CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN
for
DMID Protocol: 14-0015
Study Title:

A Phase II Study to Evaluate and Compare the Immunogenicity of Monovalent Inactivated Influenza A/H7N9 Virus Vaccine Administered with and without AS03 Adjuvant and Monovalent Inactivated Influenza A/H3N2v Virus Vaccine Administered without Adjuvant in Healthy Adults through Standard and Systems Biology Analyses

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Version 1.0

DATE: 21 NOVEMBER 2019

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 14-0015**
Development Phase:	Phase II
Products:	Monovalent Inactivated Influenza A/Shanghai/02/2013 (H7N9) Virus Vaccine Administered with and without AS03 Adjuvant Monovalent Inactivated Influenza A/Minnesota/11/2010 (H3N2)v Virus Vaccine Administered without Adjuvant
Form/Route:	Intramuscular
Indication Studied:	Influenza
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	01 November 2016
Clinical Trial Completion Date:	14 February 2018
Date of the Analysis Plan:	21 November 2019
Version Number:	1.0

This study was performed in compliance with Good Clinical Practice.

TABLE OF CONTENTS

Table of Contents *(continued)*

Table of Contents *(continued)*

LIST OF ABBREVIATIONS

A/H3N2v	Influenza A Virus of the H3N2 Variant Subtype
A/H5N1	Influenza A Virus of the H5N1 Subtype
A/H7N9	Influenza A Virus of the H7N9 Subtype
AdvantageEDC^{SM}	Electronic Data Capture System
AE	Adverse Event/Adverse Experience
AS03	Adjuvant System (03)
α	Alpha
BMI	Body Mass Index
BPM	Beats Per Minute
CDC	Centers for Disease Control and Prevention
CDF	Cumulative Distribution Function
CI	Confidence Interval
CSR	Clinical Study Report
°C	Degrees Celsius
°F	Degrees Fahrenheit
D	Day(s)
DE	Differentially Expressed
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH
eCRF	Electronic Case Report Form
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
FDR	False-discovery Rate
GCP	Good Clinical Practice
GMT	Geometric Mean Titer
GTF	Gene Transfer Format
HA	Hemagglutinin
HAI	Hemagglutination Inhibition
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IFN	Interferon
IL	Interleukin
IM	Intramuscular
IQR	Interquartile Range
ITT	Intent-to-Treat
LCPM	Log2 Counts per Million
LFC	Log_2 Fold Change
LOD	Limit of Detection
MAAEs	Medically-Attended Adverse Events
mcg or µg	Microgram(s)
MedDRA®	Medical Dictionary for Regulatory Activities

mL	Milliliter(s)
mm	Millimeter(s)
mmHg	Millimeters of Mercury
MOP	Manual of Procedures
N	Number of Subjects
Neut or NT	Neutralizing or Neutralization
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NK	Natural Killer
NIH	National Institutes of Health
NOCMCs	New-Onset Chronic Medical Conditions
PBS	Phosphate-Buffered Saline
PIMMCs	Potentially Immune-Mediated Medical Conditions
PP	Per Protocol
QC	Quality Control
RCDF	Reverse Cumulative Distribution Function
RNA	Ribonucleic Acid
RP-HPLC	Reversed-Phase High-Performance Liquid Chromatography
SAE	Serious Adverse Event/Serious Adverse Experience
SAP	Statistical Analysis Plan
SDCC	Statistical and Data Coordinating Center
SOC	System Organ Class
SRID	Single Radial Immunodiffusion
TMM	Trimmed Mean of M-values
TNF	Tumor Necrosis Factor
US	United States
V	Visit(s)
VTEU	Vaccine and Treatment Evaluation Unit
WHO	World Health Organization

1. PREFACE

The Statistical Analysis Plan (SAP) for "A Phase II Study to Evaluate and Compare the Immunogenicity of Monovalent Inactivated Influenza A/H7N9 Virus Vaccine Administered with and without AS03 Adjuvant and Monovalent Inactivated Influenza A/H3N2v Virus Vaccine Administered without Adjuvant in Healthy Adults through Standard and Systems Biology Analyses" (DMID Protocol 14-0015) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses including sample tables, listings, and figures. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provides sufficient detail to meet the requirements identified by the FDA and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains four sections: (1) a review of the study design, (2) general statistical considerations, (3) comprehensive statistical analysis methods for immunogenicity, transcriptomics, cytokine/chemokine, and safety outcomes, and (4) a list of proposed tables, figures, and listings. Within the table, figure, and listing mock-ups (Appendices 1, 2, and 3), references to CSR sections are included. Any deviation from this SAP will be described and justified in protocol amendments and/or in the CSR, as appropriate. The reader of this SAP is encouraged to also review the study protocol for details on conduct of the study and the operational aspects of clinical assessments. Tertiary and exploratory proteomics assessments and correlation analyses are presented in a separate addendum to this SAP.

2. INTRODUCTION

2.1. Purpose of the Analyses

The primary goal of these analyses is to characterize and compare gene expression responses from subjects receiving two doses of monovalent inactivated influenza A/Shanghai/02/2013 (H7N9) virus vaccine, hereafter referred to as A/H7N9 vaccine, administered with AS03 adjuvant with those subjects that received the same vaccine without AS03 post first and second dose. This direct comparison will potentially reveal gene expression signatures that are modulated by AS03 which in turn could lead to a better understanding of the immune response-enhancing capabilities of the AS03 adjuvant. As a co-primary endpoint, anti-HA hemagglutination-inhibition (HAI) antibody responses will be assessed. The secondary endpoint analysis focuses on serum neutralizing antibodies and plasma cytokine/chemokine profiles pre- and post-vaccination. As part of the tertiary analysis, A/H7N9 transcriptomics responses will be compared to a control arm receiving one dose of monovalent inactivated influenza A/Minnesota/11/2010 (H3N2)v virus vaccine, hereafter referred to as A/H3N2v vaccine. The goal is to compare the innate and adaptive immune responses observed between the two avian (A/H7N9) study arms, and between the unadjuvanted avian (A/H7N9) and a swine-origin influenza vaccine (A/H3N2v) that is more similar to seasonal influenza A/H3N2.

Additional tertiary and exploratory endpoint analyses are aimed at characterizing and comparing proteomics signatures and assessing the correlation between omics and serum antibody and plasma cytokines/chemokines as well as safety outcomes. The goal of the correlation analysis is to integrate the different data to develop a systems model of the human immune response to unadjuvanted monovalent inactivated influenza A/H3N2v virus vaccine and monovalent inactivated influenza A/H7N9 virus vaccine given with and without AS03 adjuvant.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Primary Objectives

1. To assess the serum anti-HA hemagglutination-inhibition (HAI) response to influenza A/H7N9 antigen (with and without adjuvant) at Day 57 (approximately one month after the second study vaccination with A/H7N9 vaccine ± AS03) and influenza A/H3N2v antigen at Day 29 (approximately one month after the study vaccination with A/H3N2v vaccine).
2. To identify differentially expressed genes in human immune cells on Days 2, 4, and 29 (following the first study vaccination with A/H7N9 vaccine ± AS03) and on Days 30, 32, and 36 (following the second study vaccination with A/H7N9 vaccine ± AS03), compared to baseline assessments performed prior to each study vaccination (Days -7, 1, and 29).

Secondary Objectives

1. To compare plasma cytokine and chemokine profiles at specific time points and between treatment arms:
    a. Post-vaccination time points [(Days 2 and 4; Day 8 (A/H3N2v arm only)], and Days 30, 32, and 36 (A/H7N9 arms only) with pre-vaccination time points (Days -7 and 1, prior to first study vaccination and Day 29, prior to second study vaccination (A/H7N9 arms only).
2. To assess the neutralizing antibody responses to influenza A/H7N9 antigen (with and without adjuvant) at Day 57 (approximately one month after the second study vaccination with A/H7N9 vaccine ± AS03) and influenza A/H3N2v antigen at Day 29 (approximately one month after the study vaccination with A/H3N2v vaccine).
3. To identify differentially expressed genes in human immune cells on Days 2, 4, and 8 following one intramuscular dose of influenza A/H3N2v vaccine compared to baseline assessments performed prior to study vaccination (Day -7 and Day 1).

Tertiary Objectives

1. To assess the frequency of adverse events.
2. To identify differentially abundant cellular proteins in human immune cells on Days 2, 4, and 8 following one intramuscular dose of influenza A/H3N2v vaccine compared to baseline assessments performed prior to study vaccination (Day -7 and Day 1).
3. To identify differentially abundant cellular proteins in human immune cells on Days 2, 4, and 29 (following first study vaccination with A/H7N9 vaccine ± AS03) and Days 30, 32, and 36 (following second study vaccination with A/H7N9 vaccine ± AS03), compared to baseline assessments performed prior to study vaccination (Days -7, 1, and 29).

Exploratory Objectives

1. To identify and characterize differentially expressed genes in human immune cells on Days 2, 4, and 29 (following the first study vaccination with A/H7N9 vaccine ± AS03) and on Days 30, 32, and 36 (following the second study vaccination with A/H7N9 vaccine ± AS03) that differ between treatments (A/H7N9 vaccine vs. A/H7N9 vaccine + AS03).

2. To identify and characterize differentially abundant cellular proteins in human immune cells on Days 2, 4, and 29 (following the first study vaccination with A/H7N9 vaccine ± AS03) and on Days 30, 32, and 36 (following the second study vaccination with A/H7N9 vaccine ± AS03) that differ between treatments (A/H7N9 vaccine vs. A/H7N9 vaccine + AS03).
3. To identify and characterize differentially expressed genes in human immune cells on Days 2 and 4 (following the first study vaccination) that differ in baseline responses (Days -7, and 1) between treatments (A/H3N2v vaccine vs. A/H7N9 vaccine and A/H3N2v vaccine vs. A/H7N9 vaccine + AS03).
4. To identify and characterize differentially abundant cellular proteins in human immune cells on Days 2 and 4 (following the first study vaccination) that differ in baseline responses (Days -7, and 1) between treatments (A/H3N2v vaccine vs. A/H7N9 vaccine and A/H3N2v vaccine vs. A/H7N9 vaccine + AS03).
5. To identify transcriptomic and proteomic signatures in human immune cells that correlate with influenza seroconversion and with peak HAI titers.
6. To correlate plasma cytokine profiles with transcriptomic and proteomic profiles in subjects receiving influenza A/H3N2v vaccine or influenza A/H7N9 ± AS03 vaccine.
7. Exploratory inspection of transcriptomics\proteomics response signatures for subjects with unexpected or severe safety profiles that are related to the study products.

3.2. Endpoints

Primary Endpoints

1. Percentage of subjects achieving seroconversion (defined as either a pre-vaccination HAI titer <1:10 and a post-vaccination HAI titer ≥1:40 or a pre- vaccination HAI titer ≥1:10 and a minimum four-fold rise in post-vaccination HAI antibody titer) at approximately 28 days after the second study vaccination (A/H7N9 vaccine, with and without adjuvant).
2. Percentage of subjects achieving seroconversion at approximately 28 days after the study vaccination with A/H3N2v vaccine.
3. Number of differentially expressed genes based on RNA expression as determined by RNA-Seq analysis, in human immune cells at Days 2, 4, 29, 30, 32, and 36 after study vaccination with AS03-adjuvanted and unadjuvanted A/H7N9 vaccine, as compared to baseline assessments performed prior to vaccination (Days -7, 1, and 29).

Secondary Endpoints

1. Plasma measurement of cytokines and chemokines at each study visit, comparing:
   a. Post-vaccination time points with pre-vaccination time points by treatment arms.
   b. AS03-adjuvanted influenza A/H7N9 responses to unadjuvanted influenza A/H7N9 responses.
   c. Influenza A/H3N2v vaccine to unadjuvanted influenza A/H7N9 vaccine.
   d. Influenza A/H3N2v vaccine to adjuvanted A/H7N9 vaccine.
2. Serologic response to influenza hemagglutinin:
   a. Percentage of subjects achieving seroconversion (defined as either a pre-vaccination Neut titer <1:10 and a post-vaccination Neut titer ≥1:40 or a pre-vaccination Neut titer ≥1:10 and a minimum four-fold rise in post-vaccination Neut titer) at approximately 28 days after the second study vaccination (A/H7N9 vaccine, with and without adjuvant).

b. Percentage of subjects achieving seroconversion at approximately 28 days after the study vaccination with influenza A/H3N2v vaccine.
c. Geometric Mean Titers of serum HAI and Neut antibody at baseline (Day -7 and 1) and 28 days after influenza A/H3N2v vaccination.
d. Geometric Mean Titers of serum HAI and Neut antibody at baseline (Day -7 and 1), and 28 days after both the first and the second dose of influenza A/H7N9 vaccine (with and without adjuvant).

3. Number of differentially expressed genes based on RNA-Seq analysis in human immune cells at Days 2, 4, and 8 after study vaccination, as compared to baseline assessments (Days -7 and 1) after influenza A/H3N2v vaccine.

Tertiary Endpoints

1. Occurrence of solicited local reactogenicity events within 7 days after each study vaccination.
2. Occurrence of solicited systemic reactogenicity events within 7 days after each study vaccination.
3. Occurrence of unsolicited AEs collected for approximately 28 days after last study vaccination.
4. Occurrence of SAEs and MAAEs including new-onset chronic medical conditions and potentially immune-mediated medical conditions for approximately 1 month (A/H3N2v arm) and 12 months (A/H7N9 arms) after last study vaccination.
5. Number of differentially abundant proteins based on protein abundance as determined by quantitative proteomics in human immune cells at Days 2, 4, and 8 after study vaccination, as compared to baseline assessments (Days -7 and 1) after influenza A/H3N2v vaccine.
6. Number of differentially abundant proteins based on protein abundance as determined by quantitative proteomics analysis, in human immune cells at Days 2, 4, 29, 30, 32, and 36 after study vaccination with AS03-adjuvanted and unadjuvanted A/H7N9 vaccine comparing changes in protein abundance between treatment arms (A/H7N9 vaccine vs. A/H7N9 vaccine + AS03).

Exploratory Endpoints

1. RNA expression, clusters of co-expressed genes, enriched pathways, and other functional modules as determined by RNA-Seq analysis, in human immune cells at Days 2, 4, 29, 30, 32, and 36 after study vaccination with AS03-adjuvanted and unadjuvanted A/H7N9 vaccine comparing changes in RNA expression between treatment arms (A/H7N9 vaccine vs. A/H7N9 vaccine + AS03).
2. Protein abundance, clusters of co-abundant proteins, enriched pathways, and other functional modules as determined by quantitative proteomics analysis, in human immune cells at Days 2, 4, 29, 30, 32, and 36 after study vaccination with AS03-adjuvanted and unadjuvanted A/H7N9 vaccine comparing changes in protein abundance between treatment arms (A/H7N9 vaccine vs. A/H7N9 vaccine + AS03).
3. RNA expression, clusters of co-expressed genes, enriched pathways, and other functional modules as determined by RNA-Seq analysis, in human immune cells at Days 2, 4, and 29 after study vaccination comparing baseline changes in RNA expression between treatment arms (A/H3N2v vaccine vs. A/H7N9 vaccine and A/H3N2v vaccine vs. A/H7N9 vaccine + AS03).
4. Protein abundance, clusters of co-abundant proteins, enriched pathways, and other functional modules as determined by quantitative proteomics analysis, in human immune cells at Days 2, 4, and 29 after first study vaccination comparing baseline changes (Days -7, and 1) in protein abundance between

treatment arms (A/H3N2v vaccine vs. A/H7N9 vaccine and A/H3N2v vaccine vs. A/H7N9 vaccine + AS03).

5. Changes from baseline (Days -7, 1, and 29) in RNA expression or protein abundance that best correlate with influenza A/H7N9 seroconversion and with peak HAI titers at Days 2 and 4 (following first study vaccination) as well as Days 30, 32, and 36 (following second study vaccination).

6. Changes from baseline (Days -7, 1, and 29) in RNA expression or protein abundance that best correlate with baseline changes in cytokine concentrations at Days 2, 4, 8 (A/H3N2v arm only) and 29 (following first study vaccination) as well as Days 30, 32, and 36 (following second study vaccination).
7. Exploratory summaries of transcriptomics/proteomics response signatures for subjects with unexpected or severe safety profiles.
8. Lists of differential genes and proteins identified as part of the primary and secondary objectives.

3.3. Study Definitions and Derived Variables

Derived safety variables are described in Table 3, Table 4, Table 5, Table 6, and Table 7 in this document. The following assay-specific criteria will be used to determine seroconversion for the hemagglutination inhibition (HAI) and neutralization (NT) titers:

- a pre-vaccination titer <1:10 and a post-vaccination titer ≥1:40 or a pre-vaccination titer ≥1:10 and a minimum of a four-fold rise in post-vaccination antibody titer.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a single center, randomized, partially-blinded, Phase II, small, targeted, prospective study in approximately 30 healthy male and non-pregnant female subjects aged 18 to 49 years old, inclusive, designed to evaluate and compare the immunogenicity between an intramuscular monovalent inactivated influenza A/H7N9 virus vaccine manufactured by Sanofi Pasteur given with and without AS03 adjuvant manufactured by GlaxoSmithKline, and an intramuscular unadjuvanted monovalent inactivated influenza A/H3N2v virus vaccine manufactured by Sanofi Pasteur.

This study will use a standard and systems biology approach to assess the human early gene and protein signatures expressed at baseline (approximately Days -7 and 1), and at approximately Days 2, 4, and 8 (A/H3N2v-vaccinated subjects only) after the first study vaccination in each treatment arm as well as at approximately Days 29, 30, 32, and 36 in A/H7N9-vaccinated subjects only. Cellular immunogenicity (systems biology studies) data will be integrated with serologic immunogenicity (HAI and Neut antibody assays) and reactogenicity data to develop a systems model of the human immune response to unadjuvanted monovalent inactivated influenza A/H3N2v virus vaccine and monovalent inactivated influenza A/H7N9 virus vaccine given with and without AS03 adjuvant.

This study will use venous blood samples and subject data collected from a total of thirty vaccinated subjects randomly divided into three equal treatment arms (Table 1). The first treatment arm (n=10) will be vaccinated with one dose of 15 µg of A/H3N2v HA. The second treatment arm (n=10) will be vaccinated with two doses of 3.75 µg of A/H7N9 HA given with AS03 approximately 28 days apart. The third treatment arm (n=10) will be vaccinated with two doses of 3.75 µg of A/H7N9 HA given without AS03 adjuvant approximately 28 days apart. All study vaccinations will be administered intramuscularly.

Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions from the time of each study vaccination through 8 days after each study vaccination. Unsolicited non-serious adverse events (AEs) will be collected from the time of each study vaccination through approximately 28 days after each study vaccination. Serious adverse events (SAEs) and medically-attended adverse events (MAAEs) including new-onset chronic medical conditions (NOCMCs) and potentially immune-mediated medical conditions (PIMMCs) will be collected from the time of the first study vaccination through approximately 1 month (A/H3N2v arm) and 12 months (A/H7N9 arms) after the last study vaccination.

Venous blood samples (approximately 90 mL) will be collected from subjects at approximately Days -7 and 1 (immediately prior to the first study vaccination), and at approximately Days 2, 4; and 8 (A/H3N2v-vaccinated subjects only) after the first study vaccination for systems biology studies (cytokine and chemokine levels, immune cell activation status, and whole transcriptome and proteome profiles of the major blood immune cells). Additionally, subjects in either treatment arm receiving A/H7N9 vaccine will have additional blood samples collected at approximately Days 29 (this will be collected immediately prior to the second study vaccination for subjects in either group receiving A/H7N9), 30, 32, and 36 after the first study vaccination for systems biology studies.

Serological assessment (hemagglutination inhibition (HAI) and neutralizing (Neut) antibody assays) will also be conducted on venous blood samples (approximately 10 mL) collected from subjects at Day 1 (immediately prior to the first study vaccination), and at approximately Days 29 (for A/H7N9-vaccinated subjects this will be collected immediately prior to the second study vaccination) and 57 (A/H7N9-vaccinated subjects only) after the first study vaccination. Plasma cytokine/chemokine levels, as well as transcriptomic and proteomic

profiles from individual immune cell compartments will be measured and integrated with standard serologic assessment to vaccine.

Urine samples (approximately 20 mL) will also be collected from subjects at approximately Days -7, 1, 2, 4, 8 (A/H3N2v-vaccinated subjects only), 29, 30, 32, and 36 for future research.

