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

**Protocol:** ALT-103-201

**Compound:** NasoVAX (Influenza vaccine, intranasal)

**Phase:** 2a

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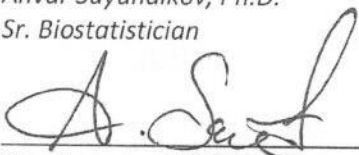


**AD ST-07**  
**Statistical Analysis Plan Approval Form**

**Sponsor:** Altimmune, Inc.  
**Protocol:** ALT-103-201  
**Protocol Title:** Single-ascending-dose Study of the Safety and Immunogenicity of NasoVAX  
  
**SAP Version:** Final V1.0  
**SAP Date:** 07MAR2018


The statistical analysis plan has been reviewed and approved.

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07 MAR 2018  
Date

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## 1 List of Abbreviations and Definition of Terms

Only abbreviations and terms relevant to the SAP are repeated herein. The reader is referred to the protocol for the complete and comprehensive list of abbreviations and definitions of terms for the study.

Abbreviation/Term	Definition
Ad5	Adenovirus Serotype 5
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
DLT	Dose-limiting Toxicity
ECG	Electrocardiogram
eCRF	Electronic Care Report Form
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
ELISpot	Enzyme-linked Immunosorbent Spot Assay
FDA	Food and Drug Administration
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HA	Hemagglutinin
HAI	Hemagglutination Inhibition
HIV	Human Immunodeficiency Virus
IgA	Immunoglobulin A
ITT	Intent-to-treat
LLOQ	Lower Limit of Quantification
MAE	Medically Attended Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
MN	Microneutralization
NCI	New-onset Chronic Illness
PBMC	Peripheral Blood Mononuclear Cells

Abbreviation/Term	Definition
PP	Per-protocol
PT	Preferred Term
qPCR	Quantitative Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCR	Seroconversion Rate
SD or sd	Standard Deviation
SDTM	Study Data Tabulation Model
SFU	Spot-forming Unit
SOC	System Organ Class
SPR	Seroprotection Rate
SRC	Safety Review Committee
TEAE	Treatment Emergent Adverse Event
TFL	Tables, Figures, and Listings
vp	Viral Particles
WHO	World Health Organization

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## 2 Introduction

This document presents a statistical analysis plan (SAP) for Altimune, Inc. Protocol ALT-103-201, Single-ascending-dose Study of the Safety and Immunogenicity of NasoVAX.

Reference materials for this statistical plan include the Protocol ALT-103-201 Version 4.0 (dated 05 October 2017) and Electronic Case Report Forms (eCRF) (dated 02 September 2017).

Additionally, this plan incorporates a previous Phase 4 study of licensed seasonal vaccine in a similar subject population, ALT-FLZ-401, Extent and Durability of Immune Response Following Seasonal Influenza Vaccination in Healthy Volunteers. The reference materials for the comparison study include the Protocol ALT-FLZ-401 Version 1.0 (dated 26 April 2017) and eCRF (dated 02 May 2017). Disposition, demographic, and immunogenicity data from ALT-FLZ-401 will be included in the summaries described below.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analyses of data pertaining to the Altimune, Inc. study ALT-103-201. This statistical plan disallows any analyses to be performed for any purpose prior to the unblinding of final study data and the submission to file of the final version of this plan. SAS programming may occur as study data accumulate in order to have analysis programs ready at the time the study finishes. In such an event, arbitrary dose group assignments must be randomly linked to subjects, effectively rendering any output of programs meaningless. For the reasons stated here the conduct of the study in the field is considered to be independent of any study outcome that might materialize upon enactment of the currently proposed statistical plan.

