STATISTICAL ANALYSIS PLAN
for
PATH Protocol CVIA 057

Study Title:

A Phase 1, randomized, controlled, observer-blind study to assess the reactogenicity, safety, and immunogenicity of a live attenuated universal influenza vaccine (cH8/1N1 LAIV) administered as a single priming dose followed three months later by a single booster dose of an inactivated universal influenza vaccine (cH5/1N1 IIV) (adjuvanted with $AS03_A$ or unadjuvanted) in 18 through 39 year-old healthy subjects, contrasted with a two dose schedule of an inactivated universal influenza vaccine (cH8/1N1 IIV+$AS03_A$ followed three months later by cH5/1N1 IIV+$AS03_A$)

Version 2.0

DATE: 18 OCTOBER 2019

Protocol Number Code:	CVIA 057
Development Phase:	Phase I
Products:	Investigational chimeric H8/1N1 live attenuated influenza vaccine (cH8/1N1 LAIV) GlaxoSmithKline (GSK) Biologicals' investigational chimeric H8/1N1 inactivated influenza vaccine (cH8/1N1 IIV) and investigational chimeric H5/1N1 inactivated influenza vaccine (cH5/1N1 IIV) $AS03_A$-like adjuvant ($AS03_A$-like will be obtained by dilution of the AS03 with PBS) Normal saline Phosphate buffered saline
Form/Route:	Intranasal/Intramuscular
Indication Studied:	Influenza
Sponsor:	PATH [redacted]
Date of the Analysis Plan:	18 October 2019
Version Number:	2.0

This study was performed in compliance with Good Clinical Practice.

CVIA 057 STATISTICAL ANALYSIS PLAN REVISION HISTORY

Version Number	Version Date	Summary of Changes
1.0	09 May 2018	Original
2.0	18 Oct 2019	• Section 3.1.2.1 Updated secondary objective for assessment of safety for MAEs, ILIs, pIMDs and SAEs through Visit 16 • Section:3.2.2.1 Updated secondary endpoint for the occurrence of MAEs, LC-ILIs, pIMDs and SAEs through Visit 16 • Section 4.3.3 Updated exclusion criteria for period between Visit 15 and Visit 16 • Section 9 Added clarification of timepoints for the collection of humoral and mucosal immune responses • Appendix 1 Table 2 Updated intervals between study visits to include Visit 16 • Appendix 1 Updated title for Table 31 • Appendix 2 Updated titles for Figures 2 through 4; 32 through 43; 62, and 65

SIGNATURE PAGE

PROTOCOL TITLE:

A Phase 1, randomized, controlled, observer-blind study to assess the reactogenicity, safety, and immunogenicity of a live attenuated universal influenza vaccine (cH8/1N1 LAIV) administered as a single priming dose followed three months later by a single booster dose of an inactivated universal influenza vaccine (cH5/1N1 IIV) (adjuvanted with $AS03_A$ or unadjuvanted) in 18 through 39 year-old healthy subjects, contrasted with a two dose schedule of an inactivated universal influenza vaccine (cH8/1N1 IIV + $AS03_A$ followed three months later by cH5/1N1 IIV + $AS03_A$)

PROTOCOL NUMBER: CVIA 057

[redacted]

[redacted]

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LIST OF ABBREVIATIONS

AE	Adverse Event
ADCC	Antibody-Dependent Cell-Mediated Cytotoxicity
ADCP	Antibody-Dependent Cellular Phagocytosis
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ARI	Acute Respiratory Illness
ASC	Antibody-Secreting Cells
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
CCHMC	Cincinnati Children's Hospital Medical Center
CDC	Centers for Disease Control and Prevention, United States
cHA	Chimeric Hemagglutinin
CFR	Code of Federal Regulations
CI	Confidence Interval
CMI	Cell-Mediated Immune Responses
CSR	Clinical Study Report
DCRI	Duke Clinical Research Institute
eCRF	Electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
ELISPOT	Enzyme-Linked ImmunoSpot
EoS	End of Study
FDA	United States Food and Drug Administration
FFA	Fluorescent Focus Assay
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
HA	Hemagglutinin
HI	Hemagglutination Inhibition
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonisation Good Clinical Practices
ICMJE	The International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IgA	Immunoglobulin A

IgG	Immunoglobulin G
IIV	Inactivated Influenza Vaccine
ILI	Influenza-Like Illness
IM	Intramuscular
IN	Intranasal
IND	Investigational New Drug
IRB	Institutional Review Board
ISMMS	Icahn School of Medicine at Mount Sinai
IWRS	Interactive Web Response System
LAIV	Live Attenuated Influenza Vaccine
LC-ILI	Laboratory-Confirmed Influenza-Like Illness
LLOQ	Lower Limit of Quantitation
mAB	Monoclonal Antibody
MAE	Medically Attended Event
MDCK	Madin Darby Canine Kidney
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MGI	Mean Geometric Increase
mL	Milliliter
MN	Microneutralization
NA	Neuraminidase
pIMD	Potential Immune-Mediated Disease
PP Population	Per Protocol Population
RCC	Reverse cumulative distribution curves
SD	Standard Deviation
SDCC	Statistical Data Coordinating Center at the Emmes Corporation
SOP	Standard Operating Procedure
TVC	Total Vaccinated Cohort
ULN	Upper Limit of the Normal Range
ULOQ	Upper Limit of Quantitation
VAERD	Vaccine-Associated Enhanced Respiratory Disease
WBC	White Blood Cell

1. PREFACE

This Statistical Analysis Plan (SAP) for "A Phase 1, randomized, controlled, observer-blind study to assess the reactogenicity, safety, and immunogenicity of a live attenuated universal influenza vaccine (cH8/1N1 LAIV) administered as a single priming dose followed three months later by a single booster dose of an inactivated universal influenza vaccine (cH5/1N1 IIV) (adjuvanted with $AS03_A$ or unadjuvanted) in 18 through 39 year-old healthy subjects, contrasted with a two dose schedule of an inactivated universal influenza vaccine (cH8/1N1 IIV + $AS03_A$ followed three months later by cH5/1N1 IIV + $AS03_A$)" (PATH protocol CVIA 057) describes and expands upon the statistical information presented in the protocol.

This document describes all planned analyses and provides reasons and justifications for these analyses. It also includes sample tables, figures, and listings planned for the final analyses (see Appendix 1, Appendix 2, and Appendix 3). Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Conference on Harmonization 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 US Food and Drug Administration (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 a review of the study design, general statistical considerations, comprehensive statistical analysis methods for efficacy and safety outcomes, and a list of proposed tables and figures. 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.

2. INTRODUCTION

The main purpose of this study is to assess in healthy adults the safety and reactogenicity of each dose of LAIV or IIV. The study will also evaluate 1) acceptability of the immune responses of the LAIV-IIV prime-boost regimen contrasted with those of the IIV-IIV two-dose prime regimen and 2) the adjuvant effect of $AS03_A$ on the immune response to the IIV booster dose in the LAIV-IIV regimen when compared to the non-adjuvanted formulation. Because influenza vaccines based on influenza virus containing a chimeric hemagglutinin (HA) have not been studied in humans previously, the study will evaluate both humoral and secretory immune responses, as well as cell-mediated immune responses. To ensure comparability of group level data across study regimens, one cohort of subjects will be recruited, enrolled, and randomized, stratified by site, to the five study arms.

Sixty-five subjects 18-39 years of age will be enrolled and randomized to five different treatment groups. All subjects will receive two doses of study vaccines (or placebo) three months apart. Subjects receiving active study vaccine will receive vaccines that are based on an influenza virus expressing a chimeric HA with the same stalk domain (H1 stalk) at each dose but which have a different exotic group A_1 head domain. Three groups totaling 40 subjects will be randomized 4:3:1 to receive a priming LAIV dose (Groups 1, 2) or placebo, (Group 3) on study Visit 03 followed by a booster IIV dose with $AS03_A$ (Group 1) or without (Group 2) or placebo (Group 3) at Visit 11. Two groups totaling 25 subjects will be randomized 3:2 to receive a first priming IIV dose with $AS03_A$ (Group 4) or placebo (Group 5) on study Visit 03 followed by a second priming IIV dose with $AS03_A$ (Group 4) or placebo (Group 5) at Visit 11. All eligible enrolled subjects will be randomized to any of the treatment arms (LAIV-IIV, Groups 1, 2, and 3; or IIV-IIV, Groups 4 and 5) under one allocation sequence, stratified by site, to preserve comparability between study groups, particularly LAIV-IIV vs IIV-IIV regimens (e.g., Groups 1 vs 4).

2.1. Purpose of the Analyses

This Statistical Analysis Plan describes the statistical methodology and summaries required to assess the demographics, safety, reactogenicity, immunogenicity, cell-mediated immune responses (CMI) and between-group assessment of an investigational live-attenuated universal influenza vaccine (prime) followed by an investigational inactivated universal influenza vaccine (boost) when administered to 18 through 39-year-old healthy subjects.

3. STUDY OBJECTIVES AND ENDPOINTS

Study objectives are listed here as in the protocol. At the time of protocol preparation, some assays had not fully completed validation and/or optimization. See Section 12 for a summary of differences from the protocol in analysis methods.

3.1. Study Objectives

3.1.1. Primary Objective

To assess the reactogenicity and safety through 28 days after each priming dose of cH8/1N1 LAIV (or placebo) and the booster dose of cH5/1N1 IIV +/- $AS03_A$ (or placebo) and through 28 days after each dose of IIV (cH8/1N1 IIV + $AS03_A$ and cH5/1N1 IIV + $AS03_A$) (or placebo) in terms of rates of solicited local and general AEs through 7 days post-vaccination, unsolicited AEs through 28 days post-vaccination, hematological and biochemical laboratory abnormalities through Visit 13, and medically attended event (MAEs), influenza-like illnesses (ILIs), potential immune-mediated disease (pIMDs), and serious adverse events (SAEs) through Visit 13.

3.1.2. Secondary Objectives

3.1.2.1. Safety

To assess the safety of each treatment group during the entire study period in terms of rates of primary endpoints and additionally hematological and biochemical laboratory abnormalities up to Visit 15, and MAEs, ILIs, pIMDs and SAEs through Visit 16.

3.1.2.2. Viral Shedding - Post-Dose 1

To describe the shedding of vaccine virus through 5 days after administration of cH8/1N1 LAIV (Groups 1, 2, and 3 only) in terms of the proportions of subjects with influenza type A vaccine virus RNA detected by RT-PCR in nasal and OP swabs and the proportion of subjects with vaccine virus isolated in cell culture each day post-vaccination.

3.1.2.3. Immunogenicity - Descriptive, post-Dose 2

To describe the anti-H1 HA-stalk humoral immune responses

- anti-H1 HA-stalk serum immunoglobulin G [IgG],
- anti-H1 HA-stalk serum neutralizing antibodies,
- anti-H1 HA-stalk serum immunoglobulin A [IgA],
- ADCC activity

28 days after the booster dose of cH5/1N1 IIV +/- $AS03_A$ (or placebo) ***(Groups 1, 2, and 3)*** and 28 days after the second dose of IIV (cH5/1N1 IIV + $AS03_A$) (or placebo) ***(Groups 4 and 5)*** in terms of seropositivity rates, geometric mean titers (GMTs), percentages of subjects with a 4-fold or greater increase in titer from Day 1, percentages of subjects with a 10-fold or greater increase in titer from Day 1, and mean geometric increases (MGIs) from Day 1.

To describe the anti-H1 HA-stalk mucosal immune responses

- anti-H1 HA-stalk salivary total IgA,
- anti-H1 HA-stalk secretory IgA in saliva,
- anti-H1 HA-stalk salivary IgG

28 days after the booster dose of cH5/1N1 IIV +/- $AS03_A$ (or placebo) ***(Groups 1, 2, and 3)*** and 28 days after the second dose of IIV (cH5/1N1 IIV + $AS03_A$) (or placebo) ***(Groups 4 and 5)*** in terms of seropositivity rates, GMTs, percentages of subjects with a 4-fold or greater increase in titer from Day 1, percentages of subjects with a 10-fold or greater increase in titer from Day 1, and MGIs from Day 1.

3.1.2.4. Immunogenicity - Descriptive, post-Dose 2 - breadth

To describe the breadth of the anti-H1 HA-stalk humoral immune responses

- anti-H2 HA-full length serum IgG,
- anti-H9 HA-full length serum IgG,
- anti-H18 HA-full length serum IgG,
- anti-H5N8 serum neutralizing antibodies,
- anti-avian-swine H1N1 serum neutralizing antibodies,
- anti-H1pdm09-like serum neutralizing antibodies

to Group 1 influenza A viruses 28 days after the booster dose of cH5/1N1 IIV +/- $AS03_A$ (or placebo) ***(Groups 1, 2, and 3)*** and 28 days after the second dose of IIV (cH5/1N1 IIV + $AS03_A$) (or placebo) ***(Groups 4 and 5)*** in terms of seropositivity rates, GMTs, percentages of subjects with a 4-fold or greater increase in titer from Day 1, percentages of subjects with a 10-fold or greater increase in titer from Day 1, and MGIs from Day 1.

3.1.2.5. Immunogenicity - Descriptive, post-Dose 2 - persistence

To describe the persistence of the anti-H1 HA-stalk humoral immune responses

- anti-H1 HA-stalk serum IgG,
- anti-H1 HA-stalk serum neutralizing antibodies,
- anti-H1 HA-stalk serum IgA,
- ADCC activity

up to 12 months after the booster dose of cH5/1N1 IIV +/- $AS03_A$ (or placebo) ***(Groups 1, 2, and 3)*** and up to 12 months after the second dose of IIV (cH5/1N1 IIV + $AS03_A$) (or placebo) ***(Groups 4 and 5)*** in terms of seropositivity rates, GMTs, percentages of subjects with a 4-fold or greater increase in titer from Day 1, percentages of subjects with a 10-fold or greater increase in titer from Day 1, and MGIs from Day 1.

To describe the persistence of the anti-H1 HA-stalk mucosal immune responses

- anti-H1 HA-stalk salivary total IgA,
- anti-H1 HA-stalk secretory IgA in saliva
- anti-H1 HA-stalk salivary IgG

up to 12 months after the booster dose of cH5/1N1 IIV +/- $AS03_A$ (or placebo) ***(Groups 1, 2, and 3)*** and up to 12 months after the second dose of IIV (cH5/1N1 IIV + $AS03_A$) (or placebo) ***(Groups 4 and 5)*** in terms of seropositivity rates, GMTs, percentages of subjects with a 4-fold or greater increase in titer from Day 1, percentages of subjects with a 10-fold or greater increase in titer from Day 1, and MGIs from Day 1.