4.2. Discussion of Study Design, Including the Choice of Control Groups

The main study arms are the two arms receiving influenza A/H7N9 virus vaccine with or without AS03 adjuvant (Study Arms 2 and 3). The goal is to better understand how the AS03 adjuvant modulates the immune response to influenza A/H7N9 virus on the molecular level. The addition of the interpandemic (seasonal) strain of influenza A/H3N2v was chosen to compare innate and adaptive immune response between avian (A/H7N9) and swine-origin influenza vaccines (A/H3N2v) more closely resembling seasonal strains of influenza A.

4.3. Selection of Study Population

Subject Inclusion Criteria

Subjects eligible to participate in this study must meet all of the following inclusion criteria:

1. Provide written informed consent prior to initiation of any study procedures.
2. Are able to understand and comply with planned study procedures and be available for all study visits.
3. Are males or non-pregnant females, 18 to 49 years old, inclusive.
4. Are in good health[1].

   [1]*As determined by medical history and targeted physical examination, if indicated based on medical history, to evaluate acute or currently ongoing chronic medical diagnoses or conditions, defined as those that have been present for at least 90 days, that would affect the assessment of the safety of subjects or the immunogenicity of study vaccinations. Chronic medical diagnoses or conditions should be stable for the last 60 days. This includes no change in chronic prescription medication, dose, or frequency as a result of deterioration of the chronic medical diagnosis or condition in the 60 days prior to enrollment. Any prescription change that is due to change of health care provider, insurance company, etc., or that is done for financial reasons, as long as in the same class of medication, will not be considered a deviation of this inclusion criterion. Any change in prescription medication due to* ***improvement*** *of a disease outcome, as determined by the site principal investigator or appropriate sub-investigator, will not be considered a deviation of this inclusion criterion. Subjects may be on chronic or as needed (prn) medications if, in the opinion of the site principal investigator or appropriate sub-investigator, they pose no additional risk to subject safety or assessment of reactogenicity and immunogenicity and do not indicate a worsening of medical diagnosis or condition. Similarly, medication changes subsequent to enrollment and study vaccination are acceptable provided there was no deterioration in the subject's chronic medical condition that necessitated a medication change, and there is no additional risk to the subject or interference with the evaluation of responses to study vaccination. Note: Topical, nasal, and inhaled medications (with the exception of inhaled corticosteroids as outlined in the Subject Exclusion Criteria (see Section 5.1.2)), herbals, vitamins, and supplements are permitted.*
5. Oral temperature is less than 100.4°F.
6. Pulse is 50 to 115 bpm, inclusive.
7. Systolic blood pressure is 85 to 150 mm Hg, inclusive.
8. Diastolic blood pressure is 55 to 95 mm Hg, inclusive.
9. Erythrocyte sedimentation rate (ESR) is less than 30 mm per hour.

10. Women of childbearing potential[2] must use an acceptable contraception method[3] from 30 days before first study vaccination until 60 days after last study vaccination.

[2]*Not sterilized via tubal ligation, bilateral oophorectomy, hysterectomy or successful Essure® placement (permanent, non-surgical, non-hormonal sterilization) with documented radiological confirmation test at least 90 days after the procedure, and still menstruating or <1 year of the last menses if menopausal.*

[3]*Includes, but is not limited to, non-male sexual relationships, abstinence from sexual intercourse with a male partner, monogamous relationship with vasectomized partner who has been vasectomized for 180 days or more prior to the subject receiving the first study vaccination, barrier methods such as condoms or diaphragms with spermicide or foam, effective intrauterine devices, NuvaRing®, and licensed hormonal methods such as implants, injectables or oral contraceptives ("the pill").*

11. Women of childbearing potential must have a negative urine or serum pregnancy test within 24 hours prior to study vaccination.

Subject Exclusion Criteria

Subjects eligible to participate in this study must not meet any of the following exclusion criteria:

1. Have an acute illness[4], as determined by the site principal investigator or appropriate sub-investigator, within 72 hours prior to study vaccination.

[4]*An acute illness which is nearly resolved with only minor residual symptoms remaining is allowable if, in the opinion of the site principal investigator or appropriate sub-investigator, the residual symptoms will not interfere with the ability to assess safety parameters as required by the protocol.*

2. Have any medical disease or condition that, in the opinion of the site principal investigator or appropriate sub-investigator, is a contraindication to study participation[5].

[5]*Including acute or chronic medical disease or condition, defined as persisting for at least 90 days that would place the subject at an unacceptable risk of injury, render the subject unable to meet the requirements of the protocol, or may interfere with the evaluation of responses or the subject's successful completion of this study.*

3. Have immunosuppression as a result of an underlying illness or treatment, or use of anticancer chemotherapy or radiation therapy (cytotoxic) within 3 years prior to study vaccination.

4. Have known active neoplastic disease (excluding non-melanoma skin cancer) or a history of any hematologic malignancy.

5. Have known human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection.

6. Have known hypersensitivity or allergy to eggs, egg or chicken protein, squalene-based adjuvants, or other components of the study vaccines.

7. Have a history of severe reactions following previous immunization with licensed or unlicensed influenza virus vaccines.

8. Have a personal or family history of narcolepsy.

9. Have a history of Guillain-Barré syndrome.

10. Have a history of convulsions or encephalomyelitis within 90 days prior to study vaccination.

11. Have a history of a potentially immune-mediated medical condition[6].

    [6]*Refer to Appendix A: List of Potentially Immune-Mediated Medical Conditions.*

12. Have a history of alcohol or drug abuse within 5 years prior to study vaccination.

13. Have any diagnosis, current or past, of schizophrenia, bipolar disease, or other psychiatric diagnosis that may interfere with subject compliance or safety evaluations.

14. Have been hospitalized for psychiatric illness, history of suicide attempt, or confinement for danger to self or others within 10 years prior to study vaccination.

15. Have taken oral or parenteral (including intra-articular) corticosteroids of any dose within 30 days prior to study vaccination.

16. Have taken high-dose inhaled corticosteroids within 30 days prior to study vaccination. High-dose defined as >840 mcg/day of beclomethasone dipropionate CFC or equivalent.

17. Received licensed live vaccine within 30 days prior to the first study vaccination, or plans to receive licensed live vaccine within 30 days before or after each study vaccination.

18. Received licensed inactivated vaccine within 14 days prior to the first study vaccination, or plans to receive licensed inactivated vaccine within 14 days before or after each study vaccination.

19. Received immunoglobulin or other blood products (with exception of Rho D immunoglobulin) within 90 days prior to study vaccination.

20. Received an experimental agent[7] within 30 days prior to the first study vaccination, or expects to receive an experimental agent[8] during the 13-month study-reporting period.

    [7]*Including vaccine, drug, biologic, device, blood product, or medication.*

    [8]*Other than from participation in this study.*

21. Are participating or plan to participate in another clinical trial with an interventional agent[9] that will be received during the 13-month study-reporting period.

    [9]*Including licensed or unlicensed vaccine, drug, biologic, device, blood product, or medication.*

22. Prior participation in a clinical trial of influenza A/H7 vaccine[10] or have a history of influenza A/H7 virus actual or potential exposure or infection prior to the first study vaccination.

    [10]*And assigned to a group receiving influenza A/H7 vaccine, does not apply to documented placebo recipients.*

23. Prior participation in a clinical trial of influenza A/H3N2v vaccine[11] or have a history of influenza A/H3N2v virus actual or potential exposure or infection prior to the first study vaccination.

    [11]*And assigned to a group receiving influenza A/H3N2v vaccine, does not apply to documented placebo recipients.*

24. Occupational exposure to or substantial direct physical contact[12] with birds in the past year or during the 28 days after each study vaccination.

[12]Casual contact with birds at petting zoos or county or state fairs or having pet birds does not exclude subjects from study participation.

25. Occupational exposure to or substantial direct physical contact[13] with pigs in the past year or during the 28 days after each study vaccination.

[13]Casual contact with pigs at petting zoos or county or state fairs does not exclude subjects from study participation.

26. Female subjects who are breastfeeding or plan to breastfeed at any given time from the first study vaccination until 30 days after the last study vaccination.

27. Plan to travel outside the US (continental US, Hawaii, and Alaska) within 28 days after each study vaccination.

28. Blood donation or planned blood donation within 30 days before enrollment until 30 days after the last blood draw for this study.

4.4. Treatments

4.4.1. Treatments Administered

A/H7N9 Vaccine

Sanofi Pasteur has developed a monovalent inactivated influenza A/H7N9 virus vaccine for intramuscular use. The manufacturing process for the production of this monovalent inactivated influenza A/H7N9 virus vaccine is similar to the manufacturing process for the production of its licensed Influenza Virus Vaccine Fluzone® family of products, except for a minor modification in the PBS diluent in the formulation step that was made according to previous experiences of manufacturing of monovalent pandemic vaccines. This monovalent inactivated split influenza virus vaccine was derived from the influenza A/Shanghai/2/2013 virus. Licensed release testing specifications were maintained, with a modification to the potency test. [redacted] A 3.75 mcg of HA (A/Shanghai/2/2013) per 0.5 mL [adjuvanted] or 0.25 mL [unadjuvanted] dose was planned for use in this study.

AS03 Adjuvant [Adjuvant System (03)]

[redacted]

A/H3N2v Vaccine

Sanofi Pasteur has developed a monovalent inactivated influenza A/H3N2v. The resulting reassortant is designated A/Minnesota/11/2010 NYMC X-203 virus vaccine for intramuscular use. The manufacturing process for the production of this monovalent inactivated influenza A/H3N2v virus vaccine is similar, with

slight modifications in the formulation step, to the manufacturing process for the production of its licensed Influenza Virus Vaccine Fluzone® and the H1N1 influenza vaccine A/California/07/2009 NYMC X-179A. Using the Fluzone® production process, an A/H3N2v reassortant was derived from the A/Minnesota/11/2010 strain produced by classical reassortant technology at New York Medical College (NYMC) and provided by the Centers for Disease Control and Prevention (CDC). This monovalent inactivated split influenza virus vaccine is prepared from influenza virus propagated in embryonated chicken eggs. Licensed release testing specifications were maintained

4.4.2. Identity of Investigational Product(s)

A/H7N9 Vaccine

The monovalent inactivated influenza A/H7N9 virus vaccine was supplied as a sterile, clear, and slightly opalescent suspension in single-dose vials containing 7.5 mcg of HA per 0.5 mL. Each vial contained a fill volume of 0.7 mL. It contained no preservative (i.e., non-thimerosal) or antibiotics. The vials containing study product had to be stored at 2°C to 8°C (35.6°F to 46.4°F) and not frozen. Vials were provided with latex-free stoppers.

AS03 Adjuvant

The AS03 adjuvant was supplied as a preservative-free, oil-in-water, whitish to yellowish homogenous milky liquid emulsion in single-use vials containing a fill volume of 3.15 mL. The vials containing study product had to be stored at 2°C to 8°C (35.6°F to 46.4°F) and not frozen. Vials were provided with latex-free stoppers.

A/H3N2v Vaccine

The monovalent inactivated influenza A/H3N2v virus vaccine was supplied as a sterile, clear, and slightly opalescent suspension. A minor modification in the PBS diluent in the formulation step was made to accommodate the nature of the diluted virus in single-dose, prefilled syringes, without needles, containing 15 mcg of HA per 0.5mL. It contained no preservative (i.e., non-thimerosal), antibiotics, or latex. The vaccine included porcine gelatin (0.05%) as a stabilizer. The prefilled syringes containing study product had to be stored at 2°C to 8°C (35°F to 46°F) and not frozen.

Each of these study products were labeled according to manufacturer specifications and included the statement “Caution: New Drug – Limited by Federal Law to Investigational Use.”

Further details are included in the respective, applicable Investigator’s Brochures and Supplemental Information for the Investigator’s Brochures for the A/H7N9 vaccine, AS03 adjuvant, and A/H3N2v vaccine as well as protocol-specific MOP.

4.4.3. Method of Assigning Subjects to Treatment Groups (Randomization)

Per International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP), screening records were kept at the participating VTEU site to document the reason why an individual was screened, but failed study entry criteria. The reasons why individuals failed screening were recorded in the Statistical and Data Coordinating Center’s (SDCC) AdvantageEDC^{SM} (Electronic Data Capture System).

Once consented and upon entry of demographic data and confirmation of eligibility for this study, the subject was enrolled. Subjects were assigned randomly to 1 of 3 treatment arms (Table 1). The first treatment arm (n=10) was vaccinated with one dose of 15 µg of A/H3N2v HA. The second treatment arm (n=10) was vaccinated with two doses of 3.75 µg of A/H7N9 HA given with AS03 approximately 28 days apart. The

third treatment arm (n=10) was vaccinated with two doses of 3.75 μg of A/H7N9 HA given without AS03 adjuvant approximately 28 days apart. All study vaccinations were administered intramuscularly.

Enrollment of subjects was done online using the enrollment module of AdvantageEDC^{SM}. The randomization code was prepared by statisticians at the SDCC and included in the enrollment module for this study. AdvantageEDC^{SM} assigned each subject to a treatment arm after the demographic and eligibility data had been entered into the system. A designated individual at the participating VTEU site was provided with a code list for emergency unblinding purposes, which was to be kept in a secure place.

4.4.4. Selection of Doses in the Study

As with other avian influenza strains, the immunogenicity of inactivated vaccines is poor. Higher doses of hemagglutinin (HA), a major target of the protective immune response, has been shown to generate more frequent and higher antibody titers. Thus, two doses of 3.75 mcg of HA (A/Shanghai/2/2013) were administered for the A/H7N9 arms. Standard dosing of 15 mcg of HA (A/H3N2v) was chosen to more closely resemble the dosing administered as part of seasonal influenza vaccination. While 15 mcg represents a 4-fold increase in HA amount, the vaccine was unadjuvanted and matches what is formulated in seasonal standard dose inactivated influenza vaccines.

4.4.5. Selection and Timing of Dose for Each Subject

The dose of vaccine was chosen primarily to mirror the amount provided in DMID 10-0074 in which 3.75 mcg of influenza A/H5N1 virus vaccine was given with or without AS03. This reduced amount represents the minimal amount of HA needed to generate an immune response in the presence of an oil-in-water adjuvant system, based on prior studies. The HA content was kept the same for the unadjuvanted dose in an effort to measure the adjuvant effect specifically. Further, in previous studies, two doses of avian-strain influenza vaccine were required to generate an adaptive response, and typically the second dose was given 3-4 weeks after the first dose.

4.4.6. Blinding

This was a partially-blind clinical study as the unadjuvanted A/H3N2v vaccine treatment arm was open-label to avoid the need for placebo administration at approximately Day 29. Investigators and study personnel remained blinded to allocation of A/H7N9 with or without AS03. The randomization scheme was generated by the SDCC and provided to unblinded study personnel (i.e., research pharmacists performing study vaccination preparations and unblinded study vaccine administrators) at the participating VTEU site. The unblinded study vaccine administrator was a study personnel member credentialed to administer vaccines and may also have participated in dose preparation but was not involved in study-related assessments or had subject contact for data collection following study vaccine administration.

4.4.7. Prior and Concomitant Therapy

Administration of any medications, therapies, or vaccines was recorded on the appropriate data collection form. Concomitant medications included all current medications and medications taken within 60 days prior to signing the informed consent form through approximately 28 days after the last study vaccination or through the early termination visit (if prior to 28 days after the last study vaccination), whichever occurred first. Medications reported in the electronic case report form (eCRF) were limited to those taken within 30 days prior to the first study vaccination through approximately 28 days after the last study vaccination. Prescription and over-the-counter drugs were included as well as herbals, vitamins and supplements. In addition, receipt of non-study influenza vaccines was solicited through approximately 28 days after the last

study vaccination and reported in the eCRF. Use of new medication should have prompted evaluation for the presence of a new diagnosis of chronic medical disease or condition. Medications that might interfere with the evaluation of the investigational product(s) should not be have been used during the study-reporting period (approximately 12 months after the last study vaccination) unless clinically indicated as part of the subject's health care. Medications in this category included the prohibited medications per the Subject Exclusion Criteria (see Section 4.3). In addition, the site principal investigator or appropriate sub-investigator may identify other medications that should not have been used due to a risk to subject safety or assessment of reactogenicity and immunogenicity.

4.4.8. Treatment Compliance

Study product was administered to subjects by an unblinded study vaccine administrator via intramuscular (IM) injection at all dosing times according to subject treatment assignment and as described in Section 6.2 in the protocol. The number of administered vaccine doses was recorded.

4.5. Immunogenicity and Safety Variables

The following section describes the collection of safety and immunogenicity variables. For a detailed schedule of activities refer to Appendix B of the protocol.

4.5.1. Immunogenicity Variables

Venous blood samples (approximately 10 mL) for HAI and Neut antibody assays were collected from subjects at Day 1 (immediately prior to the first study vaccination), and at approximately Days 29 (for A/H7N9-vaccinated subjects this was collected immediately prior to the second study vaccination) and 57 (A/H7N9-vaccinated subjects only) after the first study vaccination. Subjects who withdrew early had HAI and Neut antibody assays run on available sera, including sera from the early termination visit, if available.

Individual HAI and Neut results will be reported by the central immunology laboratory for the A/Shanghai/02/2013xPR8 vaccine strain and the A/Minnesota/11/2010 vaccine strain for the A/H3N2v study arm. Assay results will be reported as a reciprocal titer with values of $10*2^k$, where k=0, 1, 2, etc. The lower limit of detection for the HAI and Neut assays is 1:10; values below the limit of detection will be imputed for analysis using one-half the limit of detection (10/2 = 5). For analysis, the geometric mean (calculated on natural log scale) of repeated results for each sample will be computed and used as the response for all subsequent calculations. The variation arising from multiple measurements for an individual at a single time point will not be used in subsequent calculations/statistics. See Section 3.3 for definitions of derived variables for the analysis of HAI and Neut data.

Cytokine and chemokine levels in plasma obtained from venous blood samples were quantitatively measured at approximately Days -7, 1, 2, 4, and 8 (A/H3N2v-vaccinated subjects only) and at approximately Days 29, 30, 32, and 36 for A/H7N9-vaccinated subjects only using the Luminex platform. Cytokine and chemokine levels will be reported as concentrations. Values below the plate-specific LOD for each cytokine and chemokine will be imputed using 1/2 LOD.

4.5.2. -Omics Variables

Transcriptome profiling using RNA-Seq was performed on immune cell subsets collected at approximately Days -7, 1, 2, 4, and 8 (A/H3N2v-vaccinated subjects only) and at approximately Days 29, 30, 32, and 36 for A/H7N9-vaccinated subjects only. Total RNA was isolated using standard methods and subjected to ultra-

high-throughput parallel next generation sequencing. Gene expression levels for each gene were estimated based on the number of mapping sequencing reads.

Proteomics profiling was based on shotgun proteomics using multidimensional liquid chromatography coupled with tandem mass spectrometry and performed on immune cell samples collected at approximately Days -7, 1, 2, 4, and 8 (A/H3N2v-vaccinated subjects only) and at approximately Days 29, 30, 32, and 36 for A/H7N9-vaccinated subjects only. Protein abundance levels for each protein were estimated based on the sample peak intensity ratio compared to the sample that was prepared using a pool of all samples.

4.5.3. Safety Variables

Safety assessments included:

1. Study vaccine-related serious adverse events occurring from the time of the first study vaccination through approximately 1 month (A/H3N2v arm) and 12 months (A/H7N9 arms) after the last study vaccination.

2. Solicited Adverse Events – reactogenicity events occurring from the time of each study vaccination through 7 days after each study vaccination:
    a) Injection site reactions including pruritus (itching), ecchymosis (bruising), erythema (redness), induration (hardness)/swelling, pain, and tenderness.
    b) Systemic reactions including fever, feverishness (chills/shivering/sweating), fatigue (tiredness), malaise (general unwell feeling), myalgia (body aches/muscular pain exclusive of the injection site), arthralgia (joint pain exclusive of the injection site), headache, and nausea.

3. Unsolicited Adverse Events – study vaccine-related non-serious adverse events occurring from the time of each study vaccination through approximately 28 days after each study vaccination.

4. Medically-Attended Adverse Events including new-onset chronic medical conditions and potentially immune-mediated medical conditions occurring from the time of the first study vaccination through approximately 1 month (A/H3N2v arm) and 12 months (A/H7N9 arms) after the last study vaccination.