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### 3 Study Objectives and Endpoints

OBJECTIVES	ENDPOINTS
<b>Primary Objective</b>	
<ul style="list-style-type: none"> <li>To describe the safety profile of NasoVAX in healthy adults when administered by intranasal spray at a single dose of <math>1 \times 10^9</math>, <math>1 \times 10^{10}</math>, or <math>1 \times 10^{11}</math> viral particles (vp)</li> </ul>	<ul style="list-style-type: none"> <li>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</li> <li>Adverse Events (AEs): counts and percentages of subjects with AEs from Day 1 to Day 29; medically attended adverse events (MAEs), serious adverse events (SAEs), new-onset chronic illness (NCI) from Day 1 to Day 181</li> </ul>
<b>Secondary Objective</b>	
<ul style="list-style-type: none"> <li>To evaluate the humoral immune response to NasoVAX when administered by intranasal spray at a single dose of <math>1 \times 10^9</math>, <math>1 \times 10^{10}</math>, or <math>1 \times 10^{11}</math> vp</li> </ul>	<ul style="list-style-type: none"> <li>Antibody level measured by hemagglutination inhibition (HAI) in serum: <ul style="list-style-type: none"> <li>Geometric mean titer (GMT): the antilog of the mean of the log-transformed titers</li> <li>Geometric mean ratio (GMR): the ratio of postvaccination and prevaccination GMTs within the same dose group</li> <li>Seroprotection rate (SPR): the percentage of subjects with a HAI titer <math>\geq 1:40</math></li> <li>Seroconversion rate (SCR): the percentage of subjects with either a baseline HAI titer <math>&lt; 1:10</math> and a postvaccination titer <math>\geq 1:40</math> (which is 4 times the assay lower limit of quantitation), or a baseline HAI titer <math>\geq 1:10</math> and a 4-fold increase in postvaccination HAI titer relative to baseline</li> </ul> </li> <li>Antibody level measured by microneutralization (MN) in serum: <ul style="list-style-type: none"> <li>GMT</li> <li>Responder rate: the proportion of subjects with 2-fold and 4-fold rise since baseline</li> </ul> </li> </ul>

OBJECTIVES	ENDPOINTS
Exploratory Objectives	
<ul style="list-style-type: none"> <li>To evaluate the cellular immune response to NasoVAX when administered by intranasal spray at a single dose of <math>1 \times 10^9</math>, <math>1 \times 10^{10}</math>, or <math>1 \times 10^{11}</math> vp</li> </ul>	<ul style="list-style-type: none"> <li>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"> <li>Geometric mean SFUs</li> <li>Responder rate: the number and percentage of subjects with 3-fold rise since baseline and 25 SFU/million cells greater than baseline</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>To evaluate the mucosal immune response NasoVAX when administered by intranasal spray at a single dose of <math>1 \times 10^9</math>, <math>1 \times 10^{10}</math>, or <math>1 \times 10^{11}</math> vp</li> </ul>	<ul style="list-style-type: none"> <li>Immunoglobulin A (IgA) antibody level measured by enzyme-linked immunosorbent assay (ELISA): <ul style="list-style-type: none"> <li>GMT</li> <li>GMR</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>To evaluate the humoral immune response against nonrepresented influenza strains after NasoVAX administration</li> </ul>	<ul style="list-style-type: none"> <li>Antibody level measured by HAI and MN in serum against each strain tested: <ul style="list-style-type: none"> <li>GMT</li> <li>GMR</li> <li>Responder rate: the number and percentage of subjects with 2-fold and 4-fold rise since baseline</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>To evaluate the effect of predose adenovirus serotype 5 (Ad5) serum antibody levels on the immunogenicity of NasoVAX</li> </ul>	<ul style="list-style-type: none"> <li>Predose Ad5 antibody GMT measured by MN in serum</li> <li>Day 29 GMR and responder rate from antibody level measured by HAI in serum</li> </ul>
<ul style="list-style-type: none"> <li>To compare immunogenicity results to those obtained from banked samples from a previous study of licensed seasonal vaccine in a similar subject population (ALT-FLZ-401)</li> </ul>	<ul style="list-style-type: none"> <li>Antibody level measured by HAI in serum: <ul style="list-style-type: none"> <li>GMT</li> <li>GMR</li> <li>SPR</li> <li>SCR</li> </ul> </li> <li>Antibody level measured by MN in serum: <ul style="list-style-type: none"> <li>GMT</li> <li>Responder rate</li> </ul> </li> <li>SFUs to hemagglutinin peptides measured by ELISpot in PBMCs: <ul style="list-style-type: none"> <li>Geometric mean SFUs</li> <li>Responder rate</li> </ul> </li> <li>IgA antibody level measured by ELISA: <ul style="list-style-type: none"> <li>GMT</li> <li>GMR</li> </ul> </li> </ul>



## 4 Study Design

Study ALT-103-201 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 ( $1 \times 10^9$ ,  $1 \times 10^{10}$ , and  $1 \times 10^{11}$  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 4-1.