3.1.2.6. Immunogenicity - Descriptive, by vaccine regimen, post-Dose 1

To describe the anti-H1 HA-stalk humoral immune responses

- anti-H1 HA-stalk serum IgG,
- anti-H1 HA-stalk serum neutralizing antibodies,
- anti-H1 HA-stalk serum IgA,
- ADCC activity

28 days after the prime dose of cH8/1N1 LAIV (or placebo) ***(Groups 1, 2, and 3)*** and 28 days after the first dose of IIV (cH8/1N1 IIV + $AS03_A$) (or placebo) ***(Groups 4 and 5)*** in terms of seropositivity rates, GMTs, percentages of subjects with a 4-fold or greater increase in titer from Day 1, percentages of subjects with a 10-fold or greater increase in titer from Day 1, and MGIs from Day 1.

To describe the anti-H1 HA-stalk mucosal immune responses

- anti-H1 HA-stalk salivary IgA,
- anti-H1 HA-stalk secretory IgA in saliva
- anti-H1 HA-stalk salivary IgG

28 days after the prime dose of cH8/1N1 LAIV (or placebo) ***(Groups 1, 2, and 3)*** and 28 days after the first dose of IIV (cH8/1N1 IIV + $AS03_A$) (or placebo) ***(Groups 4 and 5)*** in terms of seropositivity rates, GMTs, percentages of subjects with a 4-fold or greater increase in titer from Day 1, percentages of subjects with a 10-fold or greater increase in titer from Day 1, and MGIs from Day 1.

3.1.2.7. Immunogenicity - Comparative, post-Dose 2

To compare the anti-H1 HA-stalk humoral immune responses

- anti-H1 HA-stalk serum IgG,
- anti-H1 HA-stalk serum neutralizing antibodies,
- anti-H1 HA-stalk serum IgA,
- ADCC activity

28 days after the booster dose with cH5/1N1 IIV +/- $AS03_A$ after previous receipt of cH8/1N1 LAIV ***(Groups 1 or 2)*** to that after priming with two doses of IIV (cH8/1N1 IIV + $AS03_A$ and cH5/1N1 IIV + $AS03_A$) ***(Group 4)*** in terms of the adjusted GMT ratio and the seroresponse (≥4-fold) rate difference.

To compare the anti-H1 stalk mucosal immune responses

- anti-H1 HA-stalk salivary IgA,
- anti-H1 HA-stalk secretory IgA in saliva,
- anti-H1 HA-stalk salivary IgG

28 days after the booster dose with cH5/1N1 IIV +/- $AS03_A$ after previous receipt of cH8/1N1 LAIV ***(Groups 1 or 2)*** to that after priming with two doses of IIV (cH8/1N1 IIV + $AS03_A$ and cH5/1N1 IIV + $AS03_A$) ***(Group 4)*** in terms of the adjusted GMT ratio and the seroresponse (≥4-fold) rate difference.

To evaluate the adjuvant effect of $AS03_A$ on the anti-H1 stalk humoral immune response

- anti-H1 HA-stalk serum IgG,
- anti-H1 HA-stalk serum neutralizing antibodies,
- anti-H1 HA-stalk serum IgA,
- ADCC activity

after one booster dose of cH5/1N1 IIV + $AS03_A$ after priming with cH8/1N1 LAIV ***(Group 1)*** compared to boosting with cH5/1N1 IIV, unadjuvanted ***(Group 2)*** in terms of the adjusted GMT ratio and seroresponse (≥4-fold) rate difference.

3.1.3. Tertiary Objectives

To explore the cell-mediated immune responses (B-cells and T-cells) after each vaccination.

To explore blood biomarkers associated with different vaccination regimens (transcriptomic analysis).

To explore the immune response against the HA head of cH8/1N1, cH5/1N1, cH6/1N5, and H1N1pdm2009-like virus after each vaccination using a HI assay against these viruses.

To explore the anti-H3 stalk response (i.e., influenza A Group 2).

To explore the immune response in terms of anti-NA antibodies after each vaccination.

To explore the protective effect of the stalk-reactive antibodies induced by vaccination in a passive transfer challenge experiment in mice.

To develop assays for evaluation/characterization of the humoral and cellular immune responses.

To explore the anti-stalk antibodies' activity (e.g., antibody-dependent cellular phagocytosis [ADCP], complement dependent lysis assays, or glycosylation assays).

3.2. Study Endpoints

3.2.1. Primary Endpoints

3.2.1.1. Reactogenicity and Safety

Occurrence of solicited local and general AEs post-vaccination:

- Occurrence of solicited local AEs during a 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) after the first and the second dose in each study group.
- Occurrence of solicited general AEs during a 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) after the first and the second dose in each study group.

Occurrence of unsolicited AEs post-vaccination:

- Occurrence of unsolicited AEs during a 28-day follow-up period (i.e., on the day of vaccination and 27 subsequent days) after the first and the second dose in each study group.

Occurrence of hematological and biochemical laboratory abnormalities post-vaccination:

- Any hematological (red blood cell, white blood cell, and differential count, platelets count and hemoglobin level) or biochemical (ALT, AST, creatinine, BUN and BUN-to-creatinine ratio) laboratory abnormality on Visits 9, 10, 11, 12, and 13 in each study group.

Occurrence of MAEs, LC-ILIs, pIMDs, and SAEs up to Visit 13:

- Occurrence of MAEs, LC-ILIs, pIMDs, and SAEs up to Visit 13 in each study group.

(Because Groups 1 and 2 will receive the same study LAIV at Dose 1, data for the period post-Dose 1 will be pooled for these groups.)

3.2.2. Secondary Endpoints

3.2.2.1. Reactogenicity and Safety

Occurrence of hematological and biochemical laboratory abnormalities:

- Any hematological (red blood cell, white blood cell, and differential count, platelets count and hemoglobin level) or biochemical (ALT, AST, creatinine, BUN and BUN-to-creatinine ratio) laboratory abnormality at Visit 14 and Visit 15 in each study group.

Occurrence of MAEs, LC-ILIs, pIMDs and SAEs up to study end at Visit 16:

- Occurrence of MAEs, LC-ILIs, pIMDs and SAEs up to Visit 16 in each study group.

Shedding of vaccine virus through 5 days post-vaccination (Groups 1, 2 & 3 only):

- Percentages of subjects with vaccine virus detectable by RT-PCR each day and overall (at any time).
- Percentages of subjects with recovery of viable vaccine virus in MDCK culture each day and overall (at any time).

3.2.2.2. Immunogenicity - Descriptive, post-Dose 2

Humoral and mucosal immunity in terms of anti-H1 stalk immune response measured by ELISA, neutralizing antibodies by MN assay, and activity by ADCC assay at Visit 13 (28 days post-boost):

- Levels of anti-H1 stalk antibody titers by ELISA, by MN, and by ADCC.

The following aggregate variables will be calculated for the above parameters with 95% confidence interval (CI):

- Seropositivity rates and GMTs on Day 1 and Visit 13.
- Percentage of subjects with a ≥ 4-fold increase from Day 1 to Visit 13.
- Percentage of subjects with a ≥ 10-fold increase from Day 1 to Visit 13.
- Mean geometric increase (MGI) from Day 1 to Visit 13.

(Post-dose one descriptive immunogenicity will be similarly analyzed at Visit 10. Because Groups 1 and 2 will receive the same study LAIV at Dose 1, data for the period post-Dose 1 will be pooled for these groups.)

3.2.2.3. Immunogenicity - Descriptive, post-Dose 2 - breadth

Breadth of the humoral immune response as measured by levels of anti-H2, anti-H9 and anti-H18 antibody titers by ELISA. The following aggregate variables will be calculated for the above parameters with 95% CI:

- Anti-H2, anti-H9, and anti-H18 seropositivity rates and GMTs at Day 1 and Visit 13.
- Percentage of subjects with a ≥ 4-fold increase in anti-H2, anti-H9 and anti-H18 antibody titers from Day 1 to Visit 13.
- Percentage of subjects with a ≥ 10-fold increase in anti-H2, anti-H9 and anti-H18 antibody titers from Day 1 to Visit 13.
- MGI in anti-H2, anti-H9 and anti-H18 antibody titers from Day 1 to Visit 13.

Levels of antibody titers by MN for H5N8; H1N1 avian-swine influenza, and current H1N1pdm09-like vaccine strains. The following aggregate variables will be calculated for the above parameters with 95% CI:

- Seropositivity rates and GMTs for H5N8, H1N1 avian-swine, and H1pdm09-like neutralizing antibody at Day 1 and Visit 13.
- Percentage of subjects with a ≥ 4-fold increase in H5N8, H1N1 avian-swine, and H1pdm09-like neutralizing antibody titers from Day 1 to Visit 13.

- Percentage of subjects with a ≥ 10-fold increase in H5N8, H1N1 avian-swine, and H1pdm09-like neutralizing antibody titers from Day 1 to Visit 13.
- MGI in H5N8, H1N1 avian-swine, and H1pdm09-like neutralizing antibody titers from Day 1 to Visit 13.
- (Post-Dose 1 descriptive immunogenicity for breadth will be similarly analyzed at Visit 10 and additional post-Dose 2 descriptive immunogenicity for breadth may be analyzed at Visit 15.)

3.2.2.4. Immunogenicity - Descriptive, post-Dose 2 - persistence:

Persistence of both humoral and mucosal immune responses as measured by levels of anti-H1 stalk antibody titers by ELISA, by MN, and by ADCC. The following aggregate variables will be calculated for the above parameters with 95% CI:

- Seropositivity rates and GMTs at Visit 14* and 15.
- Percentage of subjects with a ≥ 4-fold increase from Day 1 to Visit 14* and 15.
- Percentage of subjects with a ≥ 10-fold increase from Day 1 to Visit 14* and 15.
- MGI from Day 1 to Visit 14* and 15.

  **Only for anti-H1 HA-stalk IgG detection by ELISA in serum*

3.2.2.5. Immunogenicity - Comparative, post-Dose 2

Humoral and mucosal immunity in terms of anti-H1 stalk immune response as measured by ELISA, neutralizing antibodies by MN assay, and activity by ADCC assay 28 days post-boost with LAIV-IIV prime-boost compared to two doses of IIV:

- Adjusted GMT ratio of the LAIV / IIV + $AS03_A$ group (**Group 1**) versus the IIV + $AS03_A$ / IIV + $AS03_A$ group (**Group 4**), 28 days post-vaccination (i.e., at Visit 13 to evaluate the LAIV-IIV prime-boost effect).
- Seroresponse (≥4-fold) rate difference of the LAIV / IIV + $AS03_A$ group (**Group 1**) versus the IIV + $AS03_A$ / IIV + $AS03_A$ group (**Group 4**), 28 days post-vaccination (i.e., at Visit 13 to evaluate the LAIV-IIV prime-boost effect).
- Adjusted GMT ratio of the LAIV / IIV group (**Group 2**) versus the IIV + $AS03_A$ / IIV + $AS03_A$ group (**Group 4**), 28 days post-vaccination (i.e., at Visit 13 to evaluate the LAIV-IIV prime-boost effect).
- Seroresponse (≥4-fold) rate difference of the LAIV / IIV group (**Group 2**) versus the IIV + $AS03_A$ / IIV + $AS03_A$ group (**Group 4**), 28 days post-vaccination (i.e., at Visit 13 to evaluate the LAIV-IIV prime-boost effect).

LAIV-IIV groups might be pooled in an exploratory analysis if the adjuvant effect appears minimal. Adjuvant effect on the anti-stalk immune response in term of:

- GMT ratio of the LAIV- IIV + $AS03_A$ group (**Group 1**) versus the LAIV-IIV unadjuvanted group (**Group 2**), 28 days post-boost (i.e., at Visit 13 to evaluate the adjuvant effect post-boost).

3.2.3. Tertiary Endpoints

Evaluation of CMI parameters in terms of frequencies of:

- Antigen-specific IFN-γ secreting cells upon in vitro stimulation at Day 1 and Visits 9, 11, 12, and 15
- B-memory cells reactive with the H1 stalk domain and a wild-type H1N1pdm09 virus at Day 1 and Visits 10, 11, 13, and 15.
- Plasmablasts reactive with the H1 stalk domain and a wild-type H1N1pdm09 virus at Visits 9 and 12.

Levels of HI antibody to chimeric vaccine strains. The following aggregate variable will be calculated with 95% CI:

- Seropositivity rates and GMTs at Day 1, Visit 10, 11, 13, and 15.
- Seroprotection rate at each time point listed above.
- Seroconversion rate at Day 1, Visit 10, 11, 13, and 15.
- MGI from Day 1 to each subsequent time point listed above.

Evaluation of the anti-H3 stalk response by ELISA pre-and post-vaccination. Levels of anti-N1 NA antibody by ELISA at Day 1, Visits 10, 11, 13, and 15.

Assessment of the *in vivo* protective effect of the anti-stalk antibodies when transferring Day 1, Visit 13 and Visit 15 pooled serum from a subset of subjects of each vaccine groups to mice subsequently challenged with cH6/1N5, or with current H1N1pdm09-like virus recommended by the World Health Organization, using the following endpoints:

- Survival over 14 days post-challenge (day of death/euthanasia for weight loss > 25% baseline body weight) in groups of mice/serum pool/per vaccine group/time point.
- Mean weight loss (change from baseline over 14 days post-challenge) in groups of mice/serum pool/vaccine group/time point.
- Lung virus titer in plaque-forming units (pfu)/g (log_{10} fold change [Day 1 minus Visit 13]), within challenge group.

3.3. Study Definitions and Derived Variables

3.3.1. Adverse Event (AE)

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

This definition includes exacerbations of pre-existing conditions. Stable pre-existing conditions which do not change in nature or severity during the study are not considered AEs; however, these should be reported as part of the medical history. However, if this condition deteriorates (e.g., increases in frequency or severity grade) during the study, it should be recorded as an AE.

3.3.1.1. Solicited Local and General Reactions

Solicited AEs are pre-specified local and general (systemic) adverse events that are common or known to be associated with vaccinations or the study product that are actively monitored as indicators of vaccine reactogenicity. Investigators are not required to assess causality of solicited adverse events if the onset is during the solicitation periods. Solicited adverse events with onset after the solicitation period should be captured as unsolicited AEs.