5. SAMPLE SIZE CONSIDERATIONS

The sample size is not based on a formal hypothesis. Rather it is based on practical considerations with the goal of gathering enough information to learn more about immune system responses to the vaccine/adjuvant on the molecular level. DMID Protocol 10-0074, entitled: *"A Randomized, Double-Blinded, Controlled, Phase I Study in Healthy Adults to Assess the Safety, Reactogenicity, and Immunogenicity of Intramuscular Subvirion Inactivated Monovalent Influenza A/H5N1 Virus Vaccine Administered With and Without AS03 Adjuvant: Standard & Systems Biology Analyses"*, showed that sample sizes in this range are sufficient to detect key differential signals and carry out systems biology analyses.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, interquartile range (IQR), minimum, and maximum) unless otherwise specified. The frequency and percentages (based on the analysis population size) of observed levels will be reported for all categorical measures. In general, all data will be listed and sorted by study arm and subject, and when appropriate, by study visit number within subject. All summary tables will be structured with a column for each study arm in the following order: Study Arm 1, Study Arm 2, and Study Arm 3.

6.2. Timing of Analyses

The primary CSR will be completed when all primary and secondary endpoint data are available and the data have been cleaned and locked. Any available data from the long-term, tertiary safety follow-up of applicable subjects may also be included. Additional data from the long-term, tertiary safety follow-up of applicable subjects, exploratory correlation analyses, and data from the proteomics portion of the study will be included in one or more addenda to the CSR.

6.3. Analysis Populations

6.3.1. Safety Analysis Population

The Safety Analysis population includes all subjects who received at least one dose of study vaccine.

6.3.2. Intention-to-Treat Analysis (ITT) Population

The intent-to-treat (ITT) population includes all subjects who received at least one dose of study vaccine and contributed both pre- and at least one post-study vaccination blood samples for serological assessment (HAI or Neut antibody assays) for which valid results were reported.

6.3.3. Per protocol (PP) Population

The per protocol (PP) population includes all subjects in the ITT subset with the following exclusions:

- Data from all available visits for subjects found to be ineligible at baseline.
- Data from all visits subsequent to major protocol deviations, such as:
  - Second study vaccination not received,
  - Receipt of non-study licensed live vaccine within 30 days before or after each study vaccination,
  - Receipt of non-study licensed inactivated vaccine within 14 days before or after each study vaccination,
  - Receipt of immunosuppressive therapy (e.g., corticosteroids) within 30 days before or after each study vaccination.
  - Data from any visit that occurs substantially out of window. Substantially out of window is defined as any visit that occurred outside of the pre-defined protocol window except for the following visits for which windows will be redefined as:

- Day 36: +4/-4
- Day 57: +7/-4

6.3.4. The -Omics Analysis Population

The 'omics analysis population for the -omics (transcriptomics and proteomics) endpoint analyses will include all subjects who received at least one study vaccination and contributed at least one pre- and one post-vaccination sample for 'omics testing for which valid results were reported. In addition, the following exclusions will be applied:

- post-second dose samples from subjects in Study Arms 2 and 3 that did not receive second vaccination will be excluded.
- samples that were collected substantially out-of-window will be excluded. Substantially out of window is defined as any visit that occurred outside of the pre-defined protocol window except for the following visits for which windows will be redefined as:
  - Day 36: +4/-4
  - Day 57: +7/-4

6.4. Covariates and Subgroups

There is no *a priori* plan to adjust the analyses of safety and immunogenicity for covariates or to report results by subgroups.

6.5. Missing Data

For proteomics data relative protein abundance values will be imputed using the k-nearest neighbors imputation algorithm as implemented in the *impute* R package (See SAP Addendum A for further details). Otherwise, no imputation will be performed for missing values.

6.6. Interim Analyses and Data Monitoring

No interim safety or immunogenicity review was conducted.

6.7. Multicenter Studies

This was a single site study.

6.8. Multiple Comparisons/Multiplicity

No multiple testing adjustments will be carried out for the safety, immunogenicity, and cytokine/chemokine endpoints. For -omics endpoints, the false-discovery rates (FDR) based on the Benjamini-Hochberg procedure as implemented in the R *p.adjust* function will be used to control the false positive rate among significantly differentially expressed genes, proteins, and enriched pathways.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

A flowchart presenting the disposition of study subjects, adapted from the CONSORT statement will be included (Figure 1). The flowchart will summarize the number of subjects who were eligible, enrolled and randomized, lost to follow-up, and analyzed, by study arm. Screened subjects who were ineligible for enrollment in the study will be presented by inclusion and exclusion criteria (Table 10). A listing of all subjects that received study product is provided in Listing 1. A listing of subjects who discontinued or terminated early from the study will be tabulated in Listing 2. The disposition of subjects in the study will be tabulated by study arm (Table 8). This table will show the number of subjects who were screened, enrolled and received the first vaccination, received both vaccinations, completed -omics blood draws, completed follow-up, and were included in the per-protocol analysis population. For each analysis population, a summary of excluded subjects by study arm and time point will be presented as shown in Table 9. A tabular listing of all subjects, visits, and observations excluded from certain analysis populations will be provided as specified in Listing 5.

7.2. Protocol Deviations

A summary of protocol deviations will be presented by the deviation category, type, and study arm in Table 2. This table will provide both the number of subjects and the number of deviations for each category and study arm. All subject-specific protocol deviations and non-subject-specific protocol deviations will be included in Listing 3 and Listing 4, respectively.

8. IMMUNOGENICITY EVALUATION

8.1. Serum Antibody Analysis

All immunogenicity analyses will be conducted for both the ITT and PP analysis populations. For each analysis population (ITT and PP) and serum antibody assay (HAI and Neut), geometric mean titers (GMTs and two-sided 95% confidence interval (CI) based on t-distribution) and percent seroconversion ([n/N (%)] and an exact (Clopper-Pearson) two-sided 95% CI as defined in Section 3.3) will be summarized by study arm and post-vaccination time point (Table 14, Table 15, Table 16, Table 17). GMTs over time will be summarized using time trend plots (Figure 2). Subject-level serum antibody titer responses at Day 29 post-last vaccination for all three study arms will be contrasted using bar plots (Figure 3). Differences between the treatments will be evaluated at Day 29 post-last dose using two-sided t-tests adjusting for unequal variance if necessary using a standard t-test or Welch's t-test (Table 18, Table 19, Table 20, Table 21). The decision on whether to adjust for unequal variance will be based on inspection of variances for the three study arms. Differences in seroconversion rates for Day 29 post-last dose will be assessed using a two-sided Fisher's exact test (Table 22, Table 23, Table 24, Table 25). Data listings of HAI and Neut assay results will be provided in Listing 8 sorted by study group, subject ID, and visit.

8.2. Plasma Cytokines/Chemokine Analysis

Pre-first vaccination cytokine/chemokine concentration will be determined using the mean concentrations among pre-vaccination measurements at Day -7 to -1 and Day 1. Cytokine/chemokine concentrations as well as their baseline fold changes will be summarized using minimum, Q1, median, Q3, maximum, and 95% CI of the median (starting with Table 26 and ending with Table 121). The 95% CI of the median concentration and median fold change from baseline will be determined by using the bootstrap method using 1,000 bootstrap replicates and will be visualized using time trend plots (Figure 4) and radar plots (Figure 5). To identify cytokines/chemokines that show a differential response from baseline, a two-sided Wilcoxon signed-rank test will be carried out for each study arm and post-vaccination time point (Table 122, Table 123). Significant differences in fold changes between study arms for shared post-vaccination time points will be evaluated using a Wilcoxon rank-sum test (Table 124, Table 125). Data listings of cytokine/chemokine assay results will be provided as shown in Listing 9 sorted by study group, subject ID, and visit.

9. TRANSCRIPTOMICS EVALUATIONS

The following sections describe the analysis of RNA-Seq endpoint data for the main Clinical Study Report. Analysis will be based on the PP analysis population. To the extent possible, transcriptomics analyses will be implemented using the R statistical programming language [1] and will utilize published R packages such as made available via the Bioconductor online resource [2]. At the start of the analysis, the most-up-to-date Bioconductor version, R statistical software, and other third-party software will be identified and used.

9.1. RNA-Seq Data Processing and Qc

9.1.1. Human Reference Genome Alignment and Quality Assessment

The latest version of the human reference genome assembly, gene models, and associated gene and transcript annotation information in the form of a Gene Transfer Format (GTF) file will be obtained from the ENSEMBL database [3]. Reference dataset versions will be documented in the CSR. Adapter sequences and low-quality 5' ending sequences will be removed from raw sequencing reads using the Trimmomatic software [4]. The impact of quality filtering will be assessed using FastQC software [5]. Quality-filtered reads will then be aligned to the reference transcriptome/genome using the latest version of HISAT2 splice-aware sequence aligner [6]. For each sample, the quality of reference alignments will be evaluated using the RSeQC software [7]. Quality measures for each laboratory will be summarized in tabular form, univariate boxplots and multivariate starplots (Figure 6).

9.1.2. Gene Expression Quantification and Data Normalization

Gene expression quantification will be carried out on the gene level using the featureCounts function of the Subread software [8]. Reads that overlap with multiple genes or map to multiple genomic locations on the reference genome will be excluded. Known ribosomal, transfer, and mitochondrial RNA genes will be removed from the final read count analysis dataset. In addition, genes located on the X and Y chromosomes will be excluded from the final read count analysis dataset to avoid gender-related biases.

Systematic sample differences in sequencing coverage will be corrected for by calculating scaling factors for each sample using the trimmed mean of M-values (TMM) method [9] as implemented in the edgeR software [10]. TMM-normalized moderated $\log_2$ counts per million (LCPM) for each gene will be calculated using the edgeR software [10]. As part of this step, a sequencing coverage–scaled count of 0.5 reads will be added to each gene to avoid taking the log of zero. LCPM distributions will be visualized using univariate boxplots and cumulative distribution function (CDF) plots before and after TMM-normalization.

9.1.3. Global Outlier and Batch Effect Detection

TMM-normalized LCPM will be standardized (z-score: mean=0, variance=1) and LCPM distributions across samples will be inspected for outliers (potential sample mislabeling, experimental error, etc.) and systematic effects (sample ordering, batch processing, etc.) using hierarchical clustering, multidimensional scaling, and principal component analysis (Figure 7). If outlying samples are discovered, corresponding clinical and laboratory metadata will be inspected for abnormalities. Based on these findings, a decision will be made as to whether the respective RNA-Seq observation should be removed from downstream analyses. The decision will be recorded in the CSR. If a noticeable batch effect is observed, unless an imbalance across vaccine groups is observed, the batch effect may be accounted for by adding a batch blocking factor as part of the negative binomial models (see Section 9.2).

9.1.4. Pre-Vaccination Transcriptomics Activity

The two pre-first vaccination time point RNA-Seq samples (Day -7 to -1 and Day 1) measure the baseline transcriptomics activity for each subject enrolled in this study. For each subject, baseline transcriptomic activity will be represented by averaging results for the two pre-first vaccination samples by using the sum of the read counts for each gene followed by TMM normalization as described in Section 9.1.2. Globally outlying Day -7 to -1 or Day 1 RNA-Seq samples will be excluded (see Section 9.1.3). The combined pre-first vaccination sample will be used as a reference to assess transcriptomics responses at Days 2, 4, 8, or 29 post-first vaccination. The Day 29 time point RNA-Seq sample also measures the pre-second vaccination transcriptomics activity for each subject enrolled in this study. This sample will be used as a reference to assess post-second vaccination responses (Days 2, 4, and 8 post-second vaccination) for subjects that received a second vaccine dose (Study Arms 2 and 3).

9.1.5. Log Fold Change Calculations

Log_2 fold changes (LFC) per gene for each subject and post-vaccination day will be calculated by subtracting pre-vaccination LCPM values from the respective post-vaccination day LCPM value. Two sets of LFC will be determined to separately assess post-first and post-second vaccination responses:

1. Day 2, 4, 8, or 29 vs. pre-first vaccination (averaged Day -7 to -1 and Day 1 results) LCPM for Study Arms 1, 2, and 3.
2. Day 30, 32, and 36 vs. pre-second vaccination (Day 29) LCPM for Study Arms 2 and 3

9.1.6. Determination of Cut Offs for Filtering Lowly Expressed Genes

Transcriptome-wide LCPM results will be used to identify a suitable minimum LCPM filter cut off to exclude lowly expressed genes excluding outlying samples. Genes with mean normalized expression levels below X log_2 counts per million across all samples (all study arms and time points) will be considered to be lowly expressed and will be excluded from the differential expression analysis. To determine a suitable cut off value for X, reverse cumulative distribution function (RCDF) plots summarizing the percentage of genes that exceeded a certain LCPM cut off will be plotted on the y-axis (Figure 8). The goal is to choose a cut off that retains between 10,000 and 14,000 genes for differential analysis. A default cut off of 1 count per million will be used if the targeted gene coverage is met. The filtered set will be used as input for down-stream transcriptomics endpoint analysis described in subsequent sections.

9.2. Identification of Differentially Expressed Genes

Negative binomial generalized linear models as implemented in the edgeR software [10] will be applied to identify differentially expressed (DE) genes after exclusion of outlying samples and lowly expressed genes. TMM-adjusted total read counts per sample will be included in the models as an offset to account for systematic sample differences. If systematic technical bias is detected and the effect is balanced across study arms, it will be accounted for by including a covariate or factor as part of the negative binomial models.

For all study arms, DE gene analysis will be carried out for each post-first vaccination study day (Day 2, 4, 8 or 29) in relation to pre-first vaccination gene expression levels (Section 9.2.1). For Study Arms 2 and 3, DE gene analysis will be carried out for each post-second vaccination study day (Day 30, 32, and 36) in relation to pre-second vaccination (Day 29) gene expression levels (Section 9.2.2). In addition, differences in DE gene responses between Study Arms will be assessed for all possible pairwise study arm comparisons (Section 9.2.3).

To control for testing multiple genes, the false-discovery rate (FDR) based on the Benjamini-Hochberg procedure [12] as implemented in the *p.adjust* R function will be applied for each model. In all cases, genes with an absolute fold change (effect size) of ≥ 1.5 compared to pre-vaccination or between Study Arms and FDR-adjusted p-value < 0.05 will be considered significantly DE. Depending on observed magnitude of differential expression effects, the pre-specified fold change cut off of 1.5-fold may be revised. The number of DE genes will be tabulated by study arm and time point (Table 126 and Table 127). In addition, DE gene listings that include gene annotations, $\log_2$ fold change estimates, p-values, FDR-adjusted p-values, likelihood ratio statistic and average LCPMs will be provided for each post-vaccination day (Table 128).

Treatment effects in terms of overall fold changes and FDR-adjusted p-values will be summarized for all genes that passed the low expression cut off using MA plots and Volcano plots (Figure 9). Overlap in DE genes between post-vaccination days and Study Arms will be summarized using UpSet plots as outlined in Figure 10 both in terms of overall numbers and separately for up/down- regulated DE genes.

The following sections describe the negative binomial model parameterization and hypotheses that will be tested.

9.2.1. Identification of DE Genes Compared to Pre-First Vaccination

For each post-first vaccination day and study arm, a negative binomial model will be fit to pre- and post-first vaccination read counts. Each model will include coefficients to estimate subject and pre- vs. post-first vaccination effects. The subject effects for estimating subject-specific pre-first vaccination levels will be added to account for paired samples from the same subject. Effects will be parameterized in the design matrix using dummy variables with one variable for each subject and an additional variable for the vaccination effect. For vaccination effects, the value will be set to 1 for post-first vaccination and 0 for pre-first vaccination observations. For each gene, the statistical significance of the post- vs. pre-vaccination effect will be evaluated using a likelihood ratio testing the following hypothesis on the $\log_2$ scale:

$$H_0: \mu_{\text{post-vaccination}} - \mu_{\text{pre-vaccination}} = 0, H_1: \mu_{\text{post-vaccination}} - \mu_{\text{pre-vaccination}} \neq 0$$

Genes with an absolute fold change (effect size) of ≥ 1.5 compared to pre-first vaccination and FDR-adjusted p-value < 0.05 will be considered to be significantly DE.

9.2.2. Identification of DE Genes Compared to Pre-Second Vaccination

For subjects receiving a second vaccination, for each post-second vaccination day (Day 30, 32, and 36) and study arm (Study Arms 2 and 3), a negative binomial model will be fit to pre- and post-second vaccination read counts across subjects. The model will be parameterized and evaluated as described in Section 9.2.1, except using Day 29 as the pre-vaccination reference.

9.2.3. Identification of Genes with Differential Responses Between Study Arms

For each shared post-first vaccination day (Day 1, 2 and pairwise study arm comparison, a negative binomial model will be fit to pre- and post-first vaccination read counts across the respective study arm pair (Study Arms 2 vs. 3, Study Arms 2 vs. 1, Arms 3 vs. 1). Each model will include coefficients to estimate subject and pre- vs. post-first vaccination effects for each of the two study arms that are being compared. For each shared post-first vaccination day, genes that significantly differed in their post vs. pre-first vaccination response between study arms will then be identified using contrasts testing the following hypothesis for study arm pair X and Y:

$$H_0: (\mu_{\text{post-vaccination Study Arm X}} - \mu_{\text{pre-vaccination Study Arm X}}) - (\mu_{\text{post-vaccination Study Arm Y}} - \mu_{\text{pre-vaccination Study Arm Y}}) = 0$$
$$H_1: (\mu_{\text{post-vaccination Study Arm X}} - \mu_{\text{pre-vaccination Study Arm X}}) - (\mu_{\text{post-vaccination Study Arm Y}} - \mu_{\text{pre-vaccination Study Arm Y}}) \neq 0$$

Similarly, for all post-second vaccination timepoints, models will be fit to identify DE genes between Study Arm 2 vs. 3 except using Day 29 as the pre-vaccination reference.

Genes with an absolute fold change difference (effect size) of ≥ 1.5 in their response between study arms and FDR-adjusted p-value < 0.05 will be considered significantly DE between Study Arms.

9.3. Determination of higher order functional and temporal organization of differentially expressed genes

9.3.1. Subject-level Response Heatmaps

Per-subject baseline $\log_2$ fold change patterns for DE genes will be visualized across Study Arms for each post-vaccination day and fold change set (post-first vaccination and post-second vaccination) using heatmaps (Figure 11, left panel). Genes identified as DE for any of the comparisons described in Section 9.2 will be included as part of this analysis. Heatmaps will include subject and gene dendrograms based on uncentered Pearson correlation distance and complete linkage hierarchical clustering.

9.3.2. Identification of Co-Expressed Gene Clusters

Unsupervised multiscale bootstrapping as implemented in the pvclust R package [12] will be carried out to identify robust clusters of genes with correlated $\log_2$ fold change responses for each fold change set (post-first vaccination and post-second vaccination). Bootstrap resampling will be based on uncentered Pearson correlation distances between $\log_2$ fold change responses in combination with complete linkage clustering. Genes identified as DE for any of the comparisons described in Section 9.2 will be included as part of this analysis. Clusters with a bootstrap probability > 0.95 and maximum distance between cluster members of 0.5 (equivalent to minimum uncentered Pearson correlation of 0.5 among all members) will be considered robust gene clusters. Resulting robust gene cluster dendrograms will be visualized (Figure 11, middle panel) and cluster information will be tabulated (Table 129). In addition, mean $\log_2$ fold change for robust gene clusters (mean across all member genes in a cluster) and associated 95% bootstrap CIs (1000 replicates each) will be visualized by study arm across the respective post-vaccination days (Figure 11, right panel).

