER: _____

SUBJECT NUMBER: _____ - _____ SUBJECT INITIALS: _____

SUBJECT DIARY

DIARY INSTRUCTION

This diary is for you to use to record body temperature and other reactions, beginning after you receive the study vaccination. Please complete the diary card (using indelible ink only) and bring it at each visit.

- Please complete the diary at about the same time every day (after 4 PM)
- Enter date in the following format: **MM/DD/YYYY**
- Take your temperature (thermometer in your mouth) and record it in **Fahrenheit**
- Use the **Severity Rating Guideline** provided on page 5 to rate and evaluate severity scale of each symptom on the diary from 0-4 (Check **ONLY** one option). If you have questions about any of these ratings, please ask the study team.
- Check '**Yes**' or '**No**' for medication/treatment taken for symptoms and the study nurse will collect details at your next visit

Also be prepared to discuss any other health issues you may experience with the study nurse at each visit.

If you develop serious symptoms, have a significant illness or injury with emergency room or hospital care during the research study, ***please contact:***

Clinical site phone number: _____ - _____ - _____

If you need to be seen immediately by a physician, please contact your primary-care physician or visit your nearest emergency room as soon as possible.

DAY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
DATE															
TEMP (°F)															
Headache	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4
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Diarrhea	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4

DAY	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Chills	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0
	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1
	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2
	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3
	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4
Nasal Irritation	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0
	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1
	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2
	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3
	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4
Sneezing	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0
	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1
	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2
	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3
	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4
Nasal Congestion	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0
	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1
	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2
	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3
	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4
Cough	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0
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	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2
	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3
	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4
Sore Throat	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0
	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1
	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2
	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3
	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4
Change In Smell	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0
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	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2
	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3
	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4
Change In Taste	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0	<input type="checkbox"/> =0
	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1	<input type="checkbox"/> =1
	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2	<input type="checkbox"/> =2
	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3	<input type="checkbox"/> =3
	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4	<input type="checkbox"/> =4

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Change In Vision	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4	<input type="checkbox"/> = 0 <input type="checkbox"/> = 1 <input type="checkbox"/> = 2 <input type="checkbox"/> = 3 <input type="checkbox"/> = 4
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Medication or Treatment Taken?	<input type="checkbox"/> = Yes <input type="checkbox"/> = No	<input type="checkbox"/> = Yes <input type="checkbox"/> = No	<input type="checkbox"/> = Yes <input type="checkbox"/> = No	<input type="checkbox"/> = Yes <input type="checkbox"/> = No	<input type="checkbox"/> = Yes <input type="checkbox"/> = No	<input type="checkbox"/> = Yes <input type="checkbox"/> = No	<input type="checkbox"/> = Yes <input type="checkbox"/> = No	<input type="checkbox"/> = Yes <input type="checkbox"/> = No	<input type="checkbox"/> = Yes <input type="checkbox"/> = No	<input type="checkbox"/> = Yes <input type="checkbox"/> = No	<input type="checkbox"/> = Yes <input type="checkbox"/> = No	<input type="checkbox"/> = Yes <input type="checkbox"/> = No	<input type="checkbox"/> = Yes <input type="checkbox"/> = No	<input type="checkbox"/> = Yes <input type="checkbox"/> = No	

SEVERITY RATING GUIDELINE					
Grade	0	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Potentially Life Threatening)
Headache	None	No interference with daily activity	Interferes with daily activity or bad enough to take non-narcotic medicine	Prevents daily activity or required narcotic pain medicine	So bad that required ER visit or hospitalization
Fatigue	None	No interference with daily activity	Some interference with daily activity	Prevents daily activity	So bad that required ER visit or hospitalization
Muscle Ache	None	No interference with daily activity	Some interference with daily activity	Prevents daily activity	So bad that required ER visit or hospitalization
Nausea	None	No interference with daily activity	Some interference with daily activity	Prevents daily activity	So bad that required ER visit or hospitalization
Vomiting	None	1-2 episodes past 24h OR No interference with daily activity	More than 2 episodes OR Some interference with daily activity	Prevents daily activity OR Requires outpatient IV hydration	So bad that required ER visit or hospitalization
Diarrhea	None	2-3 loose stools past 24 h	4-5 stools past 24h	6 or more stools past 24h OR outpatient IV hydration	So bad that required ER visit or hospitalization
Chills	None	Felt cold, mild shivering	Shaking chills 1-2 episodes	3 or more episodes of shaking chills	So bad that required ER visit or hospitalization