3.3.1.2. Unsolicited Adverse Events

Unsolicited AEs are any AEs reported spontaneously by the subject, observed by the study personnel during study visits or identified during review of medical records or source documents, such as diary cards.

3.3.1.3. Adverse Drug Reaction / Suspected Adverse Reaction

An **adverse drug reaction** is any AE in which the causal relationship to the investigational vaccine is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Having a reasonable suspected causal relationship to the investigational vaccine qualify as an adverse drug reaction. The concept of “reasonable causal relationship” is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

A **suspected adverse reaction** is any adverse event for which there is a reasonable possibility that the drug (vaccine) caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug (vaccine) and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug (vaccine).

Adverse reaction is any adverse event caused by the drug (vaccine). Adverse reaction is a subset of suspected adverse reactions where there is reason to conclude that the drug (vaccine) caused the event.

Unexpected suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed.

3.3.2. Serious Adverse Event (SAE)

A **serious adverse event** is an AE that meets one of the following conditions:

- Results in death.
- Is life threatening (i.e., puts the subject at immediate risk of death). (The term “life-threatening” in the definition of “serious” refers to an event in which the subject is/was, in the opinion of the investigator or Sponsor, at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)

- Requires inpatient hospitalization or prolongation of existing hospitalization. (Continuation of stay in the isolation unit beyond 7 days post-administration of either dose of study vaccine or placebo because of late detected viral shedding in a subject shall not be considered a "prolongation of existing hospitalization" for SAE recording or reporting.)
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly/birth defect. (Only in the case of a woman becoming pregnant during the study period after administration of at least one dose of study vaccine. All pregnancies must be followed to term and outcome reported to the Sponsor and regulatory agencies.)
- Is an important medical event that may not meet one of the above conditions, but may jeopardize the well-being of the subject or require medical or surgical intervention to prevent one of the outcomes listed above. (Appropriate medical judgment should be exercised in deciding whether reporting these events is appropriate.)

Suspected unexpected serious adverse reaction is any suspected adverse reaction that is both unexpected and serious.

3.3.3. Definitions and Derivations used in this Study

- A baseline value will be defined as the last value obtained prior to the first vaccination of study product.
- Age will be calculated from the date of enrollment and will be presented in whole years.
- Adjusted GMT ratio will be computed after fitting an ANCOVA model on the log transformation of ELISA/MN titers adjusted for pre-vaccination titer; i.e., including vaccine group as a fixed effect and log pre-vaccination titer as covariate.
- Fever: oral temperature, $\geq$ 37.8°C or 100°F.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This trial is a prospective, multi-center, randomized, controlled, observer-blind, Phase 1 trial in healthy male and female adults 18 through 39 years of age. Up to 65 eligible subjects will participate and will be randomized 4:3:1:3:2 to one of five groups to receive a first dose of study cH8/1N1 LAIV (or placebo) or study cH8/1N1 IIV + $AS03_A$ adjuvant (or placebo) followed three months later by study cH5/1N1 IIV +/- $AS03_A$ adjuvant (or placebo). Two sites, Duke Early Phase Clinical Research Unit at Duke University and the Gamble Program for Clinical Studies at Cincinnati Children's Hospital Medical Center (CCHMC), will participate and enroll 39 and 26 subjects, respectively. Eligible enrolled subjects will be randomized to any of the treatment arms (LAIV-IIV, Groups 1, 2, and 3; or IIV-IIV, Groups 4 and 5) under one allocation sequence, stratified by site, to allow comparability between study groups, such as LAIV-IIV vs IIV-IIV regimens (Groups 1 vs 4). While subjects will be blinded to their exact treatment group and whether they received active study vaccine versus placebo, subjects in the LAIV-IIV treatment arms will be admitted into the inpatient clinical isolation unit; therefore, subjects will certainly know if they received LAIV (or placebo) vs IIV (or placebo) at Dose 1, given the different presentations and routes of administration of these products.

The Study groups and treatment and route of administration by dose and study design overview are presented in Table 1 and Table 2, Appendix 1 and Table 3 and Figure 4, Section 3 in the protocol.

Special safety monitoring during inpatient stay post-Dose 1 of cH8/1N1 LAIV or placebo: To reduce the risk that subjects bring wild-type influenza into the inpatient clinical isolation unit or that subjects receiving study cH8/1N1 LAIV return to the community while shedding potentially viable vaccine virus, all subjects in Groups 1, 2, and 3 will be monitored for acute respiratory infection and for virologic evidence of influenza infection.

Independent Data Monitoring Committee: An Independent Data Monitoring Committee (IDMC) will be established by PATH for the purpose of monitoring the study and to provide independent, non-binding advice on safety and ethics. The IDMC will be comprised of independent medical experts in vaccinology and infectious diseases who will periodically review the conduct and safety of study. The IDMC will be supported by an unblinded secretary and an unblinded biostatistician, both from Emmes. The responsibilities and procedures of the IDMC are defined in the IDMC Charter. During the whole study period, there will be IDMC reviews at pre-defined time points (The frequency of these reviews may be adapted upon IDMC recommendation if deemed necessary). At least three pre-defined meeting time points will be as follows:

- The IDMC will review safety data through Visit 10 (28 days post-Dose 1) for all subjects prior to any subject receiving Dose 2 of study vaccine.
- The IDMC will review safety data through Visit 13 (28 days post-Dose 2) for all subjects.
- The IDMC will review safety data through Visit 15 (12 months post-Dose 2) for all subjects.

- The IDMC may also be convened to review events that meet any pause rules if deemed necessary by the (Protocol Safety Review Team) PSRT. In such cases, the IDMC and PSRT may convene by teleconference to jointly review the data.

The IDMC reviews will be summarized with recommendations to the study Sponsor as to whether there are safety concerns and whether the study should continue without change, be modified, or be terminated. If at any time, a decision is made to permanently discontinue administration of study vaccinations in all subjects, the Sponsor will notify the FDA and the site PIs will notify the responsible IRBs expeditiously.

Analysis Sequence: Staged analyses will be done. Excluding any IDMC analyses, the analyses will be performed in a stepwise manner:

- Interim analyses will be performed when safety, reactogenicity, and immunogenicity (including at least H1 anti-stalk, anti-H2, anti-H18, anti-N1, and anti-H9 IgG ELISA) data from all subjects are available up to Visit 13.
- A final analysis of all data will be performed when data up to study conclusion are available. This analysis will be reported in a Study Report.

4.2. Discussion of Study Design

Detailed information on the discussion of study design is in the protocol Sections 1.3 and 3.

4.3. Selection of Study Population

4.3.1. Description of study population

This study will be conducted at two major medical research centers in the US. They are the Gamble Program for Clinical Studies at Cincinnati Children's Hospital Medical Center (CCHMC) located in Cincinnati, Ohio, and the Duke Early Phase Clinical Research Unit at Duke Clinical Research Institute in Durham, North Carolina. A total of 65 subjects aged 18 through 39 years old will be enrolled in this study.

4.3.2. Inclusion criteria for enrollment

Deviations from inclusion criteria are not allowed because they can potentially jeopardize the scientific integrity, regulatory acceptability of the study or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

All subjects must satisfy ALL the following criteria at study entry:

- Able to understand planned study procedures and demonstrate comprehension of the protocol procedures and knowledge of study by passing a written examination* prior to vaccination

  * Passing grade ≥70%

- In the opinion of the investigator, can and will comply with the requirements of the protocol (e.g., completion of the diary cards, return for follow-up visits).

- Written informed consent obtained from the subject prior to performance of any study specific procedure.
- Male or non-pregnant female between, and including, 18 and 39 years of age at the time of the first vaccination.
- Healthy subjects without acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality*.

  * As determined by medical history, physical examination, or laboratory screening tests.

- Female subjects of non-childbearing potential may be enrolled in the study.

Non-childbearing potential is defined as pre-menarche, current bilateral tubal ligation or occlusion, hysterectomy, bilateral ovariectomy or post-menopause.

- Female subjects of childbearing potential must have a negative pregnancy test within 24 hours of vaccination.
- Female subjects of childbearing potential must have practiced adequate contraception for 30 days prior to first vaccination and agree to continue adequate contraception until 2 months after completion of the vaccination series (Month 5).
- Male subjects must be surgically sterile (e.g., vasectomy) or agree to practice adequate contraception from the first vaccination until 2 months after completion of the vaccination series (Month 5).

4.3.3. Exclusion criteria for enrollment

Deviations from exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity regulatory acceptability of the study, or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following criteria should be checked at the time of study entry. If ANY exclusion criterion applies, the subject must not be included in the study:

- Use of any investigational or non-registered product (drug or vaccine) other than the study vaccines†

  †During the period starting 30 days before the first dose of study vaccines (Day -29 to Day 1), or planned use during the study period. Between Visit 15 and Visit 16, the subject may participate in other clinical studies except for those in which investigational influenza vaccines would be administered.

- Concurrently participating in another clinical study, at any time during the study period, in which the subject has been or will be exposed to an investigational or a non-investigational vaccine/product‡. Between Visit 15 and Visit 16, the subject may participate in other clinical studies except for those in which investigational influenza vaccines would be administered.

  ‡Pharmaceutical product or device.

- Any medical condition that in the judgment of the investigator would make study participation (including intramuscular injection) unsafe.
- Medically diagnosed deviated nasal septum or nasal obstruction.

- Chronic administration (defined as more than 14 days in total) of immunosuppressants or other immune-modifying drugs within 6 months before the first dose.

  For corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent.
  For high-dose inhaled corticosteroids this will mean beclomethasone dipropionate chlorofluorocarbon ≥ 840 mcg/day, or equivalent.
  Topical steroids are allowed.

- Administration of long-acting immune-modifying drugs (e.g., infliximab, rituximab) within 6 months before the first dose (Visit 03), or planned administration any time during the study period.

- Planned administration/administration of a vaccine not foreseen by the study protocol in the period starting 30 days before the first dose (Visit 03) up to Month 15 (Visit 15)[§].

  [§] 30 days before the first the first dose (Visit 03) up to the blood sampling at Day 113 (Visit 13) and in the period starting 30 days before blood sampling at Month 9 (Visit 14) and Month 15 (Visit 15)

- Persons who should be annually vaccinated against influenza, if they themselves are or they live with or care for persons at high risk for influenza-related complications, including:

  health care personnel such as physicians, nurses, and other workers in inpatient and outpatient-care settings, medical emergency-response workers, such as paramedics and emergency medical technicians) employees of nursing home and long-term care facilities who have contact with patients or residents, and students in these professions who will have contact with patients, and;
  household contacts and caregivers of persons not eligible for seasonal influenza vaccination (e.g., children aged <6 months) or among whom seasonal influenza vaccine effectiveness is diminished (e.g., the elderly ≥65 years).
  [Medical conditions that put persons at high risk for severe complications from influenza are identified by the Advisory Committee on Immunization Practices (see https://www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm) and include the following:

  – Persons who have chronic pulmonary (including asthma) or cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus);

  – Persons who have immunosuppression (including immunosuppression caused by medications or by HIV infection);

  – Persons who have extreme obesity (body mass index [BMI] ≥40).]

- History of influenza vaccination within 6 months prior to study enrollment or unwillingness to forego seasonal influenza vaccination during the entire study period.

- History of vaccination with an investigational pandemic influenza vaccine other than an H1N1pdm09 vaccine.

- Any confirmed or suspected immunosuppressive or immunodeficient condition, based on medical history and physical examination.
- Infection with human immunodeficiency virus regardless of clinical stage of immunodeficiency.
- History of current infection with hepatitis B virus or hepatitis C virus regardless of clinical presentation.
- History of or current autoimmune disease.
- Subjects diagnosed with excessive daytime sleepiness¶ or narcolepsy; or history of narcolepsy in a subject's parent or sibling.

  ¶Unintended sleep episodes during the day present almost daily for at least one month
- History of Guillain-Barré syndrome.
- History of any reaction or hypersensitivity likely to be exacerbated by any component of the vaccines (including egg proteins); a history of anaphylactic-type reaction to consumption of eggs; or a history of severe adverse reaction to a previous influenza vaccine.
- Hypersensitivity to latex.
- Administration of immunoglobulins and/or any blood products during the period starting 3 months before the first dose of study vaccines or planned administration during the study period.
- Pregnant or lactating female.
- Female planning to become pregnant or male planning to father a child or either planning to discontinue contraceptive precautions.
- Current smoker.
- During screening, have a positive test for opiates without a prescription.
- History of chronic alcohol consumption and/or drug abuse as deemed by the investigator to render the potential subject unable/unlikely to provide accurate safety reports.
- Have a history of convulsions or encephalomyelitis within 90 days prior to study vaccination.
- Have any diagnosis, current or past, of schizophrenia, bipolar disease, or other psychiatric diagnosis that may interfere with subject compliance or safety evaluations.
- 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.
- Blood donation or planned blood donation within 30 days prior to the study vaccination through 30 days after the last blood drawn for this study.

- Have signs or symptoms that could confound or confuse assessment of study vaccine reactogenicity.
- Any hematological[#] or biochemical[**] parameter that is out of range of normal[††], and is considered clinically significant by the investigator.

  [#]Complete blood cell count [red blood cells, white blood cells], white blood cells differential count [lymphocytes, neutrophils and eosinophils], platelet count or hemoglobin level

  [**]Creatinine, blood urea nitrogen [BUN], ALT or AST

  [††]Per the site clinical laboratory's reference ranges. All tests with out of range results must be repeated before any subject is allowed to be enrolled.
- The following hematological or biochemical laboratory results will be considered exclusionary, irrespective of assessment of clinical significance:
  - Hemoglobin (Male) < 13.0 g/dL
  - Hemoglobin (Female) < 11.7 g/dL
  - White Blood Cell count < 3,000 cells/mm^3
  - Neutrophil count < 1,500 cells/mm^3
  - Eosinophil count > 600 cells/mm^3
  - Platelet count < 130,000 cells/mm^3
  - Creatinine > 1.4 mg/dL
  - ALT > Upper limit of the normal range (ULN) [††]
  - AST > Upper limit of the normal range (ULN) [††]

  [††]Per the site clinical laboratory's reference ranges.

4.3.4. Temporary exclusion criteria for receipt of Dose 1

- Travel within 7 days of planned receipt of Dose 1 of study LAIV (or placebo) to a region with known or suspected ongoing influenza circulation (Groups 1, 2, and 3 only).
- Acute disease and/or fever[¶¶] at the time of planned receipt of Dose 1 of study vaccine.