9.3.3. Pathway Enrichment Analysis

Pathway enrichment analysis will be carried out separately for each DE gene set identified (post vs. pre-vaccination as well as between study arm comparisons) using published pathway information obtained from KEGG [13] (KEGG Pathways), MSigDB [14] (MSigDB Reactome Pathways, MSigDB GO Biological Process, and MSigDB Immunologic Signatures), and Blood Transcription Modules [15]. Pathway enrichment analysis will be conducted using the goseq algorithm [16] to adjust for RNA-Seq-specific gene length bias[1]. Pathways with a FDR-adjusted p-value < 0.05 will be considered significantly enriched. Due to the relatively increased number of pathways in the MSigDB Immunologic Signatures set, a more stringent FDR-adjusted

[1] For RNA-Seq, longer genes tend to obtain higher read counts compared to shorter genes as they occupy a higher proportion of the transcriptome/genome space. As such gene expression based on read counts is not only proportional to the actual expression but a combination of read length and actual expression. This results in greater statistical power for detecting differential genes if they are long and highly expressed. The effect needs to be addressed in gene set enrichment analysis as comparisons are made between sets of genes. Otherwise gene sets that on average contain larger genes will more likely be identified as significantly enriched compared to gene sets with on average smaller genes.

p-value < 0.01 will be used. Pathway enrichment results including gene set annotation, gene set size, number of DE genes in a gene set by up and down-regulation, Jaccard similarity index, p-value, and FDR-adjusted p-value will be listed (Table 130). For enriched KEGG pathways, $\log_2$ fold change from baseline will be overlaid on top of pathway maps and significantly up/and down-regulated genes (DE genes) will be highlighted to facilitate visual interpretation **(**Figure 12, left panel). Overlap between sets of identified enriched pathways will be summarized using UpSet plots (similar to Figure 10). Gene set enrichment trends across study arms and post-vaccination days will be visualized using heatmaps color-coded by enrichment score (-1 x $\log_{10}$(enrichment p-value)) (Figure 12, middle panel) as well as time trend plots of median pathway responses (based on median average $\log_2$ fold changes of all pathway members) and associated 95% bootstrap confidence intervals (CIs) (similar to Figure 11, right panel).

9.3.4. Protein-Protein Interactions Network Analysis

To further characterize DE genes, experimentally determined protein-protein interaction networks including known Influenza A-host interactions centered around DE genes will be generated using data from the IntAct database [17]. Networks will be visualized using *Cytoscape* [18] (Figure 12, right panel). This analysis will be performed for DE genes that differed between the H7N9 arms.

10. SAFETY EVALUATIONS

Summaries and analysis of safety data will be presented for the Safety Analysis Population. These include reactogenicity following each study vaccination, unsolicited adverse events, and adverse events of special interest including SAEs/MAAEs, new-onset chronic medical conditions, and potentially immune-mediated medical conditions. The goal of the safety summaries is to provide information to guide the exploratory correlation analysis to identify transcriptomic/proteomic changes that are predictive of certain safety profiles. The exploratory correlation analysis will be described in an addendum to this SAP. The following sections describe planned baseline and safety summaries.

10.1. Demographic and Other Baseline Characteristics

Summaries of age, sex, ethnicity, and race will be presented by study arm and overall for all enrolled subjects (Table 11 and Table 12). Ethnicity will be categorized as Hispanic or Latino, or not Hispanic and not Latino. In accordance with NIH reporting policy, subjects may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the CRF as "No" to each racial option. Individual subject listings will be presented for all demographics (Listing 6); pre-existing medical conditions (Listing 7); and concomitant medications (Listing 15). The number of subjects with pre-existing medical conditions by MedDRA System Organ Class and study arm will we provided as shown in Table 13. Summaries of medications that were started prior to dosing and continuing at the time of dosing will be presented by WHO Drug Level 1 and Level 2 codes and study arm for subjects in the safety population (Table 153). The number of doses of study product administered to subjects will be presented by study arm as part of the subject disposition table (Table 8).

10.2. Adverse Events

10.2.1. Solicited Events and Symptoms

Systemic and upper respiratory (local) solicited adverse events were collected pre-vaccination, and systemic and local solicited adverse events were collected 30 minutes post-vaccination and then daily for 7 days after first vaccination and graded on a scale of 0 (absent), 1 (mild), 2 (moderate) and 3 (severe). The grading scales for solicited systemic and local (administration site) adverse events are provided in Table 3, Table 4, Table 5, and Table 6. The percentage of subjects and associated exact Clopper–Pearson 95% CI reporting at least one solicited adverse event will be summarized for each solicited adverse event, any systemic symptom, any local symptom, and any symptoms (Table 132, Table 133, Table 134). In addition, for each systemic and local event, any systemic event, any local event, and any solicited event, the maximum severity over 7 days after each vaccination will be summarized for the Safety population. For each event the denominator is the number of subjects with non-missing data for the specific event (Table 135, Table 136, Table 137). The number of subjects reporting a solicited adverse event will be summarized for each day post vaccination in a summary table (Table 138, Table 139, Table 140, Table 141, Table 142) and graphically in a bar chart (Figure 13). Solicited adverse events by subject will be presented in Listing 10 and Listing 11.

10.2.2. Unsolicited Adverse Events

When calculating the incidence of unsolicited AEs (i.e., on a per subject basis), each subject will only be counted once at the highest severity and/or relationship, and any repetitions of the same AEs within a subject will be ignored; the denominator will be the total number of subjects in the safety population. The number and percentage and associated 95% CI of subjects reporting at least one unsolicited AE will be summarized by MedDRA system organ class and preferred term (Table 143, Table 144, Table 145). Denominators for

percentages are the number of subjects who received the study vaccination summarized. In addition, a summary of the percentage of subjects by MedDRA system organ class, preferred term, severity, and relationship to study product will be provided (Table 146, Table 147, Table 148). Bar charts of the incidence of non-serious adverse events by severity and MedDRA system organ class will be generated as shown in Figure 14. A listing of all reported AEs by subject sorted by study group, subject ID, and AE Number will be presented as specified in
Listing 12.

10.3. Deaths, Serious Adverse Events and other Significant Adverse Events

The number and percentage of subjects experiencing adverse events of special interest will be tabulated by study arm as presented in Table 131. The following listings will be presented including Subject ID, AE Description, AE Onset Date/End Date, Last Vaccination Received/Days Post Vaccination, Reason Reported as an SAE, Relationship to Treatment, Alternate Etiology if not Related, Outcome, and Duration of Event (days):

- Deaths and Serious Adverse Events (Table 149)
- Non-Serious, Unsolicited, Moderate or Severe Adverse Events (Table 150)
- Adverse Events of Special Interest (Table 151)

10.4. Vital Signs and Physical Evaluations

Vital signs will be tabulated by study arm in Table 152. A listing of vital signs will be presented (Listing 13). Targeted physical examinations will be performed, if indicated, based on a subject's medical history. A listing of physical exam findings will be presented (Listing 14).

11. TERTIARY AND EXPLORATORY PROTEOMICS ANALYSES

Analysis of tertiary and exploratory endpoints will be described in separate addenda to this SAP which will be finalized prior to analysis of the proteomics data.

12. EXPLORATORY CORRELATION ANALYSES

Correlation analysis between the -omics data (transcriptomics and proteomics) and serum antibody/plasma cytokines as well as correlated with certain safety profiles will be described in separate addenda to this SAP which will be finalized prior to the proteomics data lock.

13. REPORTING CONVENTIONS

P-values ≥0.0001 and ≤0.9999 will be reported to 4 decimal places; p-values less than 0.0001 will be reported as "<0.0001"; p-values greater than 0.9999 will be reported as "> 0.9999". The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, Q1, Q3, minimum and maximum will use the same number of decimal places as the original data.

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15. LISTING OF TABLES, FIGURES, AND LISTINGS

Table, figure, and listing shells are presented in Appendices 1, 2, and 3.

APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

9.1 Overall Study Design and Plan Description

Table 1: Study Design and Sample Size

Subjects	First Study Vaccination (Day 1)	Second Study Vaccination (Day 29±2 days)	Study Arm Label
10	15 µg A/H3N2v*	N/A	Study Arm 1 A/H3N2v, D1
10	3.75 µg A/H7N9 + AS03	3.75 µg A/H7N9 + AS03	Study Arm 2 A/H7N9 + AS03 D1, 29
10	3.75 µg A/H7N9+PBS	3.75 µg A/H7N9 + PBS	Study Arm 3 A/H7N9 + PBS, D1, 29
Total N=30 vaccinated subjects			

*Unadjuvanted

10.2 Protocol Deviations

Table 2: Distribution of Protocol Deviations by Category, Type, and Treatment Group

Category	Deviation Type	Study Arm 1 A/H3N2v, D1 (N=X)		Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)		Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
Eligibility/enrollment	Any type								
	Did not meet inclusion criterion	x	x			x	x	x	x
	Met exclusion criterion								
	ICF not signed prior to study procedures								
	Other								
Treatment administration schedule	Any type								
	Out of window visit								
	Missed visit/visit not conducted								
	Missed treatment administration								
	Delayed treatment administration								
	Other								
Follow-up visit schedule	Any type								
	Out of window visit								
	Missed visit/visit not conducted								
	Other								
Protocol procedure/assessment	Any type								
	Incorrect version of ICF signed								
	Blood not collected								
	Urine not collected								
	Other specimen not collected								
	Too few aliquots obtained								
	Specimen result not obtained								
	Required procedure not conducted								
	Required procedure done incorrectly								
	Study product temperature excursion								

Table 2: Distribution of Protocol Deviations by Category, Type, and Treatment Group *(continued)*

Category	Deviation Type	Study Arm 1 A/H3N2v, D1 (N=X)		Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)		Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
	Specimen temperature excursion								
	Other								
Treatment administration	Any type								
	Required procedure done incorrectly								
	Study product temperature excursion								
	Other								
Blinding policy/procedure	Any type								
	Treatment unblinded								
	Other								
N=Number of enrolled subjects.									

12.2.2 Displays of Adverse Events

Solicited Adverse Event Grading Scale

Table 3: Local (Injection Site) Reactogenicity Grading

Local (Injection Site) Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain – experienced without touching the injection site (spontaneous discomfort)	Subject is aware of pain, but it does not interfere with daily activity, **and** no pain medication is taken	There is interference with daily activity **or** it requires repeated use of a non-narcotic pain reliever for >24 hours	Pain prevents daily activity or requires any use of a narcotic pain reliever
Tenderness – hurts only when injection site is touched or the arm is moved	The area immediately surrounding the injection site hurts only when touched or with arm motion, **and** it does **not** interfere with daily activity	The area immediately surrounding the injection site hurts when touched or with arm motion, **and** it interferes with daily activity	The area immediately surrounding the injection site hurts when touched or with arm motion, **and** it prevents daily activity
Pruritus (Itching)	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Ecchymosis (Bruising)*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Erythema (Redness)*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Induration (Hardness)/Swelling*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity

* Will also be measured in mm but size will not be used as halting criteria.

Table 4: Local (Injection Site) Reactogenicity Measurements

Local (Injection Site) Reaction	Small	Medium	Large
Ecchymosis (Bruising)*	<20 mm	20 mm – 50 mm	>50 mm
Erythema (Redness)*	<20 mm	20 mm – 50 mm	>50 mm
Induration (Hardness)/Swelling*	<20 mm	20 mm – 50 mm	>50 mm

* Will not be used as halting criteria.

Table 5: Subjective Systemic Reactogenicity Grading

Systemic (Subjective)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Feverishness (Chills/Shivering/Sweating)	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Fatigue (Tiredness)	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Malaise (General Unwell Feeling)	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Myalgia (Body Aches/Muscular Pain)*	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity

Systemic (Subjective)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Arthralgia (Joint Pain)*	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Headache	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Nausea	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity

* Not at injection site.

Table 6: Quantitative Systemic Reactogenicity Grading

Systemic (Quantitative)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever* - oral†	38.0°C – 38.4°C 100.4°F – 101.1°F	38.5°C – 38.9°C 101.2°F – 102.0°F	>38.9°C >102.0°F

Note: Oral temperature assessed on Day 1 prior to the first study vaccination will be considered as baseline.
* A fever can be considered not related to the study product if an alternative etiology can be documented.
† Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.

Table 7: Additional Adverse Event Severity Grading

Physiologic Parameter	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Bradycardia - beats per minute	45 – 49	40 – 44	<40
Tachycardia - beats per minute	116 – 130	131 – 155	>155
Hypotension (systolic) mm Hg	80 – 84	75 – 79	<75
Hypotension (diastolic) mm Hg	50 – 54	45 – 49	<45
Hypertension (systolic) mm Hg	151 – 155	156 – 160	>160
Hypertension (diastolic) mm Hg	96 – 100	101 – 105	>105

14.1 Description of Study Subjects

14.1.1 Disposition of Subjects

Table 8: Subject Disposition by Treatment Group – All Enrolled Subjects

Subject Disposition	Study Arm 1 A/H3N2v, D1 (N=X)		Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)		Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)	
	n	%	n	%	n	%
Screened	x	--	x	--	x	--
Enrolled/Randomized	x	100	x	100	x	100
Received One Treatment	x	xx	x	xx	x	xx
Received All Scheduled Treatments [a]	x	xx	x	xx	x	xx
Completed Day 2 Omics Blood Draw	x	xx	x	xx	x	xx
Completed Day 4 Omics Blood Draw	x	xx	x	xx	x	xx
Completed Day 8 Omics Blood Draw	x	xx	n/a	n/a	n/a	n/a
Completed Day 29 Omics Blood Draw	n/a	n/a	x	xx	x	xx
Completed Day 30 Omics Blood Draw	n/a	n/a	x	xx	x	xx
Completed Day 32 Omics Blood Draw	n/a	n/a	x	xx	x	xx
Completed Day 36 Omics Blood Draw	n/a	n/a	x	xx	x	xx
Completed Follow-up (Study Day 29)[a]			n/a	n/a	n/a	n/a
Completed Follow-up (Study Day 366)[a]	n/a	n/a	x	xx	x	xx
Completed Per Protocol[b]	x	xx	x	xx	x	xx

N=number of enrolled subjects
[a] Refer to Listing of Early Terminations or Discontinued Subjects for reasons subjects discontinued or terminated early.
[b] Refer to Listing of Analysis Populations Exclusions for reasons subjects are excluded from the Analysis populations.

Table 9: Analysis Populations by Treatment Group and Time Point – All Enrolled Subjects

Analysis Populations	Time Point	Reason Subjects Excluded	Study Arm 1 (A/H3N2v, D1) (N=X)		Study Arm 1 (A/H3N2v, D1) (N=X)		Group 3 3.75 µg A/H7N9 + PBS (D1, 29) (N=X)	
			n	%	n	%	%	n
Safety Analysis Population	Any Time Point	Any Reason	x	xx	x	xx	x	xx
		[Reason 1, for example: Did not meet eligibility criteria]						
		[Reason 2]						
		[Reason 3]						
		[Reason 4]						
ITT Analysis Population	Any Time Point	Any Reason						
		[Reason 1]						
		[Reason 2]						
PP Analysis Population	Any Time Point	Any Reason						
		[Reason 1]						
		[Reason 2]						
	Day 29 (Post-Vaccination 1)	Any Reason						
		[Reason 1, for example: Did not meet eligibility criteria]						
		[Reason 2]						
		[Reason 3]						

N=Number of enrolled subjects.

Table 10: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x	xx
Inclusion	Any inclusion criterion	x	xx
	[inclusion criterion 1]	x	xx
	[inclusion criterion 2]	x	xx
	[inclusion criterion 3]	x	xx
Exclusion	Any exclusion criterion	x	xx
	[exclusion criterion 1]	x	xx
	[exclusion criterion 2]	x	xx
	[exclusion criterion 3]	x	xx
Eligible but not enrolled		x	xx

[a] More than one criterion may be marked per subject.
[b] Denominator for percentages is the total number of screen failures.

14.1.2 Demographic Data by Study Group

Table 11: Summary of Categorical Demographic and Baseline Characteristics by Treatment Group - All Enrolled Subjects

Variable	Characteristic	Study Arm 1 A/H3N2v, D1 (N=X)		Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)		Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%
Sex	Male	x	xx	x	xx	x	xx	x	xx
	Female								
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx	x	xx
	Hispanic or Latino								
	Not Reported								
	Unknown								
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx	x	xx
	Asian								
	Native Hawaiian or Other Pacific Islander								
	Black or African American								
	White								
	Multi-Racial								
	Unknown								
N=Number of enrolled subjects.									

Table 12: Summary of Continuous Demographic and Baseline Characteristics by Treatment Group - All Enrolled Subjects

Variable	Statistic	Study Arm 1 A/H3N2v, D1 (N=X)	Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)	Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)	All Subjects (N=X)
Age (units)	Mean	x x	x.x	x.x	x x
	Standard Deviation	x x	x.x	x.x	x x
	Median	x	x	x	x
	Minimum	x	x	x	x
	Maximum	x	x	x	x
BMI	Mean	x x	x.x	x.x	x x
	Standard Deviation	x x	x.x	x.x	x x
	Median	x	x	x	x
	Minimum	x	x	x	x
	Maximum	x	x	x	x
N=Number of enrolled subjects.					

14.1.3 Prior and Concurrent Medical Conditions

Table 13: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class and Treatment Group

MedDRA System Organ Class	Study Arm 1 A/H3N2v, D1 (N=X)		Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)		Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%	n	%
Any SOC	x	xx	x	xx	x	xx	x	xx
[SOC 1]								
[SOC 2]								

Note: N=Number of subjects in the Safety Population
n = Number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.

14.2 Immunogenicity Data

14.2.1 Serum Antibody Data

Table 14: Summaries of Hemagglutination Inhibition Antibody Titer by Study Day and Treatment Group in the Intent-to-Treat Population

Time Point	Statistic	Study Arm 1 A/H3N2v, D1 (N=X)	Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)	Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)
Day 1 (Pre-Vaccination 1)	n	x	x	x
	GMT (95% CI)	x x (x.x,x x)	x.x (x x,x.x)	x x (x x,x.x)
Day 29 (Post-Vaccination 1)	n	x	x	x
	GMT (95% CI)	x x (x.x,x x)	x.x (x x,x.x)	x x (x x,x.x)
	Seroconversion n/N (%) [95% CI]	xx/xx (xx%) [xx, xx]	xx/xx (xx%) [xx, xx]	xx/xx (xx%) [xx, xx]
Day 29 (Post-Vaccination 2)	n	n/a	x	x
	GMT (95% CI)	n/a	x.x (x x,x.x)	x x (x x,x.x)
	Seroconversion n/N (%) [95% CI]	n/a	xx/xx (xx%) [xx, xx]	xx/xx (xx%) [xx, xx]

N = Number of subjects in the Intent-to-Treat Population
n = Number of subjects with available results
GMT = Geometric mean titer

Seroconversion is defined as having a pre -vaccination titer <1:10 and a post - vaccination titer ≥1:40 or a pre - vaccination titer ≥1:10 and a minimum four -fold rise in post-vaccination antibody titer

Tables with similar format:

Table 15: Summaries of Hemagglutination Inhibition Antibody Titer by Study Day and Treatment Group in the Per-Protocol Population

Table 16: Summaries of Neutralizing Antibody by Study Day and Treatment Group in the Intent-to-Treat Population

Table 17: Summaries of Neutralizing Antibody by Study Day and Treatment Group in the Per-Protocol Population

Table 18: t-Test Results for Comparing Day 29 Post-Last Vaccination Hemagglutination Inhibition Antibody Titer between Treatment Groups in the Intent-to-Treat Population

Statistic	Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X) vs. Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)	Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X) vs. Study Arm 1 A/H3N2v, D1 (N=X)	Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X) vs. Study Arm 1 A/H3N2v, D1 (N=X)
n	xx	xx	xx
GMT Ratio (95% CI)	x xx (x xx,x xx)	x xx (x xx,x xx)	x.xx (x.xx,x.xx)
t-statistic	x xxx	x.xxx	x xxx
P-value	x xxx	x.xxx	x xxx

N = Number of subjects in the Intent-to-Treat Population
n = Number of subjects with available results
P-value = two-sided Welch's or standard t-test P-value

Tables with similar format:

Table 19: t-Test Results for Comparing Day 29 Post-Last Vaccination Hemagglutination Inhibition Antibody Titer Between Treatment Groups in the Per-Protocol Population

Table 20: t-Test Results for Comparing Day 29 Post-Last Vaccination Neutralizing Antibody Titer Between Treatment Groups in the Intent-to-Treat Population

Table 21: t-Test Results for Comparing Day 29 Post-Last Vaccination Neutralizing Antibody Titer Between Treatment Groups in the Per-Protocol Population

Table 22: Fisher's Exact Test Results for Comparing Day 29 Post-Last Vaccination Seroconversion based on Hemagglutination Inhibition Antibody Titer Between Treatment Groups in the Intent-to-Treat Population

	Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X) vs. Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)	**Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X) vs. Study Arm 1 A/H3N2v, D1 (N=X)**	**Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X) vs. Study Arm 1 A/H3N2v, D1 (N=X)**
n	xx	xx	xx
Seroconversion n/N (%) [95% CI]	xx/xx (xx%) [xx, xx]	xx/xx (xx%) [xx, xx]	xx/xx (xx%) [xx, xx]
Exact Odds Ratio(95% CI)	x.xxx	x xxx	x.xxx
p-value	x.xxx	x xxx	x.xxx

N = Number of subjects in the Intent-to-Treat Population
n = Number of subjects with available results
P-value = two-sided Fisher's Exact test P-vale.