**Table 4-1 NasoVax Study Design**

Cohort	Dose (vp)	Number of Subjects	
		NasoVAX	Placebo
1	$1 \times 10^9$	15	5
2	$1 \times 10^{10}$	15	5
3	$1 \times 10^{11}$	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 Safety Review Committee (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, using the Food and Drug Administration (FDA) toxicity grading scale [1]:

- 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 local events, systemic events, and oral temperature 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.

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, MN 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.

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 (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 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.

A complete schedule of procedures and assessments for study ALT-103-201 is in Table 4-2.

ALT-FLZ-401, Extent and Durability of Immune Response Following Seasonal Influenza Vaccination in Healthy Volunteers, was an open label study designed to generate an immunogenicity sample set similar to that of ALT-103-201 in subjects receiving a licensed influenza vaccine based on the same H1 strain (A/California 2009). The seasonal vaccine H1 component changed at the time of the ALT-103-201 study to A/Michigan, so it was logistically much easier to conduct this study non-contemporaneously with the seasonal vaccine licensed for use in 2016-17. The same site, entry criteria and schedule of assessments for immunogenicity were followed. Twenty subjects were enrolled and samples from this study were frozen and stored and then shipped to blinded laboratory for immunogenicity testing in parallel to the samples from ALT-103-201. The schedule of events for ALT-FLZ-401 is in Table 4-3.

**Table 4-2. ALT-103-201 TIME AND EVENTS SCHEDULE**

Study Visit Window (days)	Screening Day -28 to Day -1	Dosing Period							Follow-up Period	
		Day 1 Predose	Day 1 Postdose	Day 2 <sup>a</sup>	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 <sup>b</sup>		X	X	X	X		
Height and weight	X									
ECG	X							X		
Vital signs <sup>c</sup>	X	X	X <sup>b</sup>		X	X	X	X		
Drug and alcohol screen	X	X								
<b>Laboratory samples:</b>										
Hepatitis B and C and HIV tests	X									
Safety laboratory tests	X					X		X		
Serum (S)/urine (U) pregnancy test <sup>d</sup>	S	U						U		
Serum sample for humoral response		X <sup>e</sup>			X	X	X	X <sup>e</sup>	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.

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



**Table 4-3. ALT-FLZ-401 SCHEDULE OF EVENTS**

Assessment	Screen	Study Day						
		1	4 ±1	8 ±1	15 ±1	29±1/ET <sup>g</sup>	91 ±10	181 ±10
Informed Consent	X							
Demographics	X							
Medical/Surgical History	X							
Physical Examination, height <sup>h</sup> , weight <sup>h</sup> , BMI	X	X						
Limited Physical Exam (as needed)			X	X	X	X	X	X
Vital Signs <sup>a</sup>	X	X						
12-Lead ECG	X							
Inclusion/Exclusion Criteria	X	X						
Clinical Laboratory Tests (Chemistry, Hematology, UA) <sup>b</sup>	X							
Drugs of abuse <sup>c</sup> , alcohol test	X	X						
Serology (HIV, Hepatitis B And C)	X							
Pregnancy Test <sup>d</sup>	X	X						
Confirm eligibility for study <sup>c</sup>		X						
Influenza Vaccination		X						
Blood Sample (Immunogenicity)		X	X	X	X	X	X	X
PBMC sample collection and processing		X		X				
Nasopharyngeal swab		X				X		
Prior/Concomitant medications	X	X	X	X	X	X	X	X
Adverse Events <sup>f</sup>		X	X	X	X	X	X	X

<sup>a</sup> All vital signs BP, pulse rate, and body temperature) will be measured at Screening in the supine position. On Day 1, temperature, blood pressure and pulse rate will be assessed.

<sup>b</sup> See Section 10.5 for listing of tests

<sup>c</sup> Opiates, benzodiazepines, amphetamines, cocaine, barbiturates, phencyclidine

<sup>d</sup> At Screening and Day 1 WOCBP must have negative urine pregnancy test results

<sup>e</sup> Review inclusion/exclusion criteria and may also include a limited physical examination

<sup>f</sup> Any subject that experiences an AE (whether serious or non-serious) or has clinically significant abnormal laboratory tests will be followed until resolution or clinical stability up to 180 days after administration of the vaccine or longer if specified by the Investigator.