  [¶¶]Fever for this purpose is defined as temperature ≥ 38.0°C or 100.4°F. The preferred location for measuring temperature in this study will be the oral cavity.

4.4. Treatments

4.4.1. Treatments Administered

4.4.1.1. cH8/1N1 LAIV

cH8/1N1 LAIV vaccine will be administered. Detailed information on cH8/1N1 LAIV vaccine is in the protocol, Section 5.1.

4.4.1.2. cH8/1N1 IIV

cH8/1N1 IIV vaccine will be administered. Detailed information on cH8/1N1 IIV vaccine is in the protocol, Section 5.2.

4.4.1.3. cH5/1N1 IIV

cH5/1N1 IIV vaccine will be administered. Detailed information on cH5/1N1 IIV vaccine is in the protocol, Section 5.3.

4.4.1.4. AS03

AS03 adjuvant will be administered. Detailed information on AS03 adjuvant is in the protocol, Section 5.4.

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

Randomization will be stratified by site and include a blocking factor. The original intended allocation ratio for LAIV-IIV Groups 1, 2 and 3 was 3:3:1, and the original allocation ratio for IIV-IIV Groups 4-5 was 3:2. To preserve comparability of subjects across treatment groups, subjects will be randomized to all groups under one allocation sequence. Among LAIV-IIV subjects, Group 1 is the primary interest, especially for comparison to Group 4. To guard against loss of power from possible drop-out between randomization and admission into the inpatient clinical isolation unit, Group 1 will be over-randomized by five subjects, for a final randomization scheme of 4:3:1:3:2. Allocation at each site will be 12:9:3:9:6 (total 39) at Duke Clinical Research Institute and 8:6:2:6:4 (total 26) at Cincinnati Children's Hospital Medical Center (CCHMC).

The randomization scheme was generated and maintained by the Statistical Data Coordinating Center (SDCC) at the Emmes Corporation, Rockville, MD. Randomization and assignment of treatment codes was performed following the procedures below:

The unblinded pharmacist refers to a Treatment Key Listing, provided for the trial by Emmes, to determine the treatment for the subject. The pharmacist maintains the Treatment Key Listing under locked/secured conditions and does not reveal the randomization code to any other study staff member, subject, or parent. The investigational study product prepared by the qualified unblinded research pharmacist is witnessed by another unblinded study staff member then dispensed in a syringe, labeled with subject number, and administered by an unblinded study staff member. All follow-up safety and efficacy evaluations are performed by blinded clinic staff.

1. At Enrollment Visit (Visit 01), subjects who will participate in the study will be entered into a dosing cohort in Advantage eClinical. Subjects must be randomized one at a time.
2. Advantage eClinical then associates the subject with the next treatment assignment available and presents a screen confirming the subject's successful enrollment. A Sequence Number, coded Treatment Number (to correspond to the treatment assignment), and whether the subject will be inpatient or outpatient will be displayed on the Enrollment Confirmation screen.
3. The Sequence Number and Treatment Number should be recorded on the Enrollment Log, and the investigator or study coordinator will print the Enrollment Confirmation screen and provide to the unblinded pharmacist, who will be preparing the study product for administration at Visit 03.

4. The unblinded pharmacist will refer to the Treatment Key provided for this trial to determine the treatment corresponding to the coded Treatment Number. The unblinded pharmacists will place the prepared syringe in a brown bag and hand it off to the unblinded vaccine administrator. A pharmacy log will also be provided to the unblinded pharmacist to record the essential information. The printed Advantage eClinical Confirmation of Enrollment screen should be retained in the subject's clinic record per each site's SOP.

Randomization data are kept strictly confidential, and should be accessible only to authorized persons, until the time of unblinding.

4.4.3. Blinding

This is an observer-blinded study; study subjects, study personnel who perform study assessments after vaccine administration, data entry personnel at the sites, and laboratory personnel will be masked to treatment assignment. The Emmes statistician and other designated staff will have access to the unblinded treatment assignments.

4.4.3.1. Unblinding Procedure

The site investigator may require that the blind be broken for any subject experiencing an emergency when knowledge of the subject's treatment assignment may be necessary for subsequent clinical care. Unblinding will occur through the secure interactive web response system (IWRS) to which there will be 24-hour access.

Details and documentation surrounding such unblinding will be described in the Unblinding Operational Manual. Documentation of the unblinding event (including the rationale and requestor) will be captured by the IWRS. Every effort should be made to maintain the blind. Prior to unblinding, the site Investigator is encouraged (to the extent possible, without jeopardizing the subject's health) to contact the Sponsor (or designee) to discuss the decision to break the blind. The site PI will be expected to provide a rationale for the necessity of unblinding based on the expectation that knowledge of the subject's treatment assignment will have a meaningful impact on the subject's medical care in the short term. If a subject's treatment assignment is unblinded, the subject will remain in the study and continue with protocol-defined study visits, but not receive further study vaccines. The decision to unblind will be communicated to the regulatory bodies (e.g., institutional review boards [IRBs]) as required. At the end of the study, documentation of all unblinded subjects (and the rationale for unblinding) will be incorporated into the Trial Master File.

4.4.4. Treatment Compliance

All subjects should receive 2 study doses, LAIV-IIV (or placebo) for Groups 1, 2, and 3 or IIV-IIV (or placebo) for Groups 4 and 5, at the study clinic. Each subject will be observed for at least 60 minutes after administration in case of any immediate adverse reactions. If a subject experiences an immediate adverse reaction, he/she will be treated and the event will be recorded in the eCRF.

4.4.4.1.1. For violation of the protocol

A subject will be considered as not in compliance with the requirements of the protocol and may be withdrawn if any of the following conditions apply:

- The subject egregiously violates the rules of the inpatient clinical isolation unit per the opinion of the investigator;
- The subject refuses to complete the self-observation diary;
- The subject skips entirely a scheduled visit, especially Visits 11 and 13;
- Non-compliance at a scheduled visit for planned procedures; or
- Failure to inform the investigator of any AE or SAE.

4.4.4.1.2. Loss to follow-up

To prevent loss to follow-up, subjects will be reminded by phone, email, or text message of their next study visit. In the event of a missed visit, the subject will be contacted by phone within 1 day. A subject who misses two consecutive visits and cannot be reached / located after 5 attempts will be considered lost to follow-up. Efforts to contact the subject will be documented in source documents. Any subject who fails to attend the final study visit will also be classified as lost to follow-up. There will be no replacement for subjects who are lost to follow-up.

4.5. Efficacy (Immunogenicity) and Safety Variables

The following section describes the collection of immunogenicity and safety variables. For a detailed schedule of activities, refer to Table 32 and Table 33, Appendix 1 of the protocol. For a list of the primary and secondary immunogenicity and safety variables, refer to Section 3.2 and Section 8 of this report.

4.5.1. Safety Variables

4.5.1.1. Reactogenicity Events

Solicited AEs are pre-specified local and general (systemic) adverse events that are common and known to occur or are of particular interest following administration of the study vaccine. For this trial, solicited AEs will be assessed by study staff 60 (+10) minutes after each vaccination and then by study subjects daily for 7 days (day of vaccination and subsequent 6 days). Subjects were provided a diary card for recording the presence or absence and severity of solicited AEs and were instructed to measure and record their oral body temperature every evening regardless of the occurrence of any symptoms. Should additional temperature measurements be performed at other times of day, subjects were instructed to record the highest temperature in the diary card. Solicited local AEs were tailored to the site of administration of each product. However, because influenza vaccines containing chimeric HAs have not been previously administered to humans (outside of GSK's parallel Ph1/2 trial), solicited general AEs are common across both study LAIV and IIV products.

Investigators will review diary cards with the subject to ensure the solicited AEs are appropriately documented.

4.5.1.2. Unsolicited Adverse Event

Refer to Section 3.3.1 in this report or Section 8.1.1.2 in the protocol for a more detailed definition of AE. The occurrence of an AE might come to the attention of study personnel during study visits or during interviews of a study subject who presents separately for medical care. Information to be collected on AEs includes event description, time of onset, assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event.

4.5.1.3. Serious Adverse Event (SAE)

Refer to Section 3.3.2 in this report for the definition of SAE.

4.5.2. Immunogenicity Variables

Multiple assays will be used to probe humoral immunologic responses to the study LAIV and IIVs with chimeric HAs. Serological assays for quantification of 1) anti-stalk IgG and IgA and anti-neuraminidase antibodies detected by ELISA; 2) neutralizing antibodies detected by MN assay; 3) antibodies with anti-H1 stalk activity demonstrated after passive transfer in an influenza challenge model in mice; 4) antibodies with Fc-receptor ADCC activity; and 5) antibodies with Fc-receptor mediated ADCP activity will be performed at ISMMS (laboratory of Dr. Florian Krammer) or in a laboratory designated by ISMMS (e.g., Neomed) using standardized procedures. Serologic assays for quantification of antibodies with HI activity will be performed by a designated research laboratory using standardized procedures. Additional assays for quantification of anti-stalk salivary and secretory IgA will be performed at ISMMS (laboratory of Dr. Florian Krammer) or in a laboratory designated by ISMMS (e.g., Neomed) using standardized procedures. All planned assays for characterization of humoral and mucosal immune responses are listed in Section 9.

5. SAMPLE SIZE CONSIDERATIONS

In this study in which subjects must consent to participate as either inpatient subjects or outpatient subjects for Dose 1 prior to randomization and finding out to which regimen they will be assigned (LAIV-IIV vs IIV-IIV), drop-out is possible between randomization and receipt of Dose 1, especially for subjects randomized to the major commitment of staying in the inpatient clinic. While such drop-out could occur equally in any of the three LAIV-IIV (or placebo) treatment arms, since Group 1 is the primary interest and for cost control, Group 1 will be over-randomized by 5 subjects. Admittedly, loss from Group 2 could lower the power in that group as well. The hope is that drop-outs will be minimal in both groups. Drop-out is also possible between Dose 1 and primary immunogenicity sampling at Visit 13. Table 4 in Appendix 1 summarizes these assumptions, which are applied in the subsequent sample size and power tables presented in Section 11.6.1.1 and Section 11.6.1.2 of the Protocol.

5.1. Descriptive Objectives

5.1.1. Safety

The primary objectives of the study are to assess the safety of the investigational LAIV and IIVs 28 days after each dose. Because Groups 1 and 2 will receive the same study LAIV at Dose 1, data for the period post-Dose 1 will also be pooled for these groups.

Table 4 shows the true proportions associated with a 90% probability to observe an event in 35 LAIV recipients (e.g., SAE, pIMD) post-Dose 1.

Table 4 shows the true proportions associated with a 90% probability to observe an event in 15 IIV recipients (e.g., SAE, pIMD) post-Dose 1.

Table 5 shows the 95% CI for possible numbers of AEs among all LAIV recipients post-Dose 1.

Table 5 shows the 95% CI for possible numbers of AEs post-receipt of study IIV post-Dose 1.

5.1.2. Immunogenicity

Detailed information on the possible rates of immunological response is presented in the protocol, Section 11.6.1.2.

5.2. Comparative Objectives

Secondary objectives include comparisons of the immunogenicity post-Dose two between LAIV-IIV (+ $AS03_A$) and IIV-IIV groups (Group 1 vs Group 4 and Group 2 vs Group 4) as well as the assessment of the adjuvant system, which is LAIV-IIV+ $AS03_A$ and LAIV-IIV groups (Group 1 vs Group 2). These comparisons are purely descriptive with the aim to characterize the differences in immunogenicity between groups. The ratio of GMTs and 2-sided 95% CI will be computed after fitting an ANCOVA model on the log10 transformation of ELISA/MN titers, including vaccine group as fixed effect and the pre-vaccination titer as covariate. Additional comparison on pooled LAIV-IIV and IIV-IIV groups (Group 1+Group 2 vs Group 4) will be presented if results suggest $AS03_A$ did not increase immune responses post-boost in the LAIV-IIV groups. A summary table on the power to detect fold increase in GMT ratios is presented in the protocol, Section 11.7: Table 31.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

All continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, quartiles and range (maximum and minimum). Where appropriate (e.g., immunogenicity), geometric means and corresponding 95% confidence intervals will be included.

Frequency tables will be generated for categorical variables. The number and percent of subjects (based on the population sample size with data available for analysis) of observed levels will be reported for all categorical measures. Exact 95% confidence intervals for the proportion of subjects with an event will be included.

All analyses will be based on data pooled from both sites. However, because of the multi-center nature of this study with randomization stratified by site, sub-analyses by site will also be conducted. In general, all data will be listed, sorted by treatment and subject, and when appropriate by visit number within subject.

6.2. Timing of Analyses

An interim analysis will be conducted once the full set of samples for key immunogenicity variables are collected. For details, refer to Section 6.6.

A final analysis of all data will be performed when data up to study conclusion are available and after data base lock.

6.3. Analysis Populations

6.3.1. Exposed Set (ES)

The Exposed Set (ES) will include all subjects with at least one vaccine administration documented. In the study protocol, this is also referred to as the total vaccinated cohort (TVC).

6.3.2. Safety Population

The safety population is the same as the ES. Subjects will be grouped according to the actual product received. This population will be used for all safety and reactogenicity analyses. A summary of the Safety population by study group will be prepared (Table 10, Appendix 1).

6.3.3. Per Protocol Population (PP Population)

The PP population will be adapted by time point to include all eligible subjects' data up to the time of the event which has been defined in the protocol as potentially leading to exclusion from the per protocol population and confirmed at data review prior to analyses. These events may include:

- Dose of study vaccine not received or not according to protocol procedures and to their random assignment
- Randomization code broken
- Non-compliance with the procedures and intervals defined in the protocol

- Intake of any concomitant medication/product/vaccination that may adversely affect immunology results
- Occurrence of any of the following medical conditions:
  - Any investigational or non-registered product (drug or vaccine) other than the study vaccine(s)/product(s) used during the study period
  - Immunosuppressants or other immune-modifying drugs administered chronically (i.e., more than 14 days in total) during the study period. For corticosteroids, this will mean prednisone ≥ 20 mg/day, or equivalent. For high-dose inhaled corticosteroids this will mean beclomethasone dipropionate chlorofluorocarbon ≥ 840 mcg/day, or equivalent. Topical steroids are allowed.
  - Long-acting immune-modifying drugs administered at any time during the study period (e.g., infliximab, rituximab)
  - A vaccine not foreseen by the study protocol administered during the period starting 30 days before the first dose (Visit 03) up to the blood sampling at Visit 13. In case an emergency mass vaccination for an unforeseen public health threat (e.g., a pandemic) is organized by the public health authorities, outside the routine immunization program, the time period described above can be reduced if necessary for that vaccine provided it is licensed and used according to its Prescribing Information and according to the local governmental recommendations and provided a written approval of PATH is obtained.
  - Seasonal influenza vaccine administered at any time during the study period.
  - Immunoglobulins and/or any blood products administered during the study period.
  - Drug and/or alcohol abuse.