Tables with similar format:

Table 23: Fisher's Exact Test Results for Comparing Day 29 Post-Last Vaccination Seroconversion based on Hemagglutination Inhibition Antibody Titer Between Treatment Groups in the Per-Protocol Population

Table 24: Fisher's Exact Test Results for Comparing Day 29 Post-Last Vaccination Seroconversion based on Neutralizing Antibody between Treatment Groups in the Intent-to-Treat Population

Table 25: Fisher's Exact Test Results for Comparing Day 29 Post-Last Vaccination Seroconversion based on Neutralizing Antibody between Treatment Groups in the Per-Protocol Population

14.2.2 Plasma Cytokine/Chemokine Data

Table 26: Fractalkine Concentration by Study Visit Day and Treatment Group in the Intent-to-Treat Population

Time Point	Statistic	Study Arm 1 A/H3N2v, D1 (N=X)	Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)	Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)
Day 1 (Pre-Vaccination 1)	n	x	x	x
	Min	x xx	x xx	x xx
	Q1	x x	x.x	x x
	Median (95% CI)	x x (x x - x.x)	x.x (x x - x.x)	x x (x x - x x)
	Q3	x x	x.x	x x
	Max	x xx	x xx	x xx
Day 2 (Post-Vaccination 1)	n	x	x	x
	Min	x xx	x xx	x xx
	Q1	x x	x.x	x x
	Median (95% CI)	x x (x x - x.x)	x.x (x x - x.x)	x x (x x - x x)
	Q3	x x	x.x	x x
	Max	x xx	x xx	x xx
Day 4 (Post-Vaccination 1)	n	x	x	x
	Min	x xx	x xx	x xx
	Q1	x x	x.x	x x
	Median (95% CI)	x x (x x - x.x)	x.x (x x - x.x)	x x (x x - x x)
	Q3	x x	x.x	x x
	Max	x xx	x xx	x xx
Day 8 (Post-Vaccination 1)	n	x	n/a	n/a
	Min	x xx	n/a	n/a
	Q1	x x	n/a	n/a
	Median (95% CI)	x x (x x - x.x)	n/a	n/a
	Q3	x x	n/a	n/a

Time Point	Statistic	Study Arm 1 A/H3N2v, D1 (N=X)	Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)	Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)
	Max	x xx	n/a	n/a
Day 29 (Post-Vaccination 1)	n	n/a	x	x
	Min	n/a	x xx	x xx
	Q1	n/a	x.x	x x
	Median (95% CI)	n/a	x.x (x x - x.x)	x x (x x - x x)
	Q3	n/a	x.x	x x
	Max	n/a	x xx	x xx
Day 2 (Post-Vaccination 2)	n	n/a	x	x
	Min	n/a	x xx	x xx
	Q1	n/a	x.x	x x
	Median (95% CI)	n/a	x.x (x x - x.x)	x x (x x - x x)
	Q3	n/a	x.x	x x
	Max	n/a	x xx	x xx
Day 4 (Post-Vaccination 2)	n	n/a	x	x
	Min	n/a	x xx	x xx
	Q1	n/a	x.x	x x
	Median (95% CI)	n/a	x.x (x x - x.x)	x x (x x - x x)
	Q3	n/a	x.x	x x
	Max	n/a	x xx	x xx
Day 8 (Post-Vaccination 2)	n	n/a	x	x
	Min	n/a	x xx	x xx
	Q1	n/a	x.x	x x
	Median (95% CI)	n/a	x.x (x x - x.x)	x x (x x - x x)
	Q3	n/a	x.x	x x
	Max	n/a	x xx	x xx

Time Point	Statistic	Study Arm 1 A/H3N2v, D1 (N=X)	Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)	Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)
N= Number of subjects in the Intent-to-Treat analysis population n= Number of subjects with valid results Min=Minimum Q1= First quartile Q3=Third quartile Max=Maximum The 95% CI of the median is based on the bootstrap method.				

Tables with similar format:

Table 27: Fractalkine Concentration by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 28: GM-CSF Concentration by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 29: GM-CSF Concentration by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 30: Interferon-gamma Concentration by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 31: Interferon-gamma Concentration by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 32: Interleukin 1 beta Concentration by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 33: Interleukin 1 beta Concentration by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 34: Interleukin 2 Concentration by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 35: Interleukin 2 Concentration by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 36: Interleukin 4 Concentration by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 37: Interleukin 4 Concentration by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 38: Interleukin 5 Concentration by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 39: Interleukin 5 Concentration by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 40: Interleukin 6 Concentration by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 41: Interleukin 6 Concentration by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 42: Interleukin 7 Concentration by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 74: Fractalkine Fold Change by Study Visit Day and Study Group in the Intent-To-Treat Population

Time Point	Statistic	Study Arm 1 A/H3N2v, D1 (N=X)	Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)	Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)
Day 2 (Post-Vaccination 1)	n	x	x	x
	Min	x xx	x xx	x xx
	Q1	x x	x.x	x x
	Median (95% CI)	x x (x x - x.x)	x.x (x x - x.x)	x x (x x - x x)
	Q3	x x	x.x	x x
	Max	x xx	x xx	x xx
Day 4 (Post-Vaccination 1)	n	x	x	x
	Min	x xx	x xx	x xx
	Q1	x x	x.x	x x
	Median (95% CI)	x x (x x - x.x)	x.x (x x - x.x)	x x (x x - x x)
	Q3	x x	x.x	x x
	Max	x xx	x xx	x xx
Day 8 (Post-Vaccination 1)	n	x	n/a	n/a
	Min	x xx	n/a	n/a
	Q1	x x	n/a	n/a
	Median (95% CI)	x x (x x - x.x)	n/a	n/a
	Q3	x x	n/a	n/a
	Max	x xx	n/a	n/a
Day 29 (Post-Vaccination 1)	n	n/a	x	x
	Min	n/a	x xx	x xx
	Q1	n/a	x.x	x x
	Median (95% CI)	n/a	x.x (x x - x.x)	x x (x x - x x)
	Q3	n/a	x.x	x x
	Max	n/a	x xx	x xx

Time Point	Statistic	Study Arm 1 A/H3N2v, D1 (N=X)	Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)	Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)
Day 2 (Post-Vaccination 2)	n	n/a	x	x
	Min	n/a	x xx	x xx
	Q1	n/a	x.x	x x
	Median (95% CI)	n/a	x.x (x x - x.x)	x x (x x - x x)
	Q3	n/a	x.x	x x
	Max	n/a	x xx	x xx
Day 4 (Post-Vaccination 2)	n	n/a	x	x
	Min	n/a	x xx	x xx
	Q1	n/a	x.x	x x
	Median (95% CI)	n/a	x.x (x x - x.x)	x x (x x - x x)
	Q3	n/a	x.x	x x
	Max	n/a	x xx	x xx
Day 8 (Post-Vaccination 2)	n	n/a	x	x
	Min	n/a	x xx	x xx
	Q1	n/a	x.x	x x
	Median (95% CI)	n/a	x.x (x x - x.x)	x x (x x - x x)
	Q3	n/a	x.x	x x
	Max	n/a	x xx	x xx

N= Number of subjects in the Intent-to-Treat population
n= Number of subjects with valid results
Min=Minimum
Q1= First quartile
Q3=Third quartile
Max=Maximum
The 95% CI of the median is based on the bootstrap method.

Tables with similar format:

Table 75: Fractalkine Fold Change by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 76: GM-CSF Fold Change by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 77: GM-CSF Fold Change by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 78: Interferon-gamma Fold Change by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 79: Interferon-gamma Fold Change by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 80: Interleukin 1 beta Fold Change by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 81: Interleukin 1 beta Fold Change by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 82: Interleukin 2 Fold Change by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 83: Interleukin 2 Fold Change by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 84: Interleukin 4 Fold Change by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 85: Interleukin 4 Fold Change by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 86: Interleukin 5 Fold Change by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 87: Interleukin 5 Fold Change by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 88: Interleukin 6 Fold Change by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 89: Interleukin 6 Fold Change by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 90: Interleukin 7 Fold Change by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 91: Interleukin 7 Fold Change by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 92: Interleukin 8 Fold Change by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 93: Interleukin 8 Fold Change by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 94: Interleukin 10 Fold Change by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 95: Interleukin 10 Fold Change by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 96: Interleukin-12, p70 Fold Change by Study Visit Day and Treatment Group in the Intent-To-Treat Population

Table 97: Interleukin-12, p70 Fold Change by Study Visit Day and Treatment Group in the Per-Protocol Population

Table 122: Wilcoxon Signed-Rank Test Results for Comparing Cytokine/Chemokine Concentrations between Pre- and Post-Vaccination Time Points in the Intent-To-Treat Population

		Study Arm 1 A/H3N2v, D1 (N=X)	Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)	Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)
Cytokine	**Comparison**	**Wilcoxon Statistic (P-value)**	**Wilcoxon Statistic (P-value)**	**Wilcoxon Statistic (P-value)**
Fractalkine	Day 2 (Post -Vaccination 1) vs. Pre-Vaccination 1	x xxx (x xxx)	x xxx (x xxx)	x.xxx (x xxx)
Fractalkine	Day 4 (Post-Vaccination 1) vs. Pre-Vaccination 1	x xxx (x.xxx)	x xxx (x xxx)	x.xxx (x xxx)
Fractalkine	Day 8 (Post-Vaccination 1) vs. Pre-Vaccination 1	x xxx (x.xxx)	n/a	n/a
Fractalkine	Day 29 (Post-Vaccination 1) vs. Pre-Vaccination 1	n/a	x xxx (x xxx)	x.xxx (x xxx)
Fractalkine	Day 2 (Post-Vaccination 2) vs. Pre-Vaccination 2	n/a	x xxx (x xxx)	x.xxx (x xxx)
Fractalkine	Day 4 (Post-Vaccination 2) vs. Pre-Vaccination 2	n/a	x xxx (x xxx)	x.xxx (x xxx)
Fractalkine	Day 8 (Post-Vaccination 2) vs. Pre-Vaccination 2	n/a	x xxx (x xxx)	x.xxx (x xxx)
GM-CSF	Day 2 (Post -Vaccination 1) vs. Pre-Vaccination 1	x xxx (x xxx)	x xxx (x xxx)	x.xxx (x xxx)
GM-CSF	Day 4 (Post-Vaccination 1) vs. Pre-Vaccination 1	x xxx (x.xxx)	x xxx (x xxx)	x.xxx (x xxx)
GM-CSF	Day 8 (Post-Vaccination 1) vs. Pre-Vaccination 1	x xxx (x.xxx)	n/a	n/a
GM-CSF	Day 29 (Post-Vaccination 1) vs. Pre-Vaccination 1	n/a	x xxx (x xxx)	x.xxx (x xxx)
GM-CSF	Day 2 (Post-Vaccination 2) vs. Pre-Vaccination 2	n/a	x xxx (x xxx)	x.xxx (x xxx)
GM-CSF	Day 4 (Post-Vaccination 2) vs. Pre-Vaccination 2	n/a	x xxx (x xxx)	x.xxx (x xxx)
GM-CSF	Day 8 (Post-Vaccination 2) vs. Pre-Vaccination 2	n/a	x xxx (x xxx)	x.xxx (x xxx)
Interferon-gamma	Day 2 (Post -Vaccination 1) vs. Pre-Vaccination 1	x xxx (x xxx)	x xxx (x xxx)	x.xxx (x xxx)
Interferon-gamma	Day 4 (Post-Vaccination 1) vs. Pre-Vaccination 1	x xxx (x.xxx)	x xxx (x xxx)	x.xxx (x xxx)
Interferon-gamma	Day 8 (Post-Vaccination 1) vs. Pre-Vaccination 1	x xxx (x.xxx)	n/a	n/a
Interferon-gamma	Day 29 (Post-Vaccination 1) vs. Pre-Vaccination 1	n/a	x xxx (x xxx)	x.xxx (x xxx)
Interferon-gamma	Day 2 (Post-Vaccination 2) vs. Pre-Vaccination 2	n/a	x xxx (x xxx)	x.xxx (x xxx)
Interferon-gamma	Day 4 (Post-Vaccination 2) vs. Pre-Vaccination 2	n/a	x xxx (x xxx)	x.xxx (x xxx)
Interferon-gamma	Day 8 (Post-Vaccination 2) vs. Pre-Vaccination 2	n/a	x xxx (x xxx)	x.xxx (x xxx)
Colored in blue= p-value < 0.05				

Continue for the remaining cytokine/chemokines IL-1b, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, IL-17A, IL-21, IL-23, ITAC, MIP 1a, MIP1b, MIP3a, TNF-alpha, IP-10, IFNa, IFNb

Table with similar format:

Table 123: Wilcoxon Signed-Rank Test Results for Comparing Cytokine/Chemokine Concentrations between Pre- and Post-Vaccination Time Points in the Per-Protocol Population

Table 124: Wilcoxon Rank Sum Test Results for Comparing Fold Changes between Study Groups in the Intent-To-Treat Population

		Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X) vs. Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)	Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X) vs. Study Arm 1 A/H3N2v, D1 (N=X)	Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X) vs. Study Arm 1 A/H3N2v, D1 (N=X)
Cytokine	**Comparison**	**Wilcoxon Statistic (p-value)**	**Wilcoxon Statistic (p-value)**	**Wilcoxon Statistic (p-value)**
Fractalkine	Day 2 (Post -Vaccination 1) vs. Pre-Vaccination 1	x xxx (x xxx)	x xxx (x xxx)	x.xxx (x xxx)
Fractalkine	Day 4 (Post-Vaccination 1) vs. Pre-Vaccination 1	x xxx (x xxx)	x xxx (x xxx)	x.xxx (x xxx)
Fractalkine	Day 29 (Post-Vaccination 1) vs. Pre-Vaccination 1	x xxx (x xxx)	n/a	n/a
Fractalkine	Day 2 (Post-Vaccination 2) vs. Pre-Vaccination 2	x xxx (x xxx)	n/a	n/a
Fractalkine	Day 4 (Post-Vaccination 2) vs. Pre-Vaccination 2	x xxx (x xxx)	n/a	n/a
Fractalkine	Day 8 (Post-Vaccination 2) vs. Pre-Vaccination 2	x xxx (x xxx)	n/a	n/a
GM-CSF	Day 2 (Post -Vaccination 1) vs. Pre-Vaccination 1	x xxx (x xxx)	x xxx (x xxx)	x.xxx (x xxx)
GM-CSF	Day 4 (Post-Vaccination 1) vs. Pre-Vaccination 1	x xxx (x xxx)	x xxx (x xxx)	x.xxx (x xxx)
GM-CSF	Day 29 (Post-Vaccination 1) vs. Pre-Vaccination 1	x xxx (x xxx)	n/a	n/a
GM-CSF	Day 2 (Post-Vaccination 2) vs. Pre-Vaccination 2	x xxx (x xxx)	n/a	n/a
GM-CSF	Day 4 (Post-Vaccination 2) vs. Pre-Vaccination 2	x xxx (x xxx)	n/a	n/a
GM-CSF	Day 8 (Post-Vaccination 2) vs. Pre-Vaccination 2	x xxx (x xxx)	n/a	n/a
Interferon-gamma	Day 2 (Post -Vaccination 1) vs. Pre-Vaccination 1	x xxx (x xxx)	x xxx (x xxx)	x.xxx (x xxx)
Interferon-gamma	Day 4 (Post-Vaccination 1) vs. Pre-Vaccination 1	x xxx (x xxx)	x xxx (x xxx)	x.xxx (x xxx)
Interferon-gamma	Day 29 (Post-Vaccination 1) vs. Pre-Vaccination 1	x xxx (x xxx)	n/a	n/a
Interferon-gamma	Day 2 (Post-Vaccination 2) vs. Pre-Vaccination 2	x xxx (x xxx)	n/a	n/a
Interferon-gamma	Day 4 (Post-Vaccination 2) vs. Pre-Vaccination 2	x xxx (x xxx)	n/a	n/a
Interferon-gamma	Day 8 (Post-Vaccination 2) vs. Pre-Vaccination 2	x xxx (x xxx)	n/a	n/a
Colored in blue= p-value < 0.05				

Continue for the remaining cytokine/chemokines IL-1b, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, IL-17A, IL-21, IL-23, ITAC, MIP 1a, MIP1b, MIP3a, TNF-alpha, IP-10, IFNa, IFNb

Table with similar format:

Table 125: Wilcoxon Rank Sum Test Results for Comparing Fold Changes between Study Groups in the Per-Protocol Population

14.3 Transcriptomics Data

Table 126: Genes Differentially Expressed Compared to Pre-Vaccination by Treatment Group, Cell Type, and Post-Vaccination Day

		Study Arm 1 A/H3N2v, D1 (N=X)	Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)	Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)
Time Point	**Cell Type**	**DE Genes [#]**	**DE Genes [#]**	**DE Genes [#]**
Day 2 (Post Vaccination 1 vs. Pre-Vaccination 1)	Monocytes	xxx	xxx	xxx
	Dendritic cells	xxx	xxx	xxx
	Neutrophils	xxx	xxx	xxx
	NK-cells	xxx	xxx	xxx
	T-cells	xxx	xxx	xxx
	B-cells	xxx	xxx	xxx
Day 4 (Post Vaccination 1 vs. Pre-Vaccination 1)	Monocytes	xxx	xxx	xxx
	Dendritic cells	xxx	xxx	xxx
	Neutrophils	xxx	xxx	xxx
	NK-cells	xxx	xxx	xxx
	T-cells	xxx	xxx	xxx
	B-cells	xxx	xxx	xxx
Day 8 (Post Vaccination 1 vs. Pre-Vaccination 1)	Monocytes	xxx	n/a	n/a
	Dendritic cells	xxx	n/a	n/a
	Neutrophils	xxx	n/a	n/a
	NK-cells	xxx	n/a	n/a
	T-cells	xxx	n/a	n/a
	B-cells	xxx	n/a	n/a
Day 29 (Post Vaccination 1 vs. Pre-Vaccination 1)	Monocytes	n/a	xxx	xxx
	Dendritic cells	n/a	xxx	xxx
	Neutrophils	n/a	xxx	xxx
	NK-cells	n/a	xxx	xxx

		Study Arm 1 A/H3N2v, D1 (N=X)	Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)	Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)
	T-cells	n/a	xxx	xxx
	B-cells	n/a	xxx	xxx
Day 2 (Post Vaccination 2 vs. Pre-Vaccination 2)	Monocytes	n/a	xxx	xxx
	Dendritic cells	n/a	xxx	xxx
	Neutrophils	n/a	xxx	xxx
	NK-cells	n/a	xxx	xxx
	T-cells	n/a	xxx	xxx
	B-cells	n/a	xxx	xxx
Day 4 (Post Vaccination 2 vs. Pre-Vaccination 2)	Monocytes	n/a	xxx	xxx
	Dendritic cells	n/a	xxx	xxx
	Neutrophils	n/a	xxx	xxx
	NK-cells	n/a	xxx	xxx
	T-cells	n/a	xxx	xxx
	B-cells	n/a	xxx	xxx
Day 8 (Post Vaccination 2 vs. Pre-Vaccination 2)	Monocytes	n/a	xxx	xxx
	Dendritic cells	n/a	xxx	xxx
	Neutrophils	n/a	xxx	xxx
	NK-cells	n/a	xxx	xxx
	T-cells	n/a	xxx	xxx
	B-cells	n/a	xxx	xxx

N=Number of subjects in the Omics analysis population
DE Gene = differentially expressed gene

Table 127: Genes Differentially Expressed Between Treatment Groups by Immune Cell Type, and Post-Vaccination Day

Table 127: Genes Differentially Expressed Between Treatment Groups by Immune Cell Type, and Post-Vaccination Day

		Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X) vs. Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)	Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X) vs. Study Arm 1 A/H3N2v, D1 (N=X)	Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X) vs. Study Arm 1 A/H3N2v, D1 (N=X)
Time Point	**Cell Type**	**DE Genes [#]**	**DE Genes [#]**	**DE Genes [#]**
Day 2 (Post Vaccination 1 vs. Pre-Vaccination 1)	Monocytes	xxx	xxx	xxx
	Dendritic cells	xxx	xxx	xxx
	Neutrophils	xxx	xxx	xxx
	NK-cells	xxx	xxx	xxx
	T-cells	xxx	xxx	xxx
	B-cells	xxx	xxx	xxx
Day 4 (Post Vaccination 1 vs. Pre-Vaccination 1)	Monocytes	xxx	xxx	xxx
	Dendritic cells	xxx	xxx	xxx
	Neutrophils	xxx	xxx	xxx
	NK-cells	xxx	xxx	xxx
	T-cells	xxx	xxx	xxx
	B-cells	xxx	xxx	xxx
Day 29 (Post Vaccination 1 vs. Pre-Vaccination 1)	Monocytes	xxx	n/a	n/a
	Dendritic cells	xxx	n/a	n/a
	Neutrophils	xxx	n/a	n/a
	NK-cells	xxx	n/a	n/a
	T-cells	xxx	n/a	n/a
	B-cells	xxx	n/a	n/a
Day 2 (Post Vaccination 2 vs. Pre-Vaccination 2)	Monocytes	xxx	n/a	n/a
	Dendritic cells	xxx	n/a	n/a

		Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X) vs. Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)	**Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X) vs. Study Arm 1 A/H3N2v, D1 (N=X)**	**Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X) vs. Study Arm 1 A/H3N2v, D1 (N=X)**
	Neutrophils	xxx	n/a	n/a
	NK-cells	xxx	n/a	n/a
	T-cells	xxx	n/a	n/a
	B-cells	xxx	n/a	n/a
Day 4 (Post Vaccination 2 vs. Pre-Vaccination 2)	Monocytes	xxx	n/a	n/a
	Dendritic cells	xxx	n/a	n/a
	Neutrophils	xxx	n/a	n/a
	NK-cells	xxx	n/a	n/a
	T-cells	xxx	n/a	n/a
	B-cells	xxx	n/a	n/a
Day 8 (Post Vaccination 2 vs. Pre-Vaccination 2)	Monocytes	xxx	n/a	n/a
	Dendritic cells	xxx	n/a	n/a
	Neutrophils	xxx	n/a	n/a
	NK-cells	xxx	n/a	n/a
	T-cells	xxx	n/a	n/a
	B-cells	xxx	n/a	n/a

N=Number of subjects in the Omics analysis population
DE Gene = differentially expressed gene

Table 128: Genes Differentially Expressed at Day 2 Compared to Pre-First Vaccination (RNA-Seq, Monocytes, Study Arm 1 A/H3N2v, D1)

Generate tables for each applicable post-vaccination day, treatment group, pairwise treatment group comparisons (Group 1 vs. 2, Group 1 vs. 3, Group 1 vs. 3, and Group 2 vs. 3), and cell type (monocytes, neutrophils, dendritic cells, NK cells B cell, and T cells). For Group 1 include tables for days 2, 4, and 8 post-first vaccination. For Groups 2 and 3 provide tables for post-vaccination days 2, 4, 29, 30, 32, and 36 post-first vaccination. For pairwise group comparisons that include Group 1, generate tables for days 2 and 4 post-first vaccination. Otherwise, prepare comparison results for days 2,4, 29, 30, 32, and 36 post-first vaccination.