<sup>g</sup> ET= early termination for any subject that discontinues prior to Day 29 visit, ET occurs after Day 29, the procedures for Day 181 will be followed.

<sup>h</sup> Height and weight are not required at Day 1



## 5 Analysis Populations

The following analysis populations will be used:

- **Safety Population:** All ALT-103-201 and ALT-FLZ-401 subjects who provide informed consent, are randomized, and receive at least 1 vaccination. The Safety Population will be used for all safety analyses and will be analyzed according to the treatment received.
- **Intent-to-treat (ITT) Population:** All ALT-103-201 and ALT-FLZ-401 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. Analyses based on the ITT Population will be undertaken and presented only if >5% of subjects in any 1 dose group are excluded from the per-protocol population. The ITT population will be analyzed according to treatment as randomized.
- **Per-protocol (PP) Population:** All ALT-103-201 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 and 29; and had no major protocol deviations affecting the primary immunogenicity outcomes as determined by the Sponsor prior to database lock. ALT-FLZ-401 subjects are included if they received the assigned dose of the test article in accordance with the protocol and have HAI assay results on Days 1 and 29. The PP Population is the primary population for immunogenicity analyses and will be presented regardless of whether subjects are excluded. The PP population will be analyzed as randomized.

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## 6 Analysis Variables

In what follows, variables to be analyzed have been grouped under the headings 6.1 to 6.4. Additional variables may be added as further drafts of the eCRF and this SAP are developed and/or as discussion unfolds concerning the usefulness of *derived* variables formulated using the information presented below.

### 6.1 Study Drug Dosing

- Vaccine administered
- Treatment dose

### 6.2 Demographics and Baseline Characteristics

- Sex
- Age
- Race
- Ethnicity
- Weight
- Height
- Body mass index (BMI)
- Medical/surgical history
- Prior medications

### 6.3 Endpoints

Primary, secondary, and exploratory endpoints are listed in Section 3.

### 6.4 Safety Variables

Safety assessments, some of which are listed as endpoints, include the following:

- Reactogenicity (local events, systemic events, and oral temperature)
- AEs and SAEs (events not already included in reactogenicity)
- Safety laboratory tests (hematology, serum chemistry, urinalysis)
- Vital signs (blood pressure, heart rate, body temperature)
- ECG
- Nasopharyngeal swabs for vector shedding
- Viral culture
- Concomitant medications
- Physical exam



## 7 Statistical Methodology

### 7.1 Sample Size

The sample size for ALT-103-201 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%.

Approximately 60 subjects will be enrolled in ALT-103-201.

The sample size for ALT-FLZ-401 was 20 healthy subjects; this size was based on practical considerations.

### 7.2 Randomization

ALT-103-201 Subjects will be enrolled into 3 sequential cohorts of 20 subjects each defined by the viral particle dose ( $1 \times 10^9$ ,  $1 \times 10^{10}$ , or  $1 \times 10^{11}$  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 of the ALT-103-201 protocol) 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.

No randomization was required for the ALT-FLZ-401 study.

### 7.3 Interim Analysis

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

The study and sponsor's biostatisticians and statistical programmers will be unblinded when all clinical data through the Day 29 visit are collected and cleaned, and will

perform the interim analysis. Other study personnel, including Investigators and investigational site staff, 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.

## 7.4 Analysis of the Study

All statistical tests will be two-sided and a difference resulting in a p-value of less than or equal to 0.05 will be considered statistically significant. All p-values will be rounded to and displayed in four decimals. If a p-value less than 0.0001 occurs it will be shown in tables as <0.0001.

There will be no multiplicity adjustments.

To integrate the 2 studies for the immunogenicity tables, figures, and listings (TFL), subjects enrolled in ALT-FLZ-401 will be treated as an additional arm in the ALT-103-201 study. ALT-FLZ-401 subjects will be denoted as "Fluzone" subjects in the TFL, while ALT-103-201 will be denoted as "NasoVAX" if they are assigned to an active dose, or placebo if appropriate.