This population will be used for all immunogenicity analyses. A summary of the PP population by study group will be prepared (Table 10, Appendix 1).

6.4. Covariates and Subgroups

As described in Section 4.4.2 Randomization, sub-analysis by site will also be conducted in addition to pooling from both sites. Viral shedding analysis will be performed on Groups 1-3 only. For the comparative analysis of immunogenicity data, GMT ratios and their 2-sided 95% CI will be computed after fitting an ANCOVA model on the $\log_{10}$ transformation of ELISA/MN titers, including vaccine group as a fixed effect and the pre-vaccination titer as a covariate.

6.5. Missing Data and Outliers

All attempts will be made to collect all data per protocol. As missing data are expected to be minimal, no imputation will be performed for missing values. Any data point that appears to be erroneous or inexplicable based on clinical judgment will be investigated as a possible outlier. If data points are identified as outliers, sensitivity analyses will be performed to examine the impact of including or excluding the outliers. Any substantive differences in these analyses will be reported.

The analysis of immunogenicity will be performed primarily on the Per-Protocol set. If 10% or more of the vaccinated subjects are eliminated from the Per-Protocol set (for a given endpoint), a second analysis will be performed on the TVC/ES. This percentage will be applied to missing data across study groups simultaneously.

6.6. Interim Analyses and Data Monitoring

6.6.1. Interim Analysis

Interim analyses will be performed when safety, reactogenicity, and immunogenicity (including at least H1 anti-stalk ELISA) data from all subjects are available up to Visit 13. A final analysis of all data will be performed when data up to study conclusion are available. This analysis will be reported in a Clinical Study Report.

The decision to pursue development will be based on the final assessment of Visit 13 data performed at the interim analysis. No statistical adjustment will be made for the interim analyses, which are intended to provide final outputs related to the different endpoints and time points in a phased manner.

At the time of the interim analysis, PATH will neither have access to the individual treatment assignments, nor to the unblinded safety report, but will be provided with aggregated immunogenicity results per group to allow strategic decisions for the future of the project.

The interim data will be presented in the following two reports:

- Blinded report: This report will contain aggregate of safety and viral shedding data without the group level information. The aggregate in this case would be summary data combining all groups and listings blinded at group level. This report will contain aggregate immunogenicity data per unblinded study group. The aggregate in this case would be summary data by group and not subject level listing.
- Unblinded report: This report will contain safety and viral shedding data per unblinded study group. The report may contain subject level listings. This report will contain aggregate immunogenicity data per unblinded study group. The aggregate in this case would be summary data by group and not subject level listing. This report will be created for IDMC, PATH will not have access to this report.

The following interim analyses will be performed by group (and also pooling Groups 1 and 2 prior to 2nd dose) when safety, reactogenicity, and immunogenicity (including at least H1 anti-stalk, anti-H2, anti-H18, and anti-H9 IgG ELISA) data from all subjects are available up to Visit 13. All analyses will be performed in the safety population, except the analyses related to immunogenicity assays, which will be performed in the per-protocol population. Solicited local and general AEs will also be summarized according to product, following the 2nd dose (combined Groups 1 and 4, and combined Groups 3 and 5).

1. Occurrence of solicited local AEs during a 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) after the first and the second dose.
2. Occurrence of solicited general AEs during a 7-day follow-up period (i.e., on the day of vaccination and 6 subsequent days) after the first and the second dose.

3. Occurrence of unsolicited AEs during a 28-day follow-up period (i.e., on the day of vaccination and 27 subsequent days) after the first and the second dose.
4. Occurrence of any hematological (red blood cell, white blood cell, and differential count, platelets count and hemoglobin level) or biochemical (ALT, AST, creatinine, BUN and BUN-to-creatinine ratio) laboratory abnormality on Visit 9, 10, 11, 12, 13.
5. Occurrence of MAEs, LC-ILIs, pIMDs, and SAEs up to Visit 13/the data cutoff date for interim analysis.
6. Percentages of subjects with vaccine virus detectable by RT-PCR (among combined nasal/ oropharyngeal swab specimens) each day and overall (at any time).
7. Percentages of subjects with recovery of viable vaccine virus in MDCK culture each day and overall (at any time).
8. Anti-H1 HA-stalk, anti-H2, anti-H18, and anti-H9 serum IgG (all assays performed by Neomed):
    - Seropositivity rates and GMTs at Day 1 and Visit 13 and Day 1 to Visit 10 (descriptive immunogenicity)
    - Percentage of subjects with a ≥ 4-fold increase in antibody titers from Day 1 to Visit 13 and Day 1 to Visit 10 (descriptive immunogenicity)
    - Percentage of subjects with a ≥ 10-fold increase in antibody titers from Day 1 to Visit 13 and Day 1 to Visit 10 (descriptive immunogenicity)
    - Mean geometric increase from Day 1 to Visit 13 and Day 1 to Visit 10 (descriptive immunogenicity)
9. Anti-H1 HA-stalk serum IgG adjusted GMT ratio of the LAIV / IIV + $AS03_A$ group (Group 1) versus the IIV + $AS03_A$ / IIV + $AS03_A$ group (Group 4), 28 days post-vaccination (i.e., at Visit 13 to evaluate the LAIV-IIV prime-boost effect).
10. Anti-H1 HA-stalk serum IgG seroresponse (≥4-fold) rate difference of the LAIV / IIV + $AS03_A$ group (Group 1) versus the IIV + $AS03_A$ / IIV + $AS03_A$ group (Group 4), 28 days post-vaccination (i.e., at Visit 13 to evaluate the LAIV-IIV prime-boost effect).
11. Anti-H1 HA-stalk serum IgG adjusted GMT ratio of the LAIV / IIV group (Group 2) versus the IIV + $AS03_A$ / IIV + $AS03_A$ group (Group 4), 28 days post-vaccination (i.e., at Visit 13 to evaluate the LAIV-IIV prime-boost effect).
12. Anti-H1 HA-stalk serum IgG seroresponse (≥4-fold) rate difference of the LAIV / IIV group (Group 2) versus the IIV + $AS03_A$ / IIV + $AS03_A$ group (Group 4), 28 days post-vaccination (i.e., at Visit 13 to evaluate the LAIV-IIV prime-boost effect).
13. Summaries of antigen and antibody-specific plasmablast frequencies measured via ELISPOT among all groups in samples recovered 7 days following each vaccine dose.

6.6.2. Data Monitoring

An IDMC will be established by PATH to monitor the study and to provide independent, non-binding advice on safety and ethics. The IDMC will be composed of independent medical experts in vaccinology and infectious diseases who will periodically review the conduct and safety of study. The IDMC will be supported by an unblinded secretary and an unblinded biostatistician, both from Emmes. The responsibilities and procedures of the IDMC are defined in the IDMC Charter. During the whole study period, there will be IDMC reviews at pre-defined time points (the frequency of these reviews may be adapted upon IDMC recommendation if deemed necessary). At least three pre-defined meeting time points will be as follows:

- The IDMC will review safety data through 28 days post-Dose 1 for all subjects prior to any subject receiving Dose 2 of study vaccine.
- The IDMC will review safety data through 28 days post-Dose 2 for all subjects.
- The IDMC will review safety data through 12 months post-Dose 2 for all subjects.
- Additionally, the IDMC may also be convened to review events meeting pause rules if deemed necessary by the PSRT. In such cases, the IDMC and PSRT may convene by teleconference to jointly review the data.

The IDMC reviews will be summarized with recommendations to the study Sponsor as to whether there are safety concerns and whether the study should continue without change, be modified, or be terminated. If at any time, a decision is made to permanently discontinue administration of study vaccinations in all subjects, the Sponsor will notify the FDA and the site PIs will notify the responsible IRBs expeditiously.

6.7. Multicenter Studies

Data will be pooled across both clinical sites. Center effects are not anticipated because the sites are using standardized procedures for vaccination and assessment of solicited and unsolicited adverse events, and the study relies on central laboratories for the assessment of immunogenicity and clinical efficacy endpoints.

Nevertheless, to evaluate systemic differences owing to factors associated with site/geographic region, descriptive sub-analyses by site will also be conducted.

6.8. Multiple Comparisons/Multiplicity

No adjustments for multiple testing are planned.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

The disposition of subjects and exposure to study vaccinations will be tabulated by site and study group in the safety population and listed for all subjects. Summary of subject disposition will include number of subjects screened/enrolled, number of subjects completed study, and discontinuation/termination reason (Table 9, Appendix 1). A CONSORT diagram of the study will also be prepared (Figure 1, Appendix 2).

7.2. Protocol Deviations

A summary of subject-specific protocol deviations will be presented by the reason for the deviation, the deviation category, and study group for all subjects (Table 6, Appendix 1). All major/subject-specific protocol deviations and non-subject-specific protocol deviations will be included as data listings (Listing 2 and Listing 3, Appendix 3). Protocol deviations will not necessarily always lead to exclusion from the Per-Protocol analysis population. Determination of exclusion will be established before breaking the blind and based on the blinded review of protocol violations and other criteria for inclusion.

8. SAFETY EVALUATION

Safety is the primary objective of this study. All analyses will be descriptive. For continuous measures: mean, standard deviation, median, range; for categorical measures: frequencies and proportions with exact 95% confidence intervals. All percentages will be presented to one decimal place. Means, medians, standard deviations and confidence intervals will be presented as integers if the absolute value is greater than or equal to 100 in magnitude, to one decimal place if greater than or equal to 10, and 2 decimal places if less than 10. In general, results will be shown for each site and for both sites combined. For safety assessments presented by time point, unscheduled assessments will be summarized as separate time points in chronological order with scheduled study visits.

All analyses will be presented by group, and in certain cases noted below, will also be presented combined by product (post Dose 1 for Groups 1 and 2, post Dose 2 for Groups 1 and 4, Groups 3 and 5).

8.1. Demographic and Other Baseline Characteristics

A summary table of continuous measures (age, height, weight) and categorical measures (gender, race, ethnicity) will be prepared (Table 12 and Table 13 Appendix 1). Demographic listing will also be prepared (Listing 4, Appendix 3).

8.1.1. Prior and Concurrent Medical Conditions

All current illnesses and past pre-existing medical conditions will be MedDRA® coded using MedDRA dictionary version 20.1 or higher. Summaries of subjects' pre-existing medical conditions will be prepared (Table 14, Appendix 1), and individual subject listings will be prepared for all pre-existing medical conditions (Listing 5, Appendix 3).

8.1.2. Prior and Concomitant Medications

Summaries of medications that were started prior to dosing and continuing at the time of dosing will be presented by WHO Drug Terms 2 and 3 (Table 86 and Table 87, Appendix 1). Individual subject listings will be prepared for all concomitant medications (Listing 18, Appendix 3). A separate summary for influenza vaccination history will also be prepared (Table 88, Appendix 1).

8.2. Measurements of Treatment Compliance

The number of doses of study product administered to subjects will be prepared as part of the subject disposition table (Table 9, Appendix 1). In addition, a listing will also be prepared (Listing 6, Appendix 3).

8.3. Adverse Events

For all summaries of adverse events regarding time intervals prior to the 2nd vaccination, data will be presented by group. For those analyses concerning specific time periods, data will also be presented combined by product (post Dose 1 for Groups 1 and 2, post Dose 2 for Groups 1 and 4, Groups 3 and 5).

8.3.1. Solicited Events and Symptoms

Local and general (systemic) solicited AEs commonly associated with intranasal or intramuscular influenza vaccination are collected within 60 minutes of vaccination, and through 7 days following any dose (day of vaccination and subsequent 6 days) and graded on a scale of 0 (normal), 1 (mild), 2 (moderate) and 3 (severe). All general and local reactions are listed below.

Local Reactions:

- Post LAIV: Nasal Congestion, Rhinorrhea
- Post IIV: Pain, Redness, Swelling

General Reactions:

- Any Dose: Abdominal Pain, Arthralgia, Cough, Diarrhea, Fatigue, Fever, Headache, Myalgia, Nausea, Shivering, Sore throat, Vomiting, Wheezing

Solicited adverse events collected within 60-minutes post-dose will be presented, as well as a combined analysis of those immediate post-dose events along with those occurring within 7 days post dose (Solicited Reactions, Appendix 1). The number and proportion of subjects reporting at least one solicited adverse event will be summarized for each solicited adverse event, any general event, any local event, and any event. The 95% CI calculated using Clopper-Pearson methodology from a binomial distribution will also be presented, and a two-sided Fisher's exact test will be used as a global test for a difference among groups, grouping by product where possible.

For each general and local event, any general event, any local event, and any solicited event, the maximum severity over 7 days after each vaccination will be summarized for the Safety population (Local Reactions and Solicited General Reactions, Appendix 1) and graphically in a bar charts (Figure 79, Figure 80, Figure 81, and Figure 82, Appendix 2). The number and percentage of subjects per study group reporting each event will be summarized by the maximum severity, separately for each vaccination by group/product and over all vaccinations by group. For each event the denominator is the number of subjects with any follow-up during the specified period.

The number of subjects reporting a solicited adverse event will be summarized for each day post vaccination for each vaccination and for all vaccinations combined both in a summary table (Table 41, Appendix 1). Solicited AEs that are ongoing after 7 days post-vaccination will be presented (Table 48, Appendix 1).

Listings of all solicited adverse events by subject will be prepared (Listing 11, Appendix 1).

8.3.2. Unsolicited Adverse Events

Unsolicited adverse events will be categorized by MedDRA® system organ class (SOC) and preferred term (PT). When calculating the incidence of adverse events (i.e., on a per subject basis), each subject will only be counted once per category and any repetition of adverse events within a subject will be ignored. Per protocol, all adverse events occurring within 28 days of a vaccination will be presented (Table 57, Table 58, and Table 59, Appendix 1 and Listing 12, Appendix 3); SAEs/pIMDs/MAEs/LC-ILIs occurring at any point will also

be presented (Table 60, Table 61, Table 62, and Table 63, Appendix 1). All events reported on the adverse event CRF will be included.