Ensembl Gene ID	Ensembl Gene Name	Ensembl Gene Description	Gene Type	Log_2 Fold Change (Day 2 vs. Pre-First Vaccination)	Average Log_2 CPM*	Likelihood Ratio Test Statistic	P-Value	FDR Adjusted P-value
ENSG00000115415	STAT1	signal transducer and activator of transcription 1, 91kDa [Source:HGNC Symbol;Acc:11362]	protein coding	1.94	2.034	5.324	0.000034	0.000613
ENSG00000125347	IRF1	interferon regulatory factor 1 [Source:HGNC Symbol;Acc:6116]	protein coding	0.672	2.506	4.324	0.0343	0.00234
ENSG00000247275	AL160008.1		lincRNA	0.80	0.96	3.42	0.043	0.0483
*: average gene expression levels across Day 2 and Pre-First Vaccination samples measured in average log_2 CPM								

Table 129: Clusters of Co-Expressed Differential Genes (Monocytes, Days 2-29)

Generate tables for each fold change set (Day 2-29 post-first vaccination and Day 2-8 post-second vaccination) and cell type (monocytes, neutrophils, dendritic cells, NK cells B cell, and T cells)

Cluster ID	Cluster Size	Ensembl Gene ID	Ensembl Gene Name	Ensembl Gene Description	Gene Type	KEGG Pathway
CCD229-001	3	ENSG00000115415	STAT1	signal transducer and activator of transcription 1, 91kDa [Source:HGNC Symbol;Acc:11362]	protein coding	Jak-STAT signaling pathway
		ENSG00000125347	IRF1	interferon regulatory factor 1 [Source:HGNC Symbol;Acc:6116]	protein coding	Pertussis Prolactin signaling pathway Hepatitis C Human papillomavirus infection
		ENSG00000247275	AL160008.1		lincRNA	
CCD229-002	2	ENSG00000108984	MAP2K6	protein coding	protein coding	MAPK signaling pathway
		ENSG00000152689	RASGRP3	RAS guanyl releasing protein 3 (calcium and DAGregulated)	protein coding	MAPK signaling pathway Ras signaling pathway Rap1 signaling pathway B cell receptor signaling pathway Pathways in cancer

Table 130: KEGG Pathways Enriched in Differentially Expressed Genes at Day 2 Compared to Pre-First Vaccination (RNA-Seq, Monocytes, Study Arm 1 A/H3N2v, D1)

Generate tables for each gene set category (KEGG Pathways, MSigDB Reactome Pathways, and MSigDB Immunologic Signatures), post-first vaccination day (Day 2, 4, 8, 29), Study Arm (Study Arm 1, 2, 3), all pairwise Study Arm Comparison (1 vs. 2, 1 vs. 3, 2 vs. 3), and cell type (monocytes, neutrophils, dendritic cells, NK cells B cell, and T cells). Repeat for post-second vaccination time points relative to pre-second vaccination for Study Arms 2 and 3.

Gene Set ID	Gene Set Genes #	Differentially Expressed Genes N (%)	Up-regulated Differentially Expressed Genes N (%)	Down-regulated Differentially Expressed Genes N (%)	Jaccard Index	P-Value	FDR Adjusted P-value
Influenza A	62	9 (15)	9 (15)	0	0.234	<0.0001	0.0006
Antigen processing and presentation	59	4 (7)	3 (5)	1 (2)	0.231	<0.0001	0.0004

14.4 Safety Data

14.4.1 Adverse Events

14.4.1.1 Adverse Events of Special Interest

Table 131: Number and Percentage of Subjects Experiencing Adverse Events of Special Interest

	Study Arm 1 A/H3N2v, D1 (N=X)		Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)		Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)	
Category	**n**	**%**	**n**	**%**	**n**	**%**
Serious Adverse Event (SAE)	x	xx	x	xx	x	xx
Medically-Attended Adverse Event (MAAE)	x	xx	x	xx	x	xx
New-Onset Chronic Medical Condition (NOCMC)	x	xx	x	xx	x	xx
Potentially Immune-Mediated Medical Condition (PIMMC)	x	xx	x	xx	x	xx
N = Number of subjects in the Safety Analysis Population						

14.4.1.2 Solicited Adverse Events

Table 132: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom, and Treatment Group (Post-First Vaccination)

	Study Arm 1 A/H3N2v, D1 (N=X)			Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)			Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	x	xx	x x, x.x	x	xx	x x, x x	x	xx	x x, x x
Any Systemic Symptom	x	xx	x x, x.x	x	xx	x x, x x	x	xx	x x, x x
[Systemic Symptom 1]	x	xx	x x, x.x	x	xx	x x, x x	x	xx	x x, x x
[Systemic Symptom 2]	x	xx	x x, x.x	x	xx	x x, x x	x	xx	x x, x x
Any Local Symptom	x	xx	x x, x.x	x	xx	x x, x x	x	xx	x x, x x
[Local Symptom 1]	x	xx	x x, x.x	x	xx	x x, x x	x	xx	x x, x x
[Local Symptom 2]	x	xx	x x, x.x	x	xx	x x, x x	x	xx	x x, x x
N= Number of subjects in the per safety analysis population.									

Tables with similar format:

Table 133: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom, and Treatment Group (Post-Second Vaccination)

Table 134: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom, and Treatment Group (Post-Any Vaccination)

Table 135: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, and Treatment Group (Post-First Vaccination)

		Study Arm 1 A/H3N2v, D1 (N=X)			Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)			Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)		
Symptom	**Severity**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Any Symptom	None	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Mild	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Moderate	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Severe	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
Systemic Symptoms										
Any Systemic Symptom	None	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Mild	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Moderate	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Severe	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
[Systemic Symptom 1]	None	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Mild	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Moderate	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Severe	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
[Systemic Symptom 2]	None	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Mild	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Moderate	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Severe	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
Local Symptoms										
Any Local Symptom	None	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Mild	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Moderate	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Severe	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x

		Study Arm 1 A/H3N2v, D1 (N=X)			Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)			Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)		
[Local Symptom 1]	None	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Mild	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Moderate	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Severe	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
[Local Symptom 2]	None	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Mild	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Moderate	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
	Severe	x	xx	x x, x.x	x	xx	x.x, x x	x	xx	x x, x.x
N = Number of subjects in the Safety Analysis Population who received the specified dose. Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.										

Tables with similar format:

Table 136: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, and Treatment Group (Post-Second Vaccination)

Table 137: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, and Treatment Group (Post-Any Vaccination)

Table 138: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Post-Vaccination Day (Post-First Vaccination, Study Arm 1 A/H3N2v, D1)

Study Arm 1 A/H3N2v, D1 (N=X)																			
Symptom	**Severity**	**Pre-Vaccination 1**		**Post-Vaccination 1**		**Day 1**		**Day 2**		**Day 3**		**Day 4**		**Day 5**		**Day 6**		**Day 7+**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any Symptom	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild																		
	Moderate																		
	Severe																		
	Not Reported																		
Systemic Symptoms																			
Any Systemic Symptom	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild																		
	Moderate																		
	Severe																		
	Not Reported																		
[Systemic Symptom 1]	None																		
	Mild																		
	Moderate																		
	Severe																		
	Not Reported																		
[Systemic Symptom 2]	None																		
	Mild																		

Study Arm 1 A/H3N2v, D1 (N=X)																			
Symptom	**Severity**	**Pre-Vaccination 1**		**Post-Vaccination 1**		**Day 1**		**Day 2**		**Day 3**		**Day 4**		**Day 5**		**Day 6**		**Day 7+**	
		n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
	Moderate																		
	Severe																		
	Not Reported																		
Local Symptoms																			
Any Local Symptom	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild																		
	Moderate																		
	Severe																		
	Not Reported																		
[Local Symptom 1]	None																		
	Mild																		
	Moderate																		
	Severe																		
	Not Reported																		
[Local Symptom 2]	None																		
	Mild																		
	Moderate																		
	Severe																		
	Not Reported																		

N = Number of subjects in the Safety Analysis Population who received the specified dose.
Severity is the maximum severity reported post dosing for each subject for each day.

Tables with similar format:

Table 139: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Post-Vaccination Day (Post-First Vaccination, Study Arm 2 A/H7N9 + AS03, D1, 29)

Table 140: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Post-Vaccination Day (Post-First Vaccination, Study Arm 3 A/H7N9 + PBS, D1, 29)

Table 141: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Post-Vaccination Day (Post-Second Vaccination, Study Arm 2 A/H7N9 + AS03, D1, D29)

Table 142: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Post-Vaccination Day (Post-Second Vaccination, Study Arm 3 A/H7N9 + PBS, D1, 29)

14.4.1.3 Unsolicited Adverse Events

Table 143: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events with 95% Confidence Intervals by MedDRA® System Organ Class and Preferred Term, and Treatment Group (Post-First Vaccination)

MedDRA® System Organ Class	MedDRA® Preferred Term	Study Arm 1 A/H3N2v, D1 (N=X)			Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)			Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI
Any SOC	Any PT	x	xx	xx, xx	x	xx	xx, xx	x	xx	xx, xx
[SOC 1]	Any PT									
	[PT 1]									
	[PT 2]									
[SOC 2]	Any PT									
	[PT 1]									
	[PT 2]									

Note: N = number of subjects in the Safety Analysis Population who received the specified dose.
This table presents number and percentage of subjects. A subject is only counted once per PT.

Tables with similar format:

Table 144: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events with 95% Confidence Intervals by MedDRA® System Organ Class and Preferred Term, and Treatment Group (Post-Second Vaccination)

Table 145: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events with 95% Confidence Intervals by MedDRA® System Organ Class and Preferred Term, and Treatment Group (Post-Any Vaccination)

Table 146: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Maximum Severity, and Relationship (Study Arm 1 A/H3N2v, D1)

Study Arm 1 A/H3N2v, D1 (N=X)													
MedDRA® System Organ Class	MedDRA® Preferred Term	Any Incidence		Severity [1]						Relationship to Treatment [2]			
				Mild		Moderate		Severe		Not Related		Related	
		n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
[SOC 1]	Any PT												
	[PT 1]												
	[PT 2]												
[SOC 2]	Any PT												
	[PT 1]												
	[PT 2]												

Note: N = Number of subjects in the Safety Analysis Population.
[1] For severity, a subject is counted once per preferred term and is summarized according to their highest severity.
[2] For relationship, a subject is only counted once per preferred term and is summarized according to their closest relationship.

Tables with similar format:

Table 147: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Maximum Severity, Relationship (Study Arm 2 A/H7N9 + AS03, D1, 29)

Table 148: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events by MedDRA® System Organ Class and Preferred Term, Maximum Severity, Relationship (Study Arm 3 A/H7N9 + PBS, D1, 29)

14.4.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 149: Listing of Serious Adverse Events

Adverse Event	Associated with Dose #	# of Days Post Associated Dose (Duration)	# of Days Post Dose the Event Became Serious	Reason Reported as an SAE	Severity	Relationship to Study Treatment	In Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA® System Organ Class	MedDRA® Preferred Term
Subject ID: , Treatment Group: , AE Number:												
Comments:												
Subject ID: , Treatment Group: , AE Number:												
Comments:												

Table 150: Listing of Non-Serious, Unsolicited, Moderate or Severe Adverse Events

Adverse Event	Associated with Dose #	# of Days Post Associated Dose (Duration)	Severity	Relationship to Study Treatment	In Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA® System Organ Class	MedDRA® Preferred Term
Subject ID: , Treatment Group: , AE Number:										
Comments:										
Subject ID: , Treatment Group: , AE Number:										
Comments:										

Table 151: Listing of Adverse Events of Special Interest

Adverse Event	Vaccination Received at Time of Event?	No. of Days Post Vaccination	Duration of Event	Severity	MedDRA System Organ Class	NOCMC ?	PIMMC	Relationship	Outcome
	Subject ID: , Study Group: , AE Number:								
	Comments:								
	Subject ID: , Study Group: , AE Number:								
	Comments:								

14.4.3 Narratives of Deaths, Other Serious and Significant Adverse Events

(not included in SAP, but this is a placeholder for the CSR)

14.4.4 Displays of Vital Signs

Table 152: Vital Signs by Assessment, Maximum Severity, Study Day, and Treatment Group – Any Assessment

		Study Arm 1 A/H3N2v, D1 (N=X)		Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)		Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)	
Study Visit Day	**Severity**	**n**	**%**	**n**	**%**	**n**	**%**
Day -7 (Screening)	None	x	xx	x	xx	x	xx
	Mild						
	Moderate						
	Severe						
	Missing						
Day 1 (Pre-Vaccination 1)	None	x	xx	x	xx	x	xx
	Mild						
	Moderate						
	Severe						
	Missing						
Day 29 (Post-Vaccination 1)	None	n/a	n/a	x	xx	x	xx
	Mild	n/a	n/a				
	Moderate	n/a	n/a				
	Severe	n/a	n/a				
	Missing	n/a	n/a				
Maximum Post-Vaccination 1	None	x	xx	x	xx	x	xx
	Mild						
	Moderate						
	Severe						
	Missing						

		Study Arm 1 A/H3N2v, D1 (N=X)	Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)	Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)
Maximum Post-Vaccination 1 indicates the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments. N = Number of subjects in the Safety Analysis Population.				

14.5 Concomitant Medications

Table 153: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification and Treatment Group

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Study Arm 1 A/H3N2v, D1 (N=X)		Study Arm 2 A/H7N9 + AS03, D1, 29 (N=X)		Study Arm 3 A/H7N9 + PBS, D1, 29 (N=X)	
		n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]						
	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						
[ATC Level 1 – 2]	[ATC 2 - 1]						
	[ATC 2 - 2]						
	[ATC 2 - 3]						

N = Number of subjects in the Safety Analysis Population
n = Number of subjects reporting taking at least one medication in the specific WHO Drug Class.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

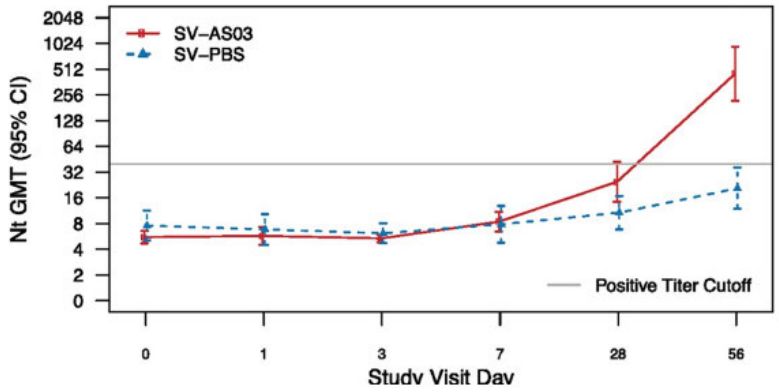
10.1 Disposition of Subjects

Figure 1: CONSORT Flow Diagram

14.2 Immunogenicity Data

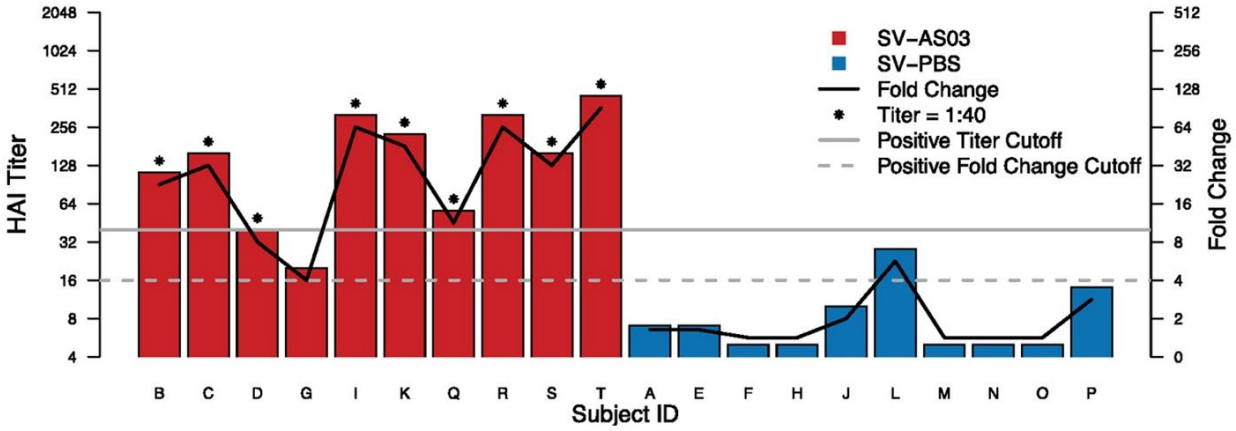
Immunogenicity Response Figures by Measure, Treatment/Vaccination, and Time Point

Figure 2: Hemagglutination Inhibition GMTs and 95% CIs by Study Arm and Post-Vaccination Day



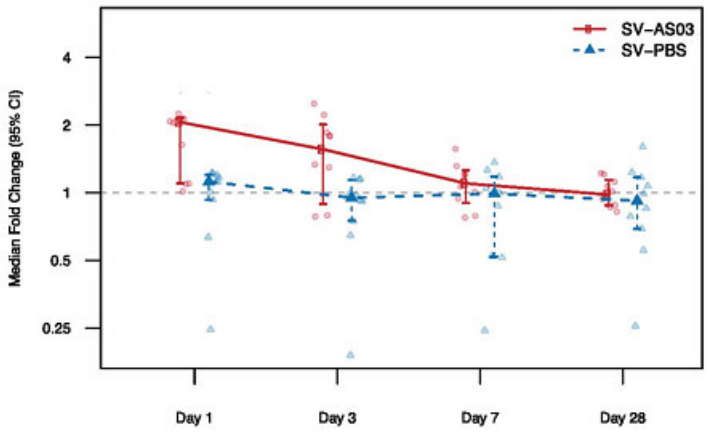
Repeat for neutralizing antibodies. Include all study arms. Label study arms as: Study Arm 1 A/H3N2v, D1; Study Arm 2 A/H7N9 + AS03, D1, 29; Study Arm 3 A/H7N9 + PBS, D1, 29.