Descriptive summaries of variables will be provided where appropriate. Continuous variables will be presented for each dose group by geometric means and 95% confidence intervals (CIs) for the immunogenicity endpoints and by summary statistics (e.g., mean, and standard deviation [SD], median, minimum, and maximum) for other endpoints. Categorical variables will be presented by frequency distributions (including percentages and 95% CIs) for the immunogenicity endpoints and frequency counts and percentages for other endpoints. Expansion of descriptive table categories within each dose group may occur if such elaborations are thought to be useful.

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included in the data listings.

Post-hoc exploratory analyses not identified in this SAP may be performed to further examine the study data. These analyses will be clearly identified as such in the final clinical study report.

### 7.4.1 Changes in Analysis in Comparison to Study Protocol

The PP population definition was modified to remove the requirement of having HAI assay results at Day 15. Otherwise, the analyses described in this analysis plan are consistent with the analyses described in the study protocols.

## 7.4.2 Study Data

For all summaries and analysis, ALT-103-201 subjects who are randomized to and/or treated with placebo from each of the 3 cohorts will be pooled into a single group.

Study data from the ALT-103-201 study will be integrated with data from the ALT-FLZ-401 in the analysis datasets; ALT-FLZ-401 will be treated as a separate dose group from the 4 arms of the ALT-103-201 study.

Study data identified in the schedule for time and events (Table 4-2) are collected, and source verified, on the electronic data capture (EDC) product Viedoc Clinic (Version 4.36) for the ALT-103-201 study, and on the ClinPlus Data Management System (3.3 SR2) for the ALT-FLZ-401 study. For the ALT-103-201 study, safety laboratory tests and viral culture are provided by ACM; the specialty laboratory vendors for tests that are not collected in the EDC tool are Altimune UK (PBMc ELISpot), MPI (qPCR lab data [nasopharyngeal swab]), Battelle (Ad5 lab data [serum]), and Southern Research Institute (HAI and influenza MN [serum], and IgA lab data [nasopharyngeal swab]). For the ALT-FLZ-401 study, the Southern Research Institute will also be used for HAI, influenza MN, and IgA lab data; the analysis of these humoral response lab data will be completed simultaneously for both studies. The ALT-FLZ-401 study will also use Altimune UK for the analysis of PBMCs, which will be completed simultaneously for both studies. Analysis of IgA lab data may be completed by a different specialty laboratory which will be determined prior to the end of the study. Samples which are being analyzed for both studies are pooled so that the lab will not know from which the study the sample was taken.

All study data will be formulated into regulatory compliant data sets to provide transparency, traceability, and integrity of trial analysis results from the collection source. Observed study data will be mapped to the CDISC Study Data Tabulation Model (SDTM) and serve as the source data from the trial. All study analyses will be completed using analysis data sets that are derived from the SDTM and follow the CDISC Analysis Data Model (ADaM) architecture. All planned analyses will be performed using the ADaM data sets developed for this study.

## 7.4.3 Coding

Coding of AEs will be performed on an ongoing basis throughout the study by Accelovance Safety. Verbatim terms that are entered into the database by the site will be coded manually; if necessary a query will be created to obtain clarification from the site. These events will be mapped to the MedDRA (Version 20.0) system for reporting (preferred term [PT] and system organ class [SOC]). Medical/surgical history will also be coded using MedDRA (Version 20.0).

Concomitant medications will be coded using World Health Organization (WHO) Drug Global Dictionary (March 1, 2017).

#### 7.4.4 Statistical Software

Data manipulation, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.2 or higher) for Windows. If the use of other software is warranted, the final clinical study report will detail what software was used and for what purposes.

#### 7.4.5 Derived Variables

- Non Treatment Emergent Adverse Events include all AEs that stopped the day prior to the vaccination, or started prior to the vaccination but did not increase in severity or relationship during treatment.
- Treatment Emergent Adverse Events (TEAEs) include all AEs that start on or after vaccination, or AEs that are present prior to vaccination, but their severity or relationship increases after the vaccination date
- Change from baseline will be calculated as the observed value at the current visit or time point minus the observed value at baseline.
- Prior medications include all medications that have a start date prior to the date of vaccination.
- Concomitant medications include all medications that are taken on or after the date of vaccination.