To assess safety, the number and percentage of subjects experiencing at least one AE, and the number and percentage of subjects experiencing each specific AE, categorized by body system and preferred term, will be tabulated by study group (for individual post-dose periods and for the entire study period) and product administered (for individual post-dose periods) along with their corresponding exact 95% confidence intervals. Overall summaries by study group and by product received include the number and percentage of subjects experiencing: (1) any adverse experience; (2) any Grade 2 or greater AE; (3) any AE judged related to study product; (4) any Grade 2 or greater AE judged related to study product. In addition, AEs will be summarized by grade.

A listing of all AEs by subject will be presented (Listing 12, Appendix 3).

The following summaries for unsolicited adverse events will be presented by SOC, PT, study product, and study group, and vaccination number:

- Subject level summary of severity that lead to study withdraw (Table 57, Appendix 1)
- Subject level summary of severity and relationship to study product (Table 65, Table 66, and Table 67, Appendix 1).
- Total frequency of AEs (Table 68, Table 69, and Table 70, Appendix 1).
- Subject listing of non-serious AEs of moderate or greater severity (Table 71, Appendix 1).
- Bar chart of non-serious AEs by severity and SOC (Figure 83 and Figure 84, Appendix 2).
- Bar chart of non-serious AEs by relationship to study product, severity, and by SOC (Figure 85 and Figure 86, Appendix 2).

8.4. Deaths, Serious Adverse Events and Other Significant Adverse Events

Deaths, SAEs, LC-ILIs, MAEs, and pIMDs will be presented (Table 64, Table 72, Table 73 and Table 74, Appendix 1), including Subject ID, Age (years), Event Description, Onset Date/End Date, Last Dose Received/Days Post Dose, Reason Reported as an SAE, Relationship to Treatment, Alternate Etiology if Not Related, Action Taken, Outcome, and Duration of Event (days). If more than 5 events are reported within a specific AE type, a subject level summary on that AE type will be presented (Table 60, Table 61, Table 62, and Table 63, Appendix 1).

8.5. Pregnancies

For any subjects in the Safety population who become pregnant during the study, every attempt will be made to follow these subjects through completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. Listing of pregnancies and outcomes will be presented (Listing 19, Listing 20, Listing 21, Listing 22, and Listing 23, Appendix 3).

8.6. Clinical Laboratory Evaluations

The distribution of laboratory results by time point and study group/product will be summarized (Table 77 and Table 78, Appendix 1). As with solicited AEs, these summaries will be presented both by study group, and combined within product, where possible. Descriptive statistics including mean, standard deviation, median, minimum and maximum values by time point for each laboratory parameter will be summarized separately for those normal, below the lower limit, and above the upper limit. Subjects with abnormal laboratory results (Grade 2 severity or higher) will be prepared (Table 75 and Table 76, Appendix 1). Shift tables will be prepared for each safety laboratory parameter displaying the frequency of changes from the baseline grade (Table 79 and Table 80, Appendix 1). Complete listings will also be provided, showing severity and with applicable reference ranges (Listing 13 and Listing 14, Appendix 3).

8.7. Vital Signs and Physical Evaluations

Vital sign measurements including systolic blood pressure (mmHg), diastolic blood pressure (mmHg), oral temperature (°C or °F), respiratory rate (breaths / minute) and heart rate (beats / minute) will be assessed at the screening visit and prior to each scheduled vaccination at Visit 03 and Visit 11. Vital signs will be tabulated by visit and study group, as well as by product (Table 83, Appendix 1). A full vital sign listing will be prepared in Listing 15, Appendix 3.

8.8. Concomitant Medications

Concomitant medications will be coded to the Anatomical Therapeutic Classification using the WHO Drug Dictionary. The use of prior and concomitant medications taken during the study will be recorded on the CRFs. A by-subject listing of concomitant medication use will be prepared (Listing 18, Appendix 3). The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and study group for the Safety population (Table 87, Appendix 1).

8.9. Other Safety Measures

8.9.1. Physical Examination

The complete physical examination will include an assessment of general appearance and examination of the head, eyes, ears, nose, oropharynx, neck, chest (by auscultation), lymph nodes (neck, supraclavicular, axillary, inguinal), abdomen (auscultation and palpation), skin and musculoskeletal system, and nervous system. Abnormal area/symptom will be summarized and tabulated by visit and study group (Table 84, Appendix 1). Physical exam abnormalities will be listed, including whether or not the abnormality was reported as a solicited/unsolicited AE (Listing 16, Appendix 3).

8.9.2. Viral Shedding

For Group 1, Group 2, and Group 3 (Groups 1 and 2 combined), the number and proportion of subjects reporting vaccine virus detectable by RT-PCR (among combined nasal/oropharyngeal swab specimens) and among those positive, with recovery of viable vaccine virus in MDCK culture each day and at any inpatient day (through Visit 08) will be prepared. The 95% CI calculated using Clopper-Pearson methodology from a binomial distribution will also be

prepared (Table 85, Appendix 1). A full listing on nasal/oropharyngeal shedding of vaccine virus will be prepared (Listing 17, Appendix 3).

For each time point at which MDCK Culture FFA assay results are available (that is, among those positive via RT-PCR), the following analyses will be performed for Group 1, Group 2, and Group 3 (Groups 1 and 2 combined):

- Positivity rate (among samples tested) with two-sided exact 95% CI
- Descriptive statistics on the log scale will be computed
- GMTs, with accompanying *t*-distribution-based two-sided 95% CI
- Distribution of virus titer using reverse cumulative distribution curves (RCCs).

When a result achieves the LLOQ (2.8 x 10), one-half of the LLOQ will be used for continuous summaries, where relevant. Estimates or confidence interval boundaries below the LLOQ will be replaced with "<2.8 x 10" or similar, where relevant.

9. IMMUNOGENICITY

Immunogenicity outcomes are secondary and exploratory endpoints of this study. The analysis of immunogenicity will be performed primarily on the Per-Protocol set. If 10% or more of the vaccinated subjects are eliminated from the Per-Protocol set, a second analysis will be performed on the total vaccinated cohort (TVC). Data from Groups 1 and 2 will be pooled for observations made prior to the 2nd vaccination.

In general, descriptive statistics (mean, SD, median, range) will be tabulated by study group and time-point, based on the log transformation, along with the GMT/GMC and its 95% confidence interval, where relevant. The two-sided 95% confidence interval (CI) for each GMT/GMC will be obtained using a *t*-distribution on log-transformed titers/concentrations. Additionally, the geometric mean fold-rise from baseline (MGI) and accompanying *t*-distribution-based two-sided 95% CI will be computed for relevant immunogenicity endpoints, where the fold-rise at post-baseline visit for each subject is computed as the antilog of the difference in log titer of post-baseline measurement minus baseline (except where otherwise specified). The default log basis for computation will be $\log_{10}$ although throughout, the basis for the log transformation used for analysis and presentation of titers will match the serial dilution used for the assay. Wherever CIs for the median are prescribed, they will be computed via the percentile bootstrap, with n = 10,000 replicates. Unless otherwise noted, CIs for the median will be computed on the log scale, then back-transformed. Unless otherwise noted, all CIs will be two-sided 95% CIs.

Wherever assay results are less than the lower limit of quantitation (LLOQ), one-half the LLOQ will be used for computation of means and SDs on the log scale. Any values achieving the ULOQ will use the ULOQ as the observed data point for such summaries. For percentiles and any accompanying CIs, values achieving the LLOQ or ULOQ will be presented as "<LLOQ" or ">ULOQ", with LLOQ/ULOQ replaced by the relevant numeric quantity. For all analyses involving parametric methods based on the *t*-distribution, if substantial non-normality and/or values achieving the upper/lower limit of quantitation are frequent, a corresponding nonparametric method may be substituted.

Categorical outcomes (seropositivity, seroresponse) will be summarized by frequency and proportion of subjects per group. For all categorical response variables, the proportion of subjects with a positive response will be paired with the 2-sided exact binomial (Clopper-Pearson) 95% CI.

Immunogenicity outcomes include the following (section numbers refer to the protocol where more details can be found on each assay). All values will be collected at baseline and at the visits shown. For the evaluation of humoral and mucosal immune responses, sera and saliva will be collected pre-vaccination and on Visits 10, 11, 13, 14, and 15. Sera and saliva will also be collected at Visit 16 with testing for humoral and mucosal immune responses dependent upon the outcome of analysis of primary and secondary objectives. If collected, responses from Visit 16 will be analyzed separately and will not be included in the CSR.

ELISA Assays

1. Anti-H1 HA-stalk IgG (serum), humoral response
   Protocol Section 7.3.1.1, cH6/1 stalk IgG by ELISA
   - Visit 10 (28 days post-Dose 1)
   - Visit 11 (pre-Dose 2)
   - Visit 13 (28 days post-Dose 2)
   - Visit 14 (6 months post-Dose 2)
   - Visit 15 (12 months post-Dose 2)

2. Anti-H1 HA-stalk IgA (serum), humoral response
   Protocol Section 7.3.1.2, cH6/1 stalk IgA by ELISA (serum)
   - Visit 10 (28 days post-Dose 1)
   - Visit 11 (pre-Dose 2)
   - Visit 13 (28 days post-Dose 2)
   - Visit 15 (12 months post-Dose 2).

3. Anti-H1 HA-stalk secretory IgA (saliva), mucosal response
   Protocol Section 7.3.1.3, cH6/1 stalk secretory IgA by ELISA (saliva)
   - Visit 10 (28 days post-Dose 1)
   - Visit 11 (pre-Dose 2)
   - Visit 13 (28 days post-Dose 2)
   - Visit 15 (12 months post-Dose 2).

4. Anti-H1 HA-stalk Total IgA (saliva), mucosal response
   Protocol Section 7.3.1.4, cH6/1 stalk Total IgA by ELISA (saliva)
   - Visit 10 (28 days post-Dose 1)
   - Visit 11 (pre-Dose 2)
   - Visit 13 (28 days post-Dose 2)
   - Visit 15 (12 months post-Dose 2)

5. Anti-H1 HA-stalk IgG (saliva), mucosal response
   Protocol Section 7.3.1.5, cH6/1 stalk Total IgG by ELISA (saliva)
   - Visit 10 (28 days post-Dose 1)
   - Visit 11 (pre-Dose 2)
   - Visit 13 (28 days post-Dose 2)
   - Visit 15 (12 months post-Dose 2).

6. Anti-H2 HA-full length IgG ELISA
   Protocol Section 7.3.1.6, H2 IgG ELISA
   - Visit 10 (28 days post-Dose 1)
   - Visit 11 (pre-Dose 2)
   - Visit 13 (28 days post-Dose 2)
   - Visit 15 (12 months post-Dose 2).

7. Anti-H9 HA-full length IgG ELISA
   Protocol Section 7.3.1.7, H9 IgG ELISA
   - Visit 10 (28 days post-Dose 1)
   - Visit 11 (pre-Dose 2)
   - Visit 13 (28 days post-Dose 2)
   - Visit 15 (12 months post-Dose 2).

8. Anti-H18 HA-full length IgG ELISA
   Protocol Section 7.3.1.8, H18 IgG ELISA
   - Visit 10 (28 days post-Dose 1)
   - Visit 11 (pre-Dose 2)
   - Visit 13 (28 days post-Dose 2)
   - Visit 15 (12 months post-Dose 2).

9. Anti-H3 HA-full length IgG ELISA
   Protocol Section 7.3.1.9, H3 IgG ELISA
   - Visit 10 (28 days post-Dose 1)
   - Visit 11 (pre-Dose 2)
   - Visit 13 (28 days post-Dose 2)
   - Visit 15 (12 months post-Dose 2).

10. Anti-N1 NA ELISA
    Protocol Section 7.3.1.10, N1 IgG ELISA
    - Visit 10 (28 days post-Dose 1)
    - Visit 11 (pre-Dose 2)
    - Visit 13 (28 days post-Dose 2)
    - Visit 15 (12 months post-Dose 2).

Microneutralization (MN) Assays

11. Anti-H1 HA-stalk MN assay
    Protocol Section 7.3.1.11, cH6/1N5 MN assay
    - Visit 10 (28 days post-Dose 1)
    - Visit 11 (pre-Dose 2)
    - Visit 13 (28 days post-Dose 2)
    - Visit 15 (12 months post-Dose 2).

12. Anti-heterosubtypic HA Group 1 virus MN assay (pandemic H1N1)
    Protocol Section 7.3.1.12, pH1N1 assay
    - Visit 10 (28 days post-Dose 1)
    - Visit 11 (pre-Dose 2)
    - Visit 13 (28 days post-Dose 2)
    - Visit 15 (12 months post-Dose 2).

13. Anti-heterosubtypic HA Group 1 virus MN assay (avian-swine H1N1)
    Protocol Section 7.3.1.13, asH1N1 assay
    - Visit 10 (28 days post-Dose 1)
    - Visit 11 (pre-Dose 2)
    - Visit 13 (28 days post-Dose 2)
    - Visit 15 (12 months post-Dose 2).

14. Anti-heterosubtypic HA Group 1 virus MN assay (H5N8)
    Protocol Section 7.3.1.14, H5N8 assay
    - Visit 10 (28 days post-Dose 1)
    - Visit 11 (pre-Dose 2)
    - Visit 13 (28 days post-Dose 2)
    - Visit 15 (12 months post-Dose 2).

Hemagglutination Inhibition (HI) Assays

15. HI with cH8/1N1 virus
    Protocol Section 7.3.1.19, cH8/1N1 HI
    - Visit 10 (28 days post-Dose 1)
    - Visit 11 (pre-Dose 2)
    - Visit 13 (28 days post-Dose 2)
    - Visit 15 (12 months post-Dose 2).

16. HI with cH5/1N1
    Protocol Section 7.3.1.20, cH5/1N1 HI
    - Visit 10 (28 days post-Dose 1)
    - Visit 11 (pre-Dose 2)
    - Visit 13 (28 days post-Dose 2)
    - Visit 15 (12 months post-Dose 2).

17. HI with cH6/1N5
    Section 7.3.1.21, cH6/1N5 HI
    - Visit 10 (28 days post-Dose 1)
    - Visit 11 (pre-Dose 2)
    - Visit 13 (28 days post-Dose 2)
    - Visit 15 (12 months post-Dose 2).