Figure 3: Barplot of Subject-Level Hemagglutination Inhibition Results at Day 29 Post-Last Vaccination



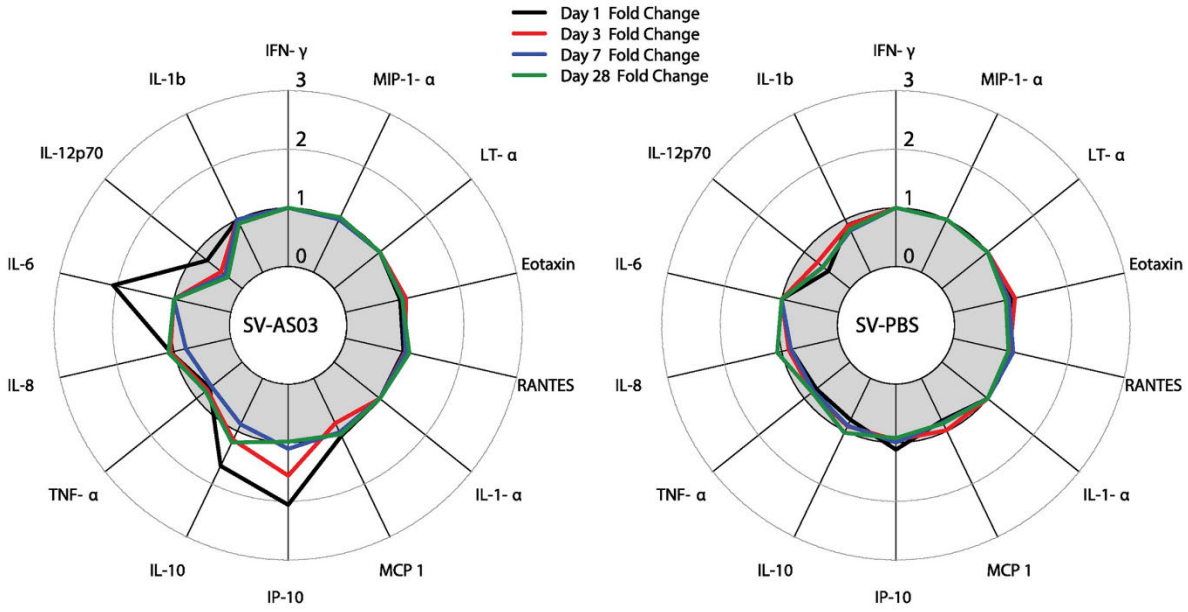
Repeat for neutralizing antibodies. Include all study arms. Label study arms as: Study Arm 1 A/H3N2v, D1; Study Arm 2 A/H7N9 + AS03, D1, 29; Study Arm 3 A/H7N9 + PBS, D1, 29.

Figure 4: Median Fold Change in Fractalkine Concentration and Associated 95% CI by Study Arm and Post-Vaccination Day



Plot individual fold change observations using treatment group-specific symbols. Include Study Arm 1 A/H3N2v. Label study arms as: Study Arm 1 A/H3N2v, D1; Study Arm 2 A/H7N9 + AS03, D1, 29; Study Arm 3 A/H7N9 + PBS, D1, 29. Repeat for GM-CSF, IFN-γ, IL-1b, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, IL-17A, IL-21, IL-23, ITAC, MIP 1a, MIP1b, MIP3a, TNF-alpha, IP-10, IFNa, IFNb.

Figure 5: Radar Plot of Median Fold Change by Study Arm and Post-Vaccination Day



Include Study Arm 1 A/H3N2v. Label study arms as: Study Arm 1 A/H3N2v, D1; Study Arm 2 A/H7N9 + AS03, D1, 29; Study Arm 3 A/H7N9 + PBS, D1, 29. Include Fractalkine GM-CSF, IFN-γ, IL-1b, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, IL-17A, IL-21, IL-23, ITAC, MIP 1a, MIP1b, MIP3a, TNF-alpha, IP-10, IFNa, IFNb.

14.3 Transcriptomics Data

Figure 6: Multivariate starplots of reference alignment statistics

Each sample is depicted by a star. Each ray represents one of the reference alignments statistics. Ray length is globally scaled so that the respective maximum alignment statistic across all samples is 1 and the minimum is 0. Stars will be color-coded by Study Arm.

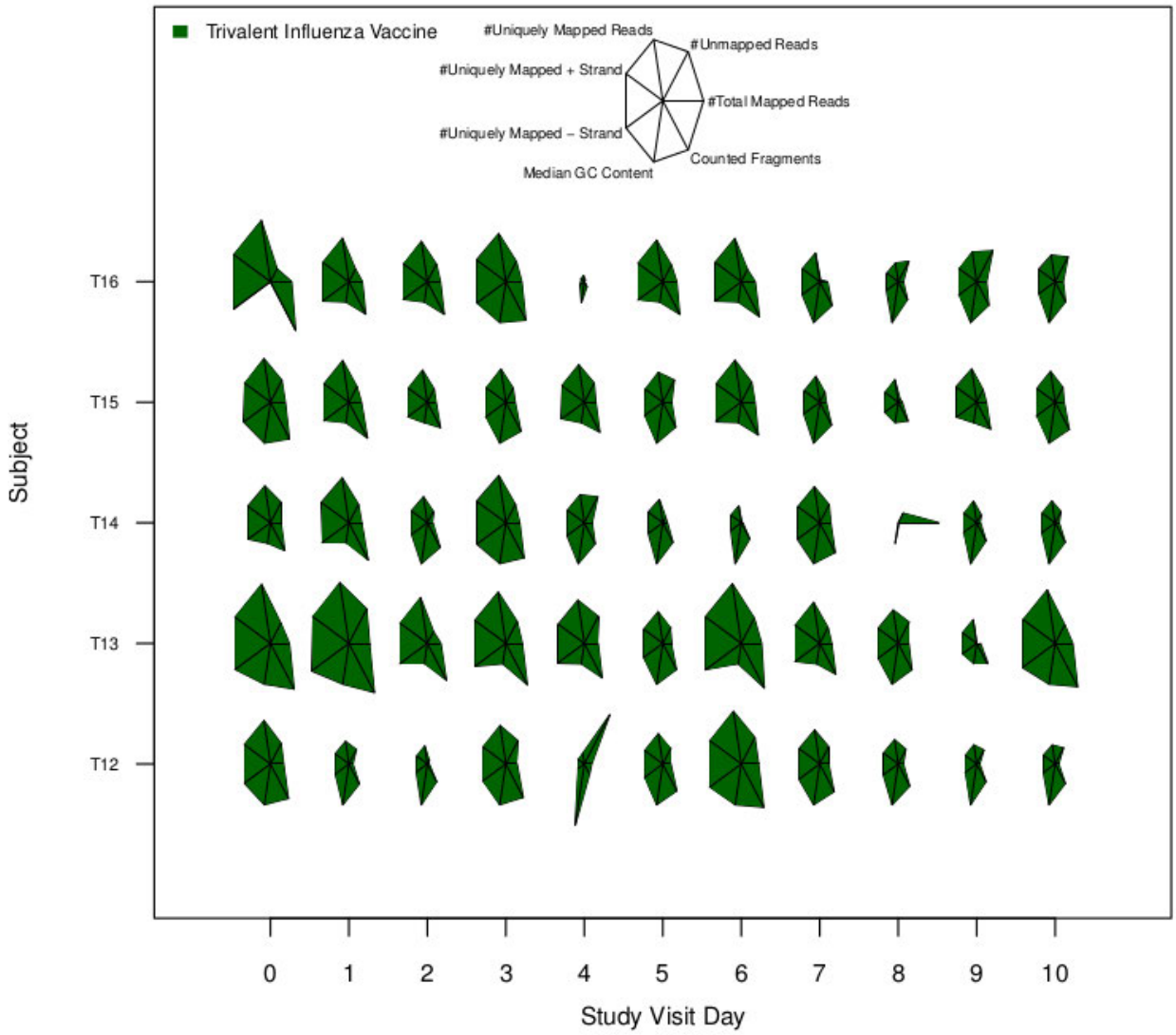


Figure 7: Multivariate PCA, MDS, and hierarchical clustering plots

Standardized LCPM distributions will be used as input for PCA (A), MDS (B, C), and hierarchical clustering (D, E). For MDS and hierarchical clustering, results will be provided for Euclidean (B, D) as well as 1-Spearman correlation distance (C, E).

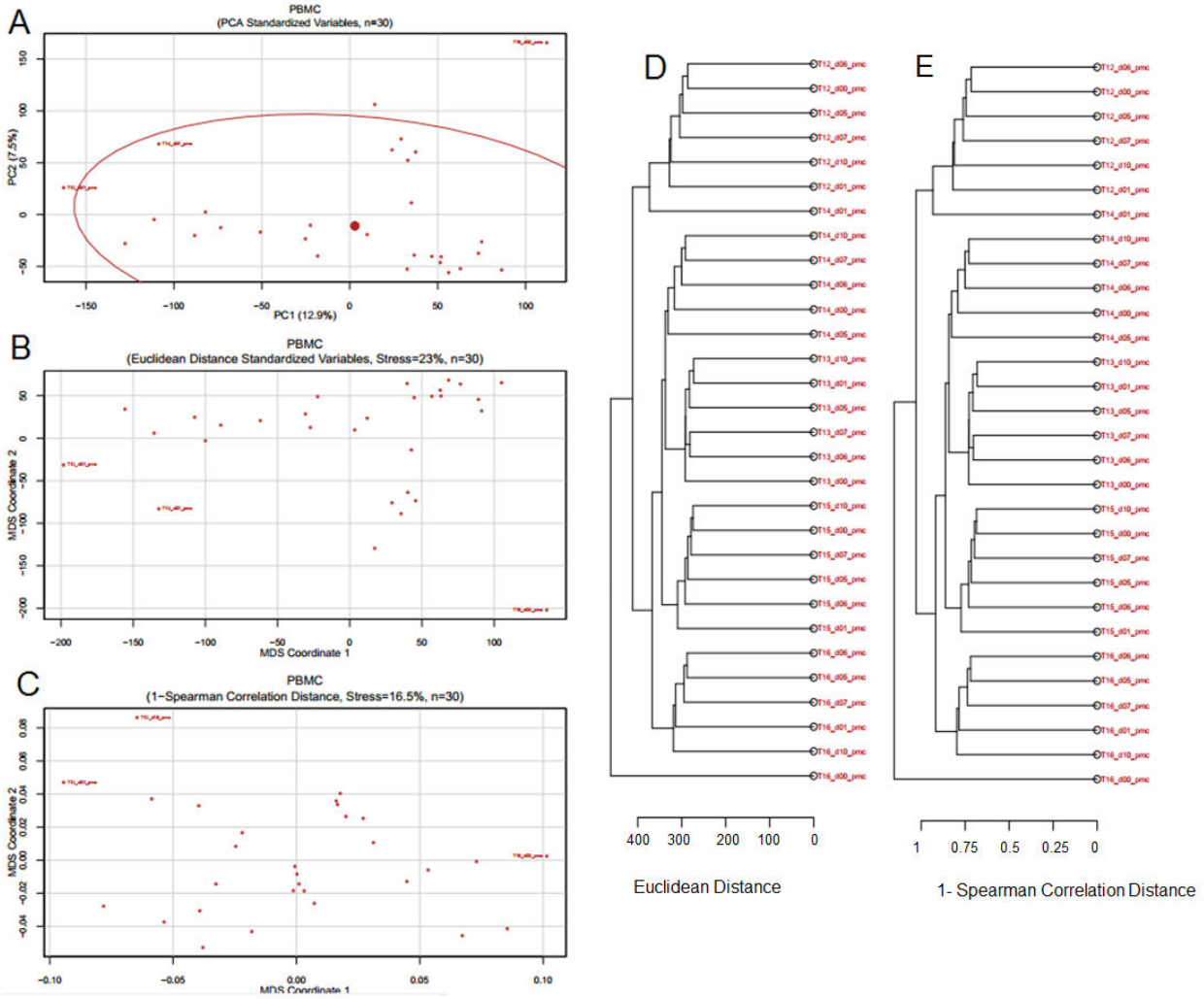


Figure 8: Reverse empirical cumulative distribution function plots to summarize the percentage of genes that pass a certain average LCPM expression cut off

The x-axis represents the $\log_2$ count per million cut off for identifying lowly expressed genes. The y-axis shows the percentage of all genes with a minimum gene expression level across all study samples that exceeds the respective cut off. The grey box indicates the target range of genes to be selected (between 10,000 and 14,000 genes). The black vertical lines represent the actual cut off that would be selected.

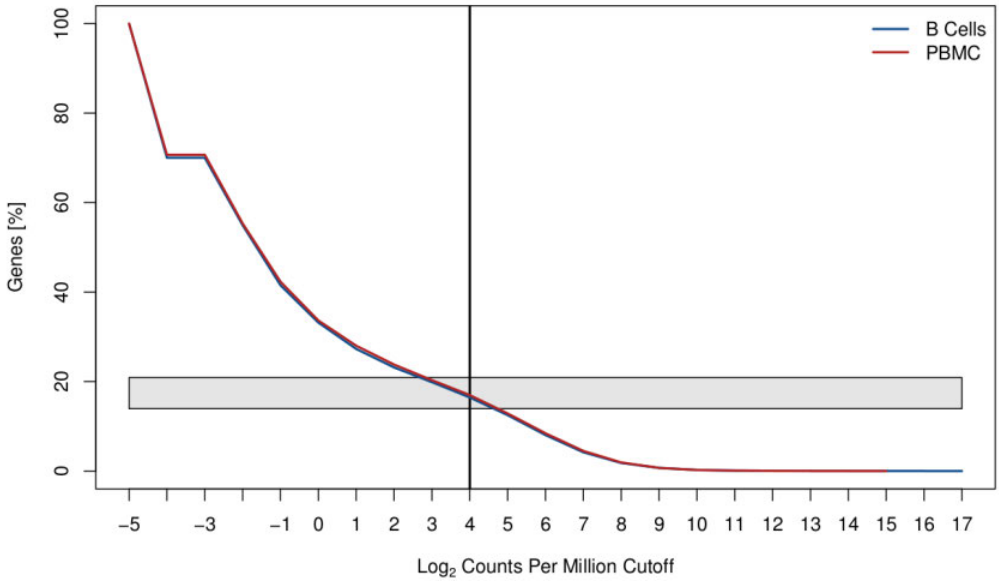
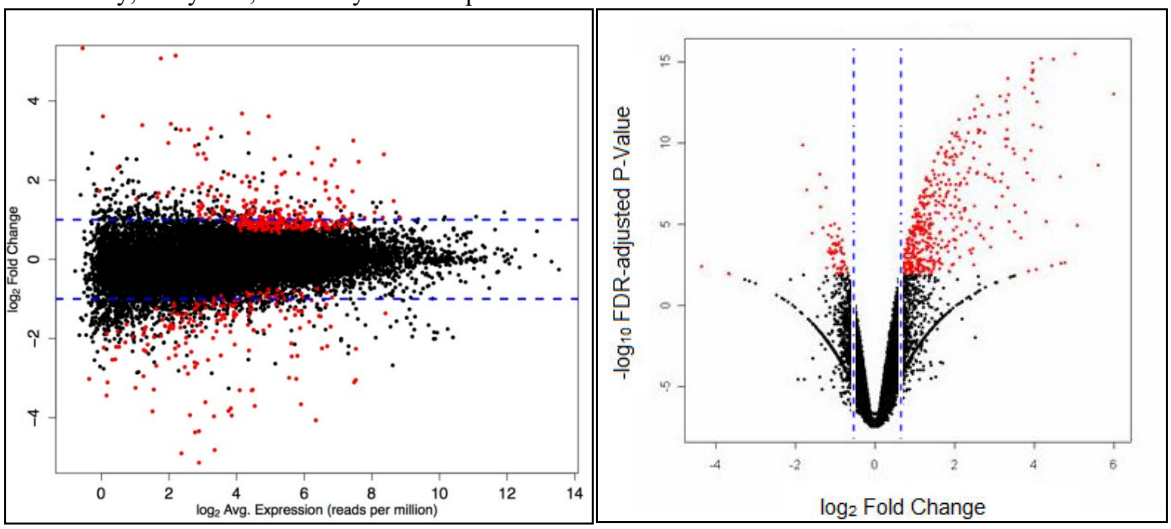


Figure 9: MA and Volcano plots

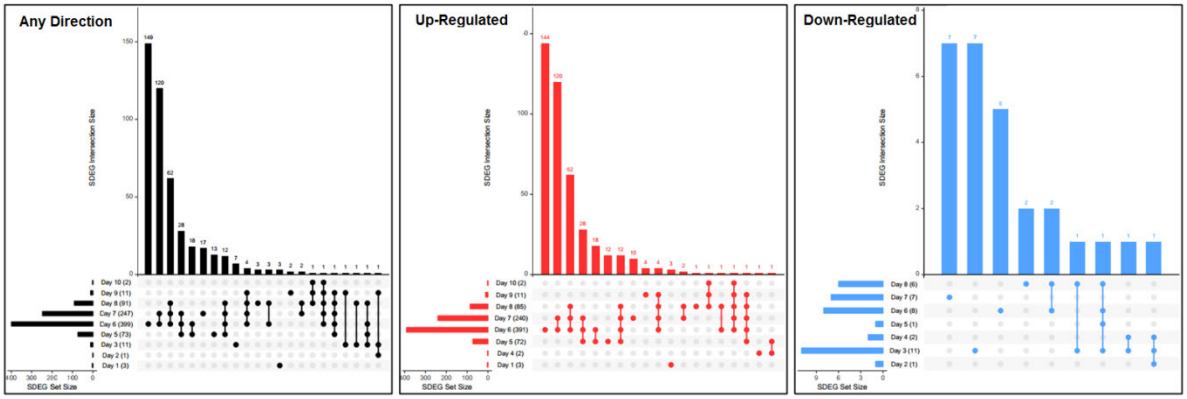
The y-axis on the MA plot (left panel) represents the $\log_2$ fold change for the respective treatment effect. The x-axis shows the average $\log_2$ expression level. The y-axis on the Volcano plot (right panel) represents the $-\log_{10}$ adjusted p-value and the x-axis the log2 fold change for the respective treatment effect. Each black dot represents a gene. In red: DE genes. Blue dashed line: fold change cut off. MA and Volcano plots will be generated for each post-vaccination day, study arm, and study arm comparison.



Generate MA and Volcano plots for each post-first vaccination day (Day 2, 4, 8 or 29), Study Arm (Study Arm 1, 2, or 3), and pairwise Study Arm Comparison (1 vs. 2, 1 vs. 3, or 2 vs. 3). Repeat for post-second vaccination time points (Day 30, 32, and 36) relative to pre-second vaccination for Study Arms 2 and 3.