#### 7.4.6 Data Handling

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

Unscheduled or repeated laboratory results will not be analyzed for the summary of continuous values but may be included in the lab shift tables (see Section 8.5.3). Repeated tests will be included only if they reflect abnormal (low or high) results and the corresponding original results are normal. Repeat vital signs will not be analyzed for the summary of continuous values.

#### 7.4.7 Handling of Early Termination Visits and Additional Treatments

Early termination visit data for safety variables (on or prior to Day 29) and for immunogenicity variables (on or prior to Day 181) will be analyzed at the closest scheduled visit. If the closest visit has valid data, the early termination data will be assigned to the next available visit.

## 7.4.8 Handling of Missing Values

### Partial or Missing Dates

The following conventions will be used to impute missing portions of dates for AEs and concomitant medications. Note that the imputed values outlined here may not always provide the most conservative date. In those circumstances, the imputed value may be replaced by a date that will lead to a more conservative analysis.

#### A. Start Dates

- 1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- 2) If the month is unknown, then:
  - i) If the year matches the first dose date year, then impute the month and day of the first dose date.
  - ii) Otherwise, assign 'January.'
- 3) If the day is unknown, then:
  - i) If the month and year match the first dose date month and year, then impute the day of the first dose date.
  - ii) Otherwise, assign the first day of the month.

#### B. Stop Dates

- 1) If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- 2) If the month is unknown, then assign 'December.'
- 3) If the day is unknown, then assign the last day of the month.

### Imputation

Any immunogenicity data that are below the limit of quantification will be imputed to one-half of the lower limit of quantification (LLOQ) for quantitative summary and analysis. For example, HAI values that are less than 10 will be imputed to 5. Otherwise, missing data will not be imputed.

## 7.4.9 Pooling of Investigator Centers

Not applicable since only 1 site each will be used for ALT-103-201 and ALT-FLZ-401.

## 7.4.10 Baseline Values

Baseline values are the values obtained prior to the vaccination on Day 1. If the baseline value is missing, the value at Screening will be treated as the baseline.

## 8 Summary of Study Data

For all summaries described below, subjects enrolled in the ALT-103-201 and randomized to an active dose will be summarized/listed under the heading "NasoVAX", while subjects enrolled in ALT-FLZ-401 will be summarized/listed under the heading "Fluzone".

### 8.1 Subject Disposition and Dosing Summary

The tabulation of number of ALT-103-201 and ALT-FLZ-401 subjects from in each dose group and overall for subjects on an active NasoVAX dose will be displayed for all subjects who are enrolled, in the Safety Population, the ITT Population, and the PP Population, respectively.

The number and percent of subjects who completed or discontinued the study will be displayed for each dose group and overall for subjects on an active NasoVAX dose together with reasons for early termination, where the percent is with respect to the total number of treated subjects in that dose group.

Vaccination administration data will be listed.

### 8.2 Demographics and Baseline Characteristics

ALT-103-201 and ALT-FLZ-401 subject demographic data and baseline characteristics will be summarized descriptively by dose group and overall for all ALT-103-201 subjects (i.e., subjects on an active NasoVAX dose and placebo). The demographic data and baseline characteristics will be summarized for the Safety, ITT, and PP Populations.

Medical/surgery history will be summarized by SOC and PT for each dose group for ALT-103-201 only. Within each level of summarization, subjects will be counted only once if they had more than one event reported. Medical/surgery history will be summarized for the Safety Population.

### 8.3 Protocol Deviations

Major protocol deviations for ALT-103-201 subjects, as determined by a sponsor-blinded review of the data prior to database lock and unblinding of the study, may result in the removal of a subject's data from the Per-protocol Population.

All protocol deviations will be presented in a data listing, with a flag to indicate if a violation resulted in the exclusion of the subject from the Per-protocol Population.

Protocol deviations were not collected for subjects in the ALT-FLZ-401 study.



## 8.4 Prior and Concomitant Medications

Prior and concomitant medications are defined in [Section 7.4.5](#). The number and percentages of all concomitant medications for ALT-103-201 and ALT-FLZ-401 subjects will be summarized by dose group and overall for subjects on an active NasoVAX dose, Anatomical Therapeutic Chemical (ATC) level 3 and PT. If a medication has no ATC Level 3 code, then ATC Level 2 will be used instead. The total number of concomitant medications and the number and percentages of subjects with at least 1 concomitant medication will be summarized by dose group for the Safety Population.