18. HI with pH1N1
    Protocol Section 7.3.1.22, H1N1 HI
    - Visit 10 (28 days post-Dose 1)
    - Visit 11 (pre-Dose 2)
    - Visit 13 (28 days post-Dose 2)
    - Visit 15 (12 months post-Dose 2).

19. HI with asH1N1
    Protocol Section 7.3.1.23, Avian-swine H1N1 HI
    - Visit 10 (28 days post-Dose 1)
    - Visit 11 (pre-Dose 2)
    - Visit 13 (28 days post-Dose 2)
    - Visit 15 (12 months post-Dose 2).

20. HI with H5N8
    Protocol Section 7.3.1.24, H5N8 HI
    - Visit 10 (28 days post-Dose 1)
    - Visit 11 (pre-Dose 2)
    - Visit 13 (28 days post-Dose 2)
    - Visit 15 (12 months post-Dose 2).

Other Assays

21. Activity, by antibody-dependent cell-mediated cytotoxic (ADCC)
    Protocol Section 7.3.1.15, Serum ADCC activity
    - Visit 10 (28 days post-Dose 1)
    - Visit 11 (pre-Dose 2)
    - Visit 13 (28 days post-Dose 2)
    - Visit 15 (12 months post-Dose 2).

22. Activity, antibody-dependent cellular phagocytosis (ADCP)
    Protocol Section 7.3.1.16, Phagocytic serum activity
    - Visit 10 (28 days post-Dose 1)
    - Visit 11 (pre-Dose 2)
    - Visit 13 (28 days post-Dose 2)
    - Visit 15 (12 months post-Dose 2).

9.1. ELISA, Microneutralization and HI Assays

For each study group at each time point at which assay results are available, and for each ELISA, MN, and HI assay endpoint as specified above for each sample type (humoral/mucosal), the following analyses will be performed:

- Positivity rates (seropositivity, for assays on serum samples), using the relevant assay cut-off to define positive/negative
- Descriptive statistics on the log scale
- GMTs/GMCs, with accompanying CI
- Mean geometric increase (MGI) from Day 1 to each post Dose 1 measurement, and from Visit 11 to each post Dose 2 measurement, each with accompanying CI
- Percentage of subjects with at least 4-fold increase from Day 1 to each post Dose 1 measurement, and from Visit 11 to each post Dose 2 measurement, each with accompanying CI

- Percentage of subjects with at least 10-fold increase from Day 1 to each post Dose 1 measurement, and from Visit 11 to each post Dose 2 measurement, each, with accompanying CI
- Distribution of antibody titers/concentrations using reverse cumulative distribution curves (RCCs)
- Bar charts displaying the geometric mean will be created, displaying all time points (labeled as nominal study day) and groups when possible, including overlaid *x*-jittered data points as well as error bars denoting the CI, using the appropriate log scale for the y axis
- For post-baseline time points, bar charts displaying the MGI from Day 1 will be created, displaying all time points (labeled as nominal study day) and groups where possible, including overlaid *x*-jittered data points as well as error bars denoting the CI, using the appropriate log scale for the y axis

Summary and listing for ELISA assays will be prepared in Table 15, Table 16, and Table 17, Appendix 1 and Listing 7, Appendix 3. Summary and listing of MN assays will be prepared in Table 23, Table 24, and Table 25, Appendix 1 and Listing 9, Appendix 3.

For comparative objectives involving continuous endpoints derived from these assays (see Section 3.1.2.7), adjusted GMT/GMC ratios and their 2-sided 95% CIs will be computed after fitting an ANCOVA model on the log transformation of titers/concentrations, including vaccine group as a fixed effect and the pre-vaccination log titer as a covariate. Least-squares means will be used to produce the log-differences, which will then be back-transformed for GMT ratios and corresponding CIs. For comparative objectives involving Groups 1, 2, and 4, the overall F test for the vaccine group will be presented, in addition to all pairwise comparisons between the three groups, unadjusted for multiplicity of testing. If results suggest $AS03_A$ did not significantly increase immune responses post-boost in the LAIV-IIV groups (if the CI of the adjusted GMT ratio of Group 1 to Group 2 includes 1), an additional ANCOVA model will be fitted combining Groups 1 and 2 and comparing to Group 4, with no correction for multiplicity of comparisons, and the adjusted GMT ratio and corresponding 95% CI will be computed.

For comparative objectives involving seroresponse, simple differences in response rates (percent of subjects with ≥4-fold rise from baseline) will be calculated, along with their corresponding 95% CIs, computed via the Miettinen-Nurminen score method for all pairwise differences, uncorrected for multiplicity; whether or not the confidence interval includes 0 will be the primary source of statistical inference, with two-sided Fisher p-values providing a supplementary summary of inference. The same pattern of analysis as described for continuous endpoints above will be followed for the binary endpoints. That is, all pairwise comparisons will be computed, and if the CI for the difference between Group 1 and Group 2 contains 0, the analysis will be repeated to compare the combined Groups 1 and 2 to Group 4.

Comparative objectives for ELISA will be prepared in Table 18, Table 19, Table 20, Table 21, and Table 22, Appendix 1. Comparative objectives for MN assays will be prepared in Table 26, Appendix 1.

The hemagglutination inhibition (HI) assay will be run in duplicate, for each sample; prior to analysis, a single result will be obtained by averaging the duplicate samples on the log scale. Values below the lower limit of quantitation (10) will be assigned a value of half the LLOQ (5),

to perform the averaging. For HI assays, the seroprotection rates (percentage of vaccinees with serum HI titer ≥ 1:40) and, for post-baseline samples, the seroconversion rates (percentage of vaccinees with either a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer ≥ 1:40, or a pre-vaccination HI titer ≥ 1:10 and at least a 4-fold increase in post vaccination HI titer) will be summarized as categorical variables including the numerator, denominator, percent, and corresponding two-sided 95% exact CI (Table 27, Appendix 1). Listing for HI assays will be prepared in Listing 10, Appendix 3.

The correlation between anti-H1 stalk serum IgG ELISA and anti-H1 HA-stalk MN assay results will be explored by plotting the two variables on the log scale, paneled by time point, and using different colors and symbols for study group, and annotating the plot with a summary table of Spearman correlation between the two variables calculated overall, and by group (Figure 68, Appendix 2).

9.2. Cell-Mediated Immunity Assessment

For each study group at each time point at which assay results are available, antigen- and antibody-specific cell-mediated immunity as measured by memory B-cell and plasmablast frequencies from ELISPOT assays will be summarized as number of cells per million PBMCs via descriptive statistics (Table 39 and Table 40, Appendix 1), and plots of median response over time will be created separately for each group, including error bars displaying the two-sided 95% CI, computed via the percentile bootstrap method with n = 10,000 replicates (Figure 77 and Figure 78, Appendix 2).

Bar charts for the median including overlaid dot plots and with error bars indicating the confidence interval will be created displaying the count of ASCs reactive to each antigen tested, for each antibody group. For these assays, plots for each group will appear on the same plot for each time point; antigens and antibodies will be in separate panels or separate plots, as necessary.

9.3. Antibody-Dependent Cell-mediated Cytotoxicity (ADCC) and Cellular Phagocytosis (ADCP)

For each study group at each time point, ADCC and ADCP activity, measured by the area under the curve (AUC) of luminescence per serial dilution, will be summarized as for ELISA/MN/HI assays described above, using the $\log_{10}$ transformation. Comparative techniques for ADCC activity will also match those for ELISA/MN/HI assays described above (Table 31, Appendix 1). Categorical summaries will include number and percent of subjects exhibiting a ≥4- and ≥10-fold changes, but will exclude positivity, as no such cutoff is yet described. Summary of ADCC activity will be prepared in Table 28, Table 29, and Table 30, Appendix 1. Summary of ADCP activity will be prepared in Table 32, Appendix 1.

9.4. Mouse Passive Transfer Challenge Study

Description

For serum collected on Day 1 (Visit 02/03), Visit 13, and Visit 15, serum from a subset of subjects of each vaccine group will be pooled for passive transfer via peritoneal injection to mice subsequently challenged intranasally with cH6/1N5 or H1N1pdm09-like virus. The conduct of this experiment is described in ISMMS SOP NAPS-6004 v1.0 rev 0.

Serum pools derived from serum collected on Day 1 (Visit 02/03), Visit 13, and Visit 15 from a subset of subjects from each group, with placebo groups pooled together, will be studied in the passive transfer experiment. The pooling of sera is described in SOP NAPS-6015 v1.0.

For each challenge virus, 20 mice per pooled group and timepoint will be challenged. The mice will be distributed as follows: 10 mice will be randomly assigned to the weight loss/survival experiment, 5 mice to the intranasally challenged group to be euthanized for assay of lung viral titers at Day 3 post-challenge, and the remaining 5 mice to the intranasally challenged group to be euthanized for assay of lung viral titers at Day 6 post-challenge. The weight loss/survival experiment and viral titer cohorts receive different challenge doses, and therefore will be analyzed entirely separately. All analyses will be conducted separately for each challenge antigen.

Specific Comparisons

For each component of the passive transfer study, comparisons will be drawn between post-vaccination time points and pre-vaccination, within group, unadjusted for multiplicity of comparisons. Between-group comparisons will also be conducted; wherever pairwise comparisons are requested, p-values will be unadjusted for multiplicity.

Statistical Analysis

In the following, "time point" refers to visits from the clinical trial, and post-challenge day refers to days from the administration of challenge dose to mice. For each challenge virus, for each group, and for each time point, the following endpoints will be assessed:

- Survival over 14 days post-challenge (day of death or euthanasia for weight loss > 25% from baseline body weight).
  - Survival (minimum of day of death or euthanasia for weight loss > 25%) will be described using Kaplan-Meier methods, utilizing right-censoring for mice surviving the 14-day post-challenge period, or death due to causes clearly not attributed to challenge (Table 33, Appendix 1).
  - The survival function, with symbols used to indicate censoring times, will be plotted along with corresponding pointwise 95% CIs for survival probability, computed via the log-log transformation, along with the 1st, 2nd, and 3rd quartiles of survival time, as well as their corresponding CIs. Plots will be generated in two ways: 1. Separately for each group, displaying all time points and annotated with the log-rank test for a difference among all time points (Figure 69 and Figure 73, Appendix 2), and 2. Separately for each time point, displaying all groups and annotated with the log-rank test for a difference among all groups (Figure 70 and Figure 74, Appendix 2). In both cases, separate panels may be used to present data in the same figure, where possible.

  - Survival time will be compared across time points (within group) via the log-rank test; if the global test is significant, this will be supplemented with pairwise tests with p-values unadjusted for multiplicity, when the global test is significant at level $\alpha = 0.05$ (Table 33, Appendix 1).
  - Survival time will be compared across group within time point via the log-rank test; if the global test is significant, this will be supplemented with pairwise tests with p-values unadjusted for multiplicity (Table 34, Appendix 1).

- Weight loss.
  - For each time point, weight and % weight loss for each post-challenge day will be summarized with descriptive statistics, including the number available for analysis, mean, SD, median, minimum and maximum. Mice who are excluded or died prior to the assessment time point will be removed from post-exclusion/death summaries (Table 35, Appendix 1).
  - A figure will be prepared displaying mean % weight loss from baseline (1-post-challenge weight/weight on day 0) over time point with groups overlaid, with corresponding pointwise 95% CIs computed via the percentile bootstrap method, with n=10,000 replicates. Mice who are excluded or died prior to end will not contribute to the summary at time points following the exclusion/death. The plot will be annotated with the % of mice available (not excluded/died) at each time point (Figure 71 and Figure 75, Appendix 2).
  - Maximum % weight loss (per mouse, over post-challenge day) will be compared across time points (pre-vaccination, Visit 13, and Visit 15) (Table 35, Appendix 1) [and across groups, for the comparisons defined above (
  - Table 36, Appendix 1)]. The comparisons will be conducted with survival analysis methods and will utilize Gehan's generalization of the Wilcoxon test for comparing distributions. If a mouse is euthanized or found dead prior to Day 14, its % weight loss will be considered right-censored at the last value obtained prior to euthanization. If, separately for each time point, the global test is significant, pairwise comparisons between time point and within group will be conducted, and will not be adjusted for multiplicity. Similarly, if the global test between group within time point is significant, all pairwise tests will be conducted, and will not be adjusted for multiplicity.

- Lung viral titer (plaque-forming units [pfu]/mL) (fold change [Day 1 minus post-baseline visit on the $\log_{10}$ scale, with the antilog taken afterward]).
  - Separately for the Day 3 and Day 6 post-challenge mouse cohorts, lung viral titers will be summarized as a continuous variable on the $\log_{10}$ scale and including the GMT and accompanying CI. The geometric mean fold change and its 95% CI computed via the *t* distribution will also be computed (Table 37, Appendix 1).
  - A figure will be prepared displaying the relationship of Day 3 and Day 6 lung viral titer (y axis) to time point, including the *x*-jittered data points along with a horizontal line for the GMT, including error bars for its CI, with multiple groups per plot as possible and appropriate (Figure 72 and Figure 76, Appendix 2).

- Separately for Day 3 and Day 6, time points (within group) will be compared via the Kruskal-Wallis test, with post hoc two-sided comparisons computed via the Conover-Iman method with p-values unadjusted for multiplicity, when the global test is significant at level $\alpha = 0.05$ (Table 37, Appendix 1).
- Separately for Day 3 and Day 6 cohorts, groups will be compared via all pairwise comparisons for post-vaccination time points with respect to the difference between post-vaccination mean and pre-vaccination mean. For each post-vaccination time point, change from pre-vaccination values will first be log-transformed and then fit using an ANOVA model with study group included as a fixed effect. An F-test will be derived from the ANOVA model to test for overall differences between groups. Under the assumption of mutual independence among time points and groups, *t*-tests will also be generated to evaluate pairwise group-differences in (log) change from baseline (e.g., [Group 1 Visit 13 minus Group 1 Visit 2] minus [Group 4 Visit 13 minus Group 4 Visit 3]). Two-sided p-values will be obtained from these critical values using the *t*-distribution, and these will be unadjusted for multiplicity (Table 38, Appendix 1). For values below LLOQ, half the LLOQ will be used. If a substantial amount of values below the LLOQ are observed, supplementary resampling-based or nonparametric methods may be used to conduct the comparisons.

10. REPORTING CONVENTIONS

P-values will be reported to 4 decimal places; p-values less than 0.0001 will be reported as "<0.0001". The mean, standard deviation and other statistics will be reported as integers for values greater than 100, to one decimal for values greater than 10, to two decimals for values greater than 1 and to three decimals for values less than 1. Percentages will be reported to one decimal and corresponding 95% CIs will be to two decimals.