Figure 10: DE gene overlap between post-first vaccination days (Study Arm 1, Day 2-29 post-first vaccination)

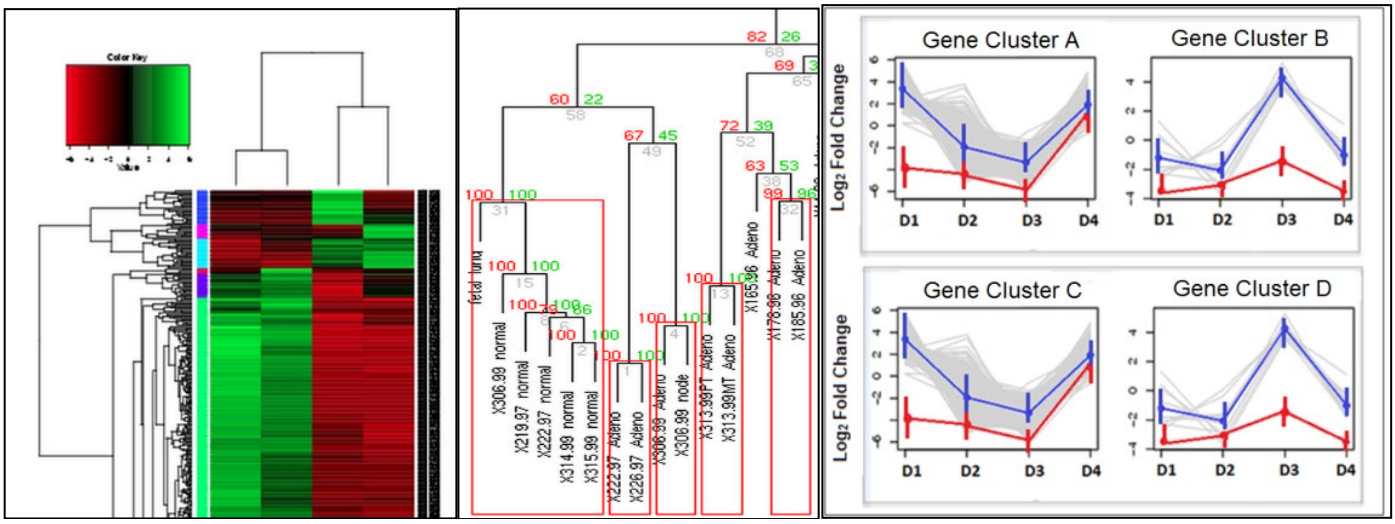
This plot summarizes the DE gene overlap between post-vaccination days for all DE (shown to the right), for up-regulated DE genes (shown in the middle), and down-regulated DE genes (shown to the right). For example, in the left panel, the bottom left horizontal barplot labeled 'SDEG Set Size' shows the total number of DE genes per post-vaccination time point. The black circles in the matrix represent what would be the different Venn diagram spaces (unique and overlapping DE genes). Connected black circles indicate a certain intersection of post-vaccination days. In the left panel, the first vertical bar/column shows those DE genes that are unique to Day 6. The second shows those DE genes that are shared only between Day 6 and 7. The third are those DE genes that are shared between Days 6, 7, and 8, and so forth.



Generate this plot for each study arm post-first vaccination. Repeat for post-second vaccination time points (Days 30, 32, and 36) relative to pre-second vaccination for Study Arms 2 and 3.

Figure 11: Heatmap, Co-Expressed Gene Cluster Dendrograms, and Cluster Time Trend Visualizations

Left: Heatmap of log_2 fold changes of DE genes color-coded by up/down–regulation. Center: Gene cluster dendrogram with bootstrap probabilities and identified co-expressed gene clusters. Right: Time trends for mean log_2 fold changes and associated 95% bootstrap CI of co-expressed gene clusters.



Left: *Generate heatmaps for each post-first vaccination day (Day 2, 4, 8 or 29), Study Arm (Study Arm 1, 2, and 3) and pairwise Study Arm Comparison (1 vs. 2, 1 vs. 3, 2 vs. 3). Repeat for post-second vaccination time points (Days 30, 32, and 36) relative to pre-second vaccination for Study Arms 2 and 3.*

Center: *Generate gene cluster dendrograms for each fold change set (Day 2-29 post-first vaccination and Day 2-8 post-second vaccination).*

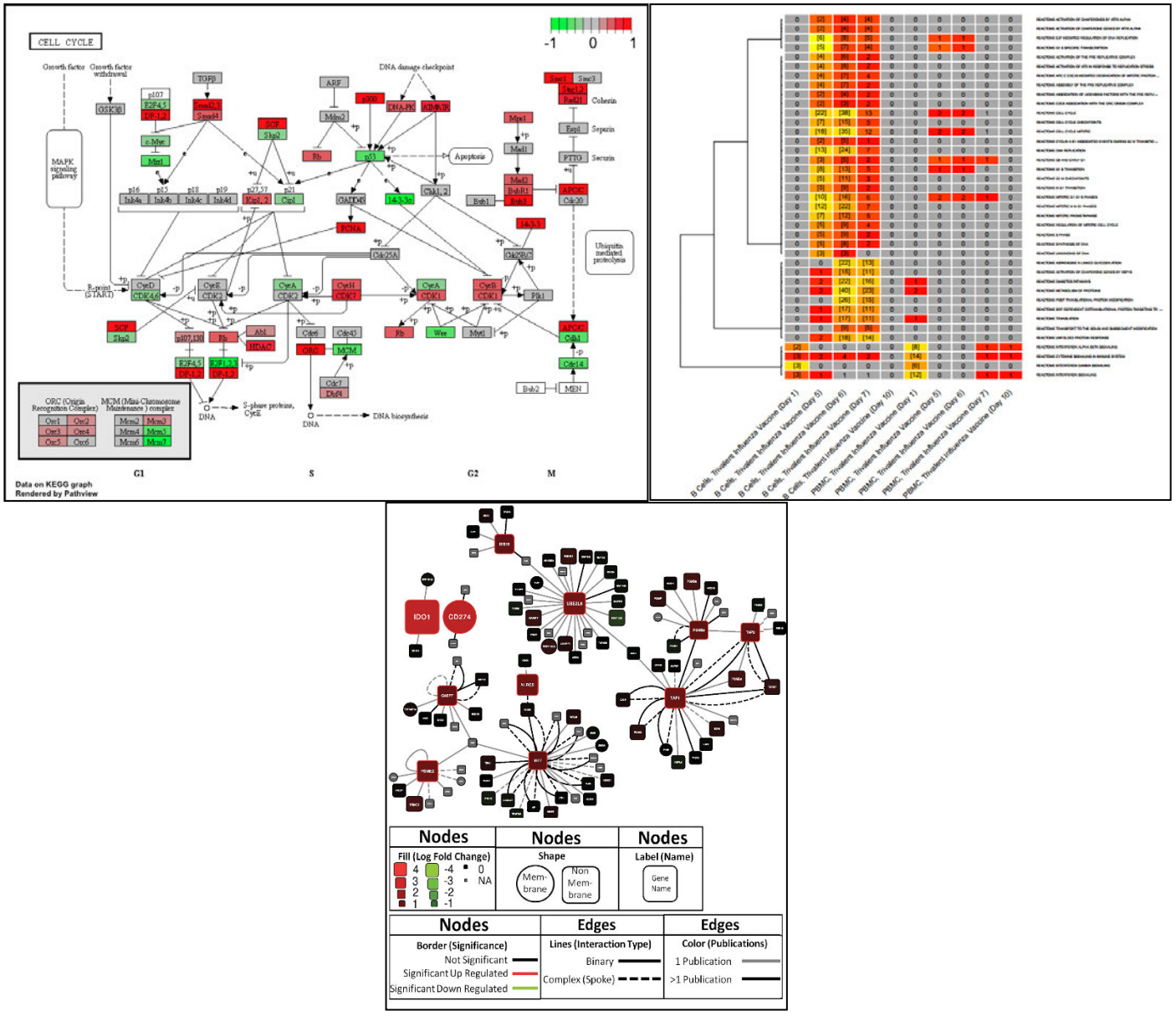
Right: *Generate cluster time trends for each cluster and fold change set (Day 2-29 post-first vaccination and Day 2-8 post-second vaccination).*

Figure 12: Pathway Enrichment Visualizations

Left: Pathway map of a significantly enriched pathway color-coded by up/down–regulation of genes.

Center: Heatmap summarizing pathway enrichment across study arms and post-vaccination days. Cells are color-coded by enrichment score: -1 x $\log_{10}$(enrichment p-value). Numbers in each cell represent the number of DE genes. Two numbers will be printed in each cell: 1) the number of up-regulated DE genes and the 2) the number of down-regulated DE genes per pathway.

Right: Protein-protein interaction network centered around proteins encoded by DE genes. Nodes will be labeled by corresponding gene name. Edges will represent experimentally determined (reported in ≥2 publications) binary protein-protein interactions or protein complex membership. Color and size of individual nodes will indicate the mean log2 fold change between conditions. Further details are provided as part of the legend within the figure.



Left: Generate KEGG pathway maps for each enriched KEGG pathway for each post-first vaccination day (Day 2, 4, 8 or 29), Study Arm (Study Arm 1, 2, and 3) and pairwise Study Arm Comparison (Study Arm 1 vs.

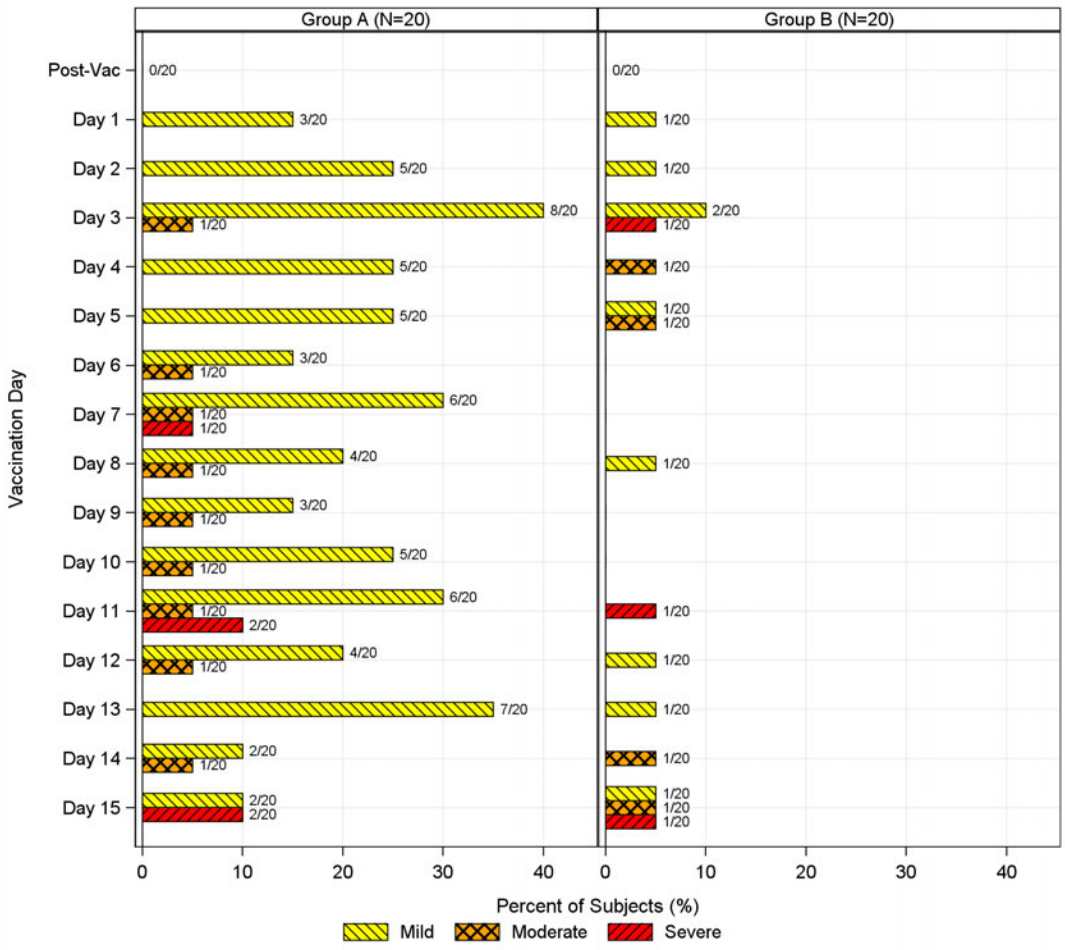
2, 1 vs. 3, 2 vs. 3). Repeat for post-second vaccination time points (Days 30, 32, and 36) relative to pre-second vaccination for Study Arms 2 and 3.

Center: Summarize for each gene set category (KEGG Pathways, MSigDB Reactome Pathways, MSigDB GO Biological Process, MSigDB Immunologic Signatures, and Blood Transcription Modules), for each post-first vaccination day (Day 2, 4, 8 or 29), Study Arm (Study Arm 1, 2, and 3) and pairwise Study Arm Comparison (1 vs. 2, 1 vs. 3, 2 vs. 3). Repeat for post-second vaccination time points (Days 30, 32, and 36) relative to pre-second vaccination for Study Arms 2 and 3.

Right: Generate protein-interaction networks for H7N9 Study Arm Comparisons (Study Arm 1 vs. 2).

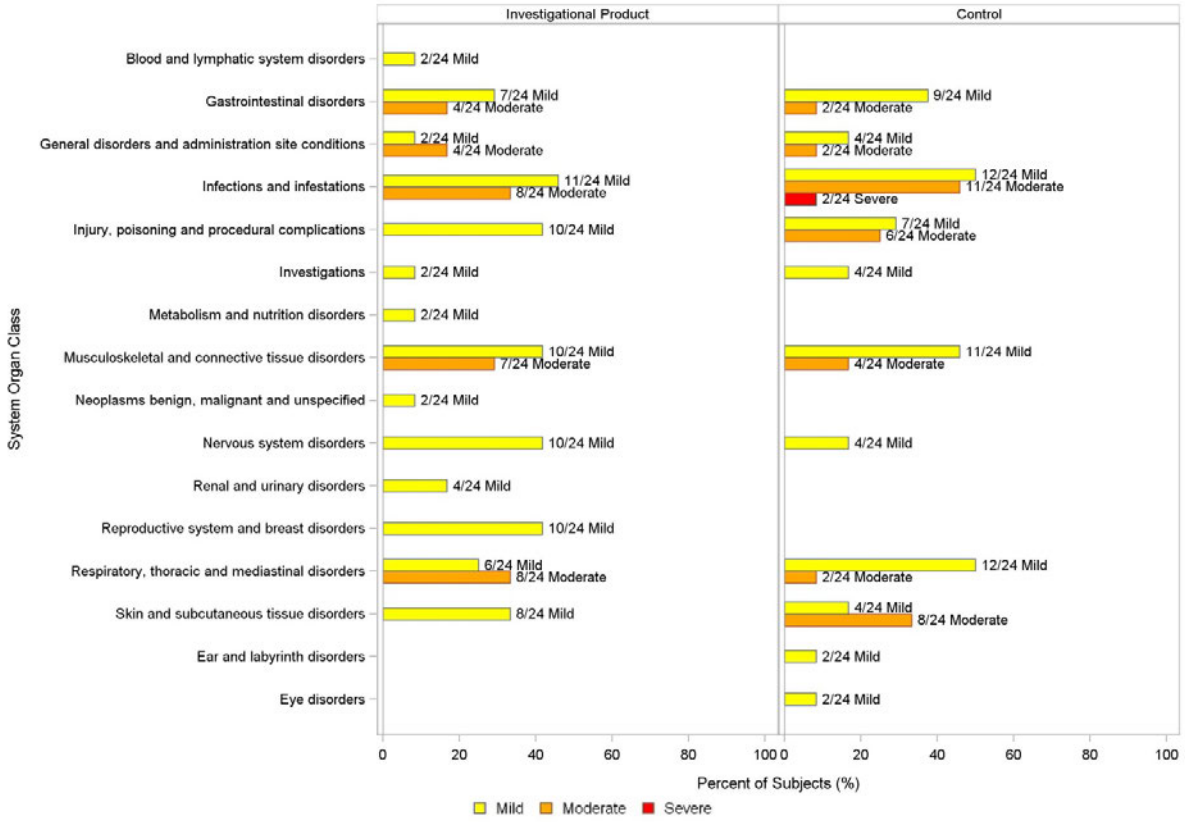
14.4 Safety Data

Figure 13: Maximum Severity of Solicited Systemic Symptoms per Subject by Day (Post-First Vaccination)



Repeat for post-second vaccination and for solicited local symptoms. Include all study arms. Label study arms as: Study Arm 1 A/H3N2v, D1; Study Arm 2 A/H7N9 + AS03, D1, 29; Study Arm 3 A/H7N9 + PBS, D1, 29.

Figure 14: Incidence of Unsolicited Adverse Events by MedDRA® System Organ Class and Severity



Include all study arms. Label study arms as: Study Arm 1 A/H3N2v, D1; Study Arm 2 A/H7N9 + AS03, D1, 29; Study Arm 3 A/H7N9 + PBS, D1, 29.

APPENDIX 3. LISTINGS MOCK-UPS

LISTINGS

Listing 1: 16.1.6 Listing of Subjects Receiving Investigational Product

Subject ID	Randomized Study Group	Product Received Study Vaccination 1	Product Received Study Vaccination 2

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 2: 16.2.1 Early Terminations or Discontinued Subjects

Treatment Group	Subject ID	Category	Reason for Early Termination or Treatment Discontinuation	Study Day

16.2.2 Protocol Deviations

Listing 3: 16.2.2.1 Subject-Specific Protocol Deviations

Treatment Group	Subject ID	DV Number	Deviation	Deviation Category	Study Day	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Comments

Listing 4: 16.2.2.2 Non-Subject-Specific Protocol Deviations

Site	Start Date	Deviation	End Date	Reason for Deviation	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Category	Deviation Resolution	Comments

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing 5: 16.2.3 Analysis Populations Exclusions

Treatment Group	Subject ID	Study Visit	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Results Available?	Reason for Exclusion
			[e.g., Safety, ITT, PP]	[e.g., Safety, ITT, PP, Day x]		

Note: "Yes" in the "Results available" column indicates that available data were removed from the analysis. "No" indicates that no data were available for inclusion in the analysis.

16.2.4 Demographic Data

Listing 6: 16.2.4.1 Demographic Data

Treatment Group	Subject ID	Sex	Age at Enrollment (years)	Ethnicity	Race

Listing 7: 16.2.4.2 Pre-Existing and Concurrent Medical Conditions

Treatment Group	Subject ID	MH Number	Medical History Term	Condition Start Day	Condition End Day	MedDRA System Organ Class	MedDRA Preferred Term

16.2.6 Individual Immunogenicity Response Data

Listing 8: 16.2.6 Individual Immunogenicity Response Data – Antibody Assays

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	HAI Titer	Neut Titer

Listing 9: 16.2.6 Individual Immunogenicity Response Data – Cytokine/Chemokine Assay

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Cytokine/Chemokine	Concentration
				[Cytokine/Chemokine]*	

*: *Fractalkine, GM-CSF, IFN-γ, IL-1b, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p70, IL-13, IL-17A, IL-21, IL-23, ITAC, MIP 1a, MIP1b, MIP3a, TNF-alpha, IP-10, IFNa, IFNb*

16.2.7 Adverse Events

Listing 10: 16.2.7.1 Solicited Events – Systemic Symptoms

Treatment Group	Subject ID	Dose Number	Post Dose Day	Assessment[a]	Symptom	Severity	Attributed to Alternate Etiology?[b]	Alternate Etiology
				MA				
				Clinic				

[a] MA = Data reported by subject on the Memory Aid and reviewed by clinic staff and reported in Solicited Events eCRF.
[b] Grade 3 events only.
Note: Clinic = Data collected by clinic staff during physical exam or symptom assessment (treatment administration record, in-clinic assessment, etc.)

Listing 11: 16.2.7.2 Solicited Events – Local Symptoms

Treatment Group	Subject ID	Dose Number	Post Dose Day	Assessment[a]	Symptom	Severity
				MA		
				Clinic		

[a] MA = Data reported by subject on the Memory Aid and reviewed by clinic staff and reported in Solicited Events eCRF.
Note: Clinic = Data collected by clinic staff during physical exam or symptom assessment (treatment administration record, in-clinic assessment, etc.)

Listing 12: 16.2.7.3 Unsolicited Adverse Events

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	Severity	SAE?	Relationship to Study Treatment	If Not Related, Alternative Etiology	Action Taken with Study Treatment	Subject Discontinued Due to AE	Outcome	MedDRA System Organ Class	MedDRA Preferred Term
Treatment Group: , Subject ID: , AE Number:											
Comments:											
Treatment Group: , Subject ID: , AE Number:											
Comments:											
Note: For additional details about SAEs, see Table 149.											

16.2.9 Vital Signs and Physical Exam Findings

Listing 13: 16.2.9.1 Vital Signs

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Temperature (°C)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Heart Rate (beats/min)	Respiratory Rate (breaths/min)	Weight (kg)	Height (cm)

Listing 14: 16.2.9.2 Physical Exam Findings

Treatment Group	Subject ID	Planned Time Point	Actual Study Day	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)

16.2.10 Concomitant Medications

Listing 15: 16.2.10 Concomitant Medications

Treatment Group	Subject ID	CM Number	Medication	Medication Start Day	Medication End Day	Indication	Taken for an AE? (AE Description; Number)	Taken for a condition on Medical History? (MH Description; Number)	ATC Level 1 (ATC Level 2)