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

## 8.5 Safety Analysis

All safety analyses will be conducted on the Safety Population, and will be performed for ALT-103-201 only. Summaries will be completed by dose group and overall for subjects on an active NasoVAX dose.

### 8.5.1 Reactogenicity

Each ALT-103-201 subject will be provided with a diary and a thermometer after each dose. The subjects will record and provide severity grades (Grade 1 – 4) for the following items in a diary daily for the first 14 days after vaccination.

- 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

Oral temperature will be converted to a severity grade using the FDA toxicity grading scale [1].

A cumulative summary of the number and percentage of subjects experiencing at least one reactogenicity event within 14 days after vaccination for each symptom type (local, systemic, temperature, and overall) will be tabulated by maximum severity and dose group. Differences between each NasoVAX dose group and placebo for cumulative symptoms (local, systemic, and overall) will be tested using Kruskal-Wallis tests. The number and percentage of subjects experiencing at least one Grade 3 or 4 reactogenicity event within 14 days after vaccination for each symptom type, as well as 95% Clopper-Pearson exact CIs, will be presented by dose group.

A summary of the number and percentage of subjects experiencing at least one reactogenicity event within 14 days after vaccination will also be tabulated by event

type, maximum severity, and dose group. In addition, a descriptive summary of the duration of symptoms (regardless of severity) will be tabulated by event and dose group.

### 8.5.2 Adverse Events

The number and percent of ALT-103-201 subjects with any TEAEs will be displayed by SOC and PT for each dose group. Within each PT, subjects will be counted only once if they had more than one event reported during the treatment period.

The number and percentage of subjects with any TEAE will be presented as well as the corresponding 95% Clopper-Pearson exact CI of the percentage.

For MedDRA SOC, the number and percentage of subjects experiencing at least one TEAE overall and at least one TEAE for a system will be tabulated by severity grade (Grades 1-4) and dose group. For MedDRA PT, the number and percentage of subjects reporting at least one TEAE within a PT category will be tabulated by relationship to study products and dose group. For the calculations in these tables, each subject's TEAEs will be counted once under the maximum severity or the strongest recorded causal relationship to study product.

Summaries will be generated for all serious TEAEs, TEAEs resulting in dose withdrawal, treatment emergent MAEs, and treatment emergent NCI, by SOC and PT for each dose group.

A listing will be produced for all subjects who reported serious TEAEs. The listing will provide details of the events including severity, relationship to study product, time between onset and last study treatment administration, and a summary of the event.

All TEAEs and non-treatment emergent AEs will be listed individually by subject.

### 8.5.3 Safety Laboratory Tests

Safety laboratory results for ALT-103-201 subjects will be summarized descriptively for each parameter with continuous values and dose group by visit for the observed value as well as for the change from baseline value. In addition, laboratory shift tables will be provided for all laboratory parameters where grades can be ascertained.

The following safety laboratory parameters will be collected for ALT-103-201 subjects:

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



- Urinalysis: glucose, protein

Any laboratory abnormality deemed clinically significant by the Investigator will be recorded as an AE.

#### **8.5.4 Vital Signs**

Vital sign data for ALT-103-201 subjects, including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), temperature (°C), and pulse rate (bpm), will be summarized descriptively for each dose group by time point for the observed value as well as for the change from baseline value. Any clinically significant abnormal vital sign value will be recorded as an AE.

#### **8.5.5 ECG**

ECG results for ALT-103-201 subjects will be summarized descriptively for each parameter and dose group by visit for the observed value as well as for the change from baseline value. In addition, a shift table will be provided comparing the baseline overall interpretation (normal, abnormal—not clinically significant, and abnormal—clinically significant) to the post-baseline value by visit.

#### **8.5.6 Vector Shedding and Viral Culture**

For the ALT-103-201 study, concentration of the Ad5 vector, as measured from nasopharyngeal swab samples to assess vaccine vector shedding by qPCR assay will be summarized descriptively for each dose group by visit. Negative results will be imputed to 1/2 LLOQ. These data will also be summarized by count and percentage of subjects with positive results by visit.