Nasal Irritation	None	Not interfering with daily activity	Bothersome enough to interfere with daily activity or treated with medication	Severe enough to prevent daily activity	So bad that required ER visit or hospitalization
Sneezing	None	Not interfering with daily activity	Bothersome enough to interfere with daily activity or treated with medication	Severe enough to prevent daily activity	So bad that required ER visit or hospitalization
Nasal Congestion	None	Not interfering with daily activity	Bothersome enough to interfere with daily activity or treated with medication	Severe enough to prevent daily activity	So bad that required ER visit or hospitalization
Cough	None	Not interfering with daily activity	Bothersome enough to interfere with daily activity or treated with medication	Severe enough to prevent daily activity or interfere with breathing or eating	So bad that required ER visit or hospitalization
Sore Throat	None	Not interfering with daily activity	interferes with eating or other daily activity OR requires medication	Prevents daily activity OR requires narcotic medication	So bad that required ER visit or hospitalization
Change in Smell	None	Not interfering with daily activity	Bothersome enough to interfere with daily activity or treated with medication	Unable to distinguish odors even after decongestant medication	So bad that required ER visit or hospitalization
Change in Taste	None	Not interfering with daily activity	Affects enjoyment of meals or other interference with daily activity	Prevents ability to eat	So bad that required ER visit or hospitalization
Change in Vision	None	Brief episode of mild blurring, floaters etc. that does not interfere with activity	Sustained visual disturbance or interference with daily activity	Loss of vision even if transient or visual symptoms that prevent daily activity	So bad that required ER visit or hospitalization
Eye Pain	None	No interference with daily activity	Interferes with daily activity or bad enough to take non-narcotic medicine	Prevents daily activity or required narcotic pain medicine	So bad that required ER visit or hospitalization

Appendix 3 Immunosuppressive Medications

Corticosteroids

- prednisone (Deltasone, Orasone)
- budesonide (Entocort EC)
- prednisolone (Millipred)

Calcineurin inhibitors

- cyclosporine (Neoral, Sandimmune, SangCya)
- tacrolimus (Astagraf XL, Envarsus XR, Prograf)

Mechanistic target of rapamycin (mTOR) inhibitors

- sirolimus (Rapamune)
- everolimus (Afinitor, Zortress)

Inosine monophosphate dehydrogenase (IMDH) inhibitors

- azathioprine (Azasan, Imuran)
- leflunomide (Arava)
- mycophenolate (CellCept, Myfortic)

Biologics

- abatacept (Orencia)
- adalimumab (Humira)
- anakinra (Kineret)
- certolizumab (Cimzia)
- etanercept (Enbrel)
- golimumab (Simponi)
- infliximab (Remicade)
- ixekizumab (Taltz)
- natalizumab (Tysabri)
- rituximab (Rituxan)
- secukinumab (Cosentyx)
- tocilizumab (Actemra)
- ustekinumab (Stelara)
- vedolizumab (Entyvio)

Monoclonal antibodies

- basiliximab (Simulect)
- daclizumab (Zinbryta)
- muromonab (Orthoclone OKT3)

Appendix 4 Protocol Amendments: Summary of Changes

The first version of this Clinical Trial Protocol implemented was Version 3.0 Amendment 2 (31 July 2017). Significant changes (changes other than clerical changes) after this version are summarized below.

Amendment 3 (Version 4.0, 05 October 2017)

Section(s)	Change	Rationale
1.1, 4.1, 7.3, 8.2.1, Appendix 2	Change to diary format and addition of collection of data on medication and treatment	FDA request
1.1, 4.1	Addition: "At each visit, the subject will also be asked about the interim medical history and use of any medications."	Clarity
5.2	Clarification of Exclusion Criterion 27	Clarity
6.4, 12.10	Clarification that individual treatment assignments will remain blinded	Clarity
6.9	Addition of salpingectomy and oophorectomy as acceptable contraception methods as stated in inclusion criteria	Consistency
7.3	Exclusion of temperature as item graded by the subject in the diary	Clarity
11.2	Clarification of study termination procedure for subject discontinuing on Day 29	Clarity
12.10	Addition of requirement for Investigator confirmation of data for interim analysis dataset	Completeness