11. TECHNICAL DETAILS

SAS version 9.3 or above will be used to generate all tables, figures and listings.

12. SUMMARY OF CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Study population definitions for the exposed set and total vaccinated cohort were conflated. In this SAP, it is clarified that the Exposed Set, Total Vaccinated Cohort, and Safety Population all have the same definition: all subjects with at least one vaccine administration documented.

Exploratory flow cytometry assays will not be conducted, and their analysis is not described herein.

There are no positivity criteria for ADCC and ADCP, so analysis of these is excluded.

Analysis of the tertiary T-cell objectives will not be produced for the clinical study report.

Descriptive summaries of MGIs from immediately prior to Dose 2 to each post Dose 2 measurement was explicitly added for immunogenicity endpoints.

13. REFERENCES

Not applicable.

APPENDIX 1. TABLES

LIST OF TABLES

A. DEMOGRAPHICS

Table 1: Dosage and Administration by Study Group

Type of contact and time point	Study group	Treatment name	Volume to be administered	Route	Site	
					Location	Laterality
Visit 03 (Day 1)	Group 1	cH8/1N1 LAIV	0.25 mL* (0.5 mL total)	IN	Nares	Bilateral
	Group 2					
	Group 3	Normal Saline	0.25 mL* (0.5 mL total)	IN	Nares	Bilateral
	Group 4	cH8/1N1 IIV + $AS03_A$-like	0.5 mL*	IM	Deltoid	Non-Dominant**
	Group 5	PBS	0.5 mL	IM	Deltoid	Non-Dominant**
Visit 11	Group 1	cH5/1N1 IIV + $AS03_A$-like	0.5 mL*	IM	Deltoid	Non-Dominant**
	Group 2	cH5/1N1 IIV	0.5 mL*	IM	Deltoid	Non-Dominant**
	Group 3	PBS	0.5 mL	IM	Deltoid	Non-Dominant**
	Group 4	cH5/1N1 IIV + $AS03_A$-like	0.5 mL*	IM	Deltoid	Non-Dominant**
	Group 5	PBS	0.5 mL	IM	Deltoid	Non-Dominant**

IN = Intranasal; IM = Intramuscular.

* After reconstitution

** The non-dominant arm is the preferred arm of injection. In case it is not possible to administer the vaccine in the non-dominant arm, an injection in the dominant arm may be performed.

Table 2: Intervals Between Study Visits

Interval	Optimal Length of Interval	Allowed Interval
Visit 00 to Visit 03	7-56	2*-56
Visit 03 → Visit 05	2 days	2 days
Visit 03 → Visit 09	7 days	7-10 days
Visit 03 → Visit 10	28 days	28-38 days
Visit 03 → Visit 11	84 days	84-94 days
Visit 11 → Visit 12	7 days	7-10 days
Visit 11 → Visit 13	28 days	28-38 days**
Visit 11 → Visit 14	168 days	168-196 days**
Visit 11 → Visit 15	336 days	336-364 days**
Visit 15 → Visit 16	504 days	504-532 days**

* Subjects should be screened no later than 2 days prior to Day 1 to allow time to complete screening.

** Subjects may not be eligible for inclusion in the Per-Protocol set for post-booster immunogenicity analysis for the specified interval if blood samples are collected outside this interval.

Table 3: Assumed losses of evaluable subjects from randomization until immunogenicity analyses at Day 113

Study Arm	Planned sample size per Group	Number of subjects assumed lost between randomization and receipt of Dose 1	Evaluable subjects for safety analyses post-Dose 1	Number of subjects assumed lost between Dose 1 and primary immunogenicity readouts at Visit 13	Evaluable subjects for primary immunogenicity analyses at Visit 13
Group 1	20	3	17	1	16
Group 2	15	2	13	1	12
Group 3	5	1	4	1	3
Group 4	15	0	15	1	14
Group 5	10	0	10	1	9

Table 4 True proportions associated with a 90% probability to observe a certain number of adverse events pooled LAIV groups (35 subjects)/within an IIV group (15 subjects)

LAIV		IIV	
True proportion	Number of adverse events observed with > 90% probability	True proportion	Number of adverse events observed with > 90% probability
0.074	> 0	0.142	> 0
0.124	> 1	0.236	> 1
0.168	> 2	0.317	> 2
0.209	> 3	0.393	> 3

Table 5: 2-sided 95% exact confidence intervals for the true adverse event rate at different possible observed adverse event rates among LAIV (35 subjects)/ IIV (15 subjects)

LAIV				IIV		
Observed number of adverse events	Observed adverse event proportion	95% Exact Confidence Interval		Observed adverse event proportion	95% Exact Confidence Interval	
		Lower Limit	Upper Limit		Lower Limit	Upper Limit
0	0.000	0.000	0.116	0.000	0.000	0.218
1	0.033	0.001	0.172	0.067	0.002	0.320
2	0.067	0.008	0.221	0.133	0.017	0.405
3	0.100	0.021	0.265	0.200	0.043	0.481
4	0.133	0.038	0.307	0.267	0.078	0.551
5	0.167	0.056	0.347	0.333	0.118	0.616
10	0.333	0.173	0.528	0.667	0.384	0.882
15	0.500	0.313	0.687	-	-	-
20	0.667	0.472	0.827	-	-	-

Table 6: Distribution of Protocol Deviations by Category, Type, and Study Group

Category	Deviation Type		Group 1 (N=X)		Group 2 (N=X)		Group 3 (N=X)		Group 4 (N=X)		Group 5 (N=X)	
			n	%	n	%	n	%	n	%	n	%
Eligibility/enrollment	Any type	Any										
		Minor										
		Major										
	Did not meet inclusion criterion	Any										
		Minor										
		Major										
	Met exclusion criterion	Any										
		Minor										
		Major										
	ICF not signed prior to study procedures	Any										
		Minor										
		Major										
	Other	Any										
		Minor										
		Major										
Treatment administration schedule	Any type	Any										
		Minor										
		Major										
	Out of window visit	Any										
		Minor										
		Major										
	Missed visit/visit not conducted	Any										
		Minor										
		Major										
	Missed treatment administration	Any										
		Minor										
		Major										
	Delayed treatment administration	Any										
		Minor										
		Major										
	Other	Any										
		Minor										
		Major										
Continue for rest of deviation category	Continue for rest of deviation type	Any										
		Minor										
		Major										
N= Number of subjects Enrolled												

Table 7: Solicited Adverse Events Grading Scale

Refer to Protocol, Section 8.3.1, Table 21

Table 8: Laboratory Adverse Event Grading Scale

Refer to Protocol, Appendix 2

Table 9: Subject Disposition by Study Group

	Pooled					CCHMC					DCRI				
Subject Disposition	**Group 1 (N=X)**	**Group 2 (N=X)**	**Group 3 (N=X)**	**Group 4 (N=X)**	**Group 5 (N=X)**	**Group 1 (N=X)**	**Group 2 (N=X)**	**Group 3 (N=X)**	**Group 4 (N=X)**	**Group 5 (N=X)**	**Group 1 (N=X)**	**Group 2 (N=X)**	**Group 3 (N=X)**	**Group 4 (N=X)**	**Group 5 (N=X)**
	n	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**
Screened															
Enrolled															
Received Treatment															
Received All Scheduled Treatments															
Completed Final Blood Draw [include appropriate endpoint milestones]															
Completed Follow-up (Study Day XXX)															
Completed Per Protocol															
Early Termination															
Any															
SAE															
AE															
Continue for rest of reasons…															
Discontinuation of Treatment															
Any															
AE															
Lost to follow-up															
Continue for rest of reasons…															

Table 10: Analysis Populations by Study Group

Analysis Populations	Reason Subjects Excluded	Group 1 (N=X)		Group 2 (N=X)		Group 3 (N=X)		Group 4 (N=X)		Group 5 (N=X)	
		n	%	n	%	%	n	%	n	%	n
Per Protocol Population	Not Excluded	x	xx	x	xx	x	xx	x	xx	x	xx
	[Reason 1]										
	[Reason 2]										
	[Reason 3]										
	[Reason 4]										
Safety Population	Not Excluded										
	[Reason 1]										
	[Reason 2]										
N= Number of subjects Enrolled											

Table 11: Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x	100
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

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

Table 12: Summary of Categorical Demographics and Baseline Characteristics by Study Group, All Enrolled Subjects

Variable	Characteristic/ Statistics	Group 1 (N=X) n (%)	Group 2 (N=X) n (%)	Group 3 (N=X) n (%)	Group 4 (N=X) n (%)	Group 5 (N=X) n (%)
Sex	Male					
	Female					
Ethnicity	Not Hispanic or Latino					
	Hispanic or Latino					
	Not Reported					
	Unknown					
Race	American Indian or Alaska Native					
	Asian					
	Native Hawaiian or Other Pacific Islander					
	Black or African American					
	White					
	Multi-Racial					
	Unknown					
Age	Mean (SD)					
	Median					
	Min/Max					
Weight	Mean (SD)					
	Median					
	Min/Max					
Height	Mean (SD)					
	Median					
	Min/Max					

Table 13: Summary of Categorical Demographics and Baseline Characteristics by Study Group and Site, All Enrolled Subjects

Similar to table above but with by site summary

Table 14: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA® System Organ Class and Study Group

	Group 1 (N=X)		Group 2 (N=X)		Group 3 (N=X)		Group 4 (N=X)		Group 5 (N=X)	
MedDRA System Organ Class	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Any SOC	x	xx	x	xx	x	xx	x	xx	x	xx
[SOC 1]										
[SOC 2]										
N= Number of Subjects Enrolled n = Number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.										

B. IMMUNOGENICITY

a. ELISA Assay

Table 15: Summary of ELISA Assay by Antigen, Antibody, Study Day, Study Group, and Priming Dose, Per Protocol Population

Sample Type	Antigen/ Antibody	Visit		Group 1 (N = X)	Group 2 (N = X)	Group 1+ Group 2 (N = X)	Group 3 (N = X)	Group 4 (N = X)	Group 5 (N = X)
Serum	Anti-H1 HA-stalk IgA	02/03	**Number of Observation**	n					
			Mean (SD) log Titer	x (x.xx)					
			Median	x					
			Seropositive	n (%)					
			Exact 95% CI	(xx,xx)					
			GMT	x					
			GMT 95% CI	(xx,xx)					
		10	**Number of Observation**						
			Mean (SD) log Titer						
			Median						
			Seropositive						
			Exact 95% CI						
			GMT						
			GMT 95% CI						
			MGI						
			MGI 95% CI						
			≥4-Fold Increase						
			≥4-Fold Increase 95% CI						
			≥10-Fold Increase						
			≥10-Fold Increase 95% CI						
		11	**Number of Observation**						
			Mean (SD) log Titer						
			Median						
			Seropositive						
			Exact 95% CI						
			GMT						

Sample Type	Antigen/ Antibody	Visit		Group 1 (N = X)	Group 2 (N = X)	Group 1+ Group 2 (N = X)	Group 3 (N = X)	Group 4 (N = X)	Group 5 (N = X)
			GMT 95% CI						
			MGI						
			MGI 95% CI						
			≥4-Fold Increase						
			≥4-Fold Increase 95% CI						
			≥10-Fold Increase						
			≥10-Fold Increase 95% CI						
		13	**Number of Observation**						
			Mean (SD) log Titer						
			Median						
			Seropositive						
			Exact 95% CI						
			GMT						
			GMT 95% CI						
			MGI (Day 1)						
			MGI 95% CI (Day 1)						
			MGI (Visit 11)						
			MGI 95% CI (Visit 11)						
			≥4-Fold Increase						
			≥4-Fold Increase 95% CI						
			≥10-Fold Increase						
			≥10-Fold Increase 95% CI						
		15	**Number of Observation**						
			Mean (SD) log Titer						
			Median						
			Seropositive						
			Exact 95% CI						
			GMT						
			GMT 95% CI						
			MGI (Day 1)						
			MGI 95% CI (Day 1)						

Sample Type	Antigen/ Antibody	Visit		Group 1 (N = X)	Group 2 (N = X)	Group 1+ Group 2 (N = X)	Group 3 (N = X)	Group 4 (N = X)	Group 5 (N = X)
			MGI (Visit 11)						
			MGI 95% CI (Visit 11)						
			≥4-Fold Increase						
			≥4-Fold Increase 95% CI						
			≥10-Fold Increase						
			≥10-Fold Increase 95% CI						
Serum	Anti-H1 HA-stalk IgG	…	**…**						
Serum	Anti-H2 HA-Full Length IgG								
Serum	Anti-H9 HA-Full Length IgG								
Serum	Anti-H18 HA-Full Length IgG								
Serum	Anti-H3 HA-Full Length IgG								
Serum	Anti-N1 NA ELISA								
Saliva	Anti-H1 HA-stalk Secretory IgA								
	Anti-H1 HA-stalk Total IgA								
	Anti-H1 HA-stalk IgG								

N= Number of Subjects in the Per-Protocol Population
GMT=Geometric Mean Titer
MGI=Geometric Mean Fold-Rise

Table 16: Summary of ELISA Assay by Antigen, Antibody, Study Day, Study Group, and Priming Dose, Per Protocol Population- CCHMC

Similar to Summary of ELISA assay but with sample type/antigen/antibody:
Serum:
Anti-H1 HA-stalk IgG
Anti-H2 HA-Full Length IgG ELISA
Anti-H9 HA-Full Length IgG ELISA
Anti-H18 HA-Full Length IgG ELISA
Saliva:
Anti-H1 HA-stalk Secretory IgA
Anti-H1 HA-stalk Total IgA
Anti-H1 HA-stalk IgG

Table 17: Summary of ELISA Assay by Antigen, Antibody, Study Day, Study Group, and Priming Dose, Per Protocol Population- DCRI

Similar to Summary of ELISA assay but with sample type/antigen/antibody:
Serum:
Anti-H1 HA-stalk IgG
Anti-H2 HA-Full Length IgG ELISA
Anti-H9 HA-Full Length IgG ELISA
Anti-H18 HA-Full Length IgG ELISA
Saliva:
Anti-H1 HA-stalk Secretory IgA
Anti-H1 HA-stalk Total IgA
Anti-H1 HA-stalk IgG

Table 18: Comparison of Anti-H1 HA-stalk IgA (Serum) Humoral Response: Adjusted GMT ratio and Seroresponse (≥4-fold) Rate, 28 Days Post-Boost