Viral culture data will be listed for ALT-103-201 subjects.

#### **8.5.7 Other Safety Variables**

Other safety variables, such as physical examination, drug and alcohol screen, pregnancy test, and serology (HIV, Hepatitis B and C) will be listed for ALT-103-201 only.

### **8.6 Immunogenicity Analysis**

All immunogenicity analyses will be conducted on 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. Summaries and analysis will be completed by dose group and overall for subjects on an active NasoVAX dose.

The variables that will be analyzed, and the endpoints generated for each variable, are listed in Table 8-1:

**Table 8-1. Immunogenicity Variables and Endpoints**

Variable Name	GMT	GMR	SPR	SCR	Responder Rate	Geometric Mean SFUs	Compare to ALT-FLZ-401
A/California 2009 antibody level measured by HAI in serum	X	X	X	X			X
A/California 2009 antibody level measured by MN in serum	X	X			X		X
Cellular response to A/California 2009 peptides measured by enzyme-linked ELISpot in PBMCs					X	X	X
IgA antibody level measured by ELISA in nasopharyngeal swab	X	X					X
Antibody level measured by HAI in serum against the following nonrepresented strains: - A/Brisbane/59/2007 (H1 strain) - A/Saint-Petersburg/61/2015 (H1 strain) - A/New Jersey/76 (H1 strain) - A/Perth/16/2009 (H3 strain) - A/Vietnam/1203/2004XPR8 (H5 strain)	X	X			X		X
Antibody level measured by MN in serum against nonrepresented strains	X	X			X		X
Ad5 antibody levels in serum	X	X			X		

Note: Refer to Section 3 for descriptions of each endpoint.

Assay data will be tabulated by visit using the applicable endpoint(s) (e.g., GMT, GMR, or geometric mean SFUs) and their 95% CIs. Graphical representations of the longitudinal immune responses will also be given.

Analysis of covariance (ANCOVA) will be used in the analysis of the antibody levels at each post-baseline visit, with log-transformed antibody level as dependent variable, dose group as a factor, and baseline log-transformed level as a covariate. This model will be generated using SAS Proc Mixed with dose group in the CLASS statement and visit in the BY statement. Comparisons of post-baseline log-transformed antibody level will be conducted for each NasoVAX dose group against the placebo group and against the Fluzone group, if applicable. Least square (LS) means and 95% CI of the LS means of dose group, difference of LS means and 95% CI of the difference in LS means will be

obtained from the model via ESTIMATE statements. Back-transforming the difference of LS mean estimates and their 95% CIs to the original scale results in a ratio of the geometric means—these ratios will be reported in the summary.

Categorical data derived from the assay data (e.g., SPR, SCR, and responder rate) will be tabulated by counts and percentages per dose group, as well as the 95% Clopper-Pearson exact CI of the percentage. 95% CIs will also be presented to compare the response rate of each NasoVAX dose group to placebo and Fluzone (if applicable). CIs will be calculated in SAS PROC FREQ using the EXACT binomial-option for the individual dose groups and by the METHOD=SCORE riskdiff-option for the differences in dose groups [2]. In addition, comparisons of responders in each NasoVAX dose group against the placebo group and against the Fluzone group (if applicable) will be conducted using Fisher's exact test.

In addition, scatterplots of baseline Ad5 antibody levels along the x-axis will be presented with each of the following variables along the y-axis: HAI antibody titer at Day 29, ELISpot response at Day 8, and IgA response at Day 29 (one plot per dependent variable).

All data related to immunogenicity collection and analysis will be listed.

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## 9 References

1. Food and Drug Administration. Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: U.S. Department of Health and Human Services; 2007b. Available at:  
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf>.
2. Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Statistics in Medicine* 1998 Apr 30;17(8):873-90



## 10 Appendices

### 10.1 List of Tables, Figures, and Listings

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14.4.1.2	Summary and Analysis of A/California 2009 Antibody Level Measured by MN in Serum by Visit	Per-protocol
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Figure No.	Description of Figure	Population
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## 10.2 Mock Tables, Figures, and Listings

Please refer to the separate document of table, figure, and listing shells and programming notes.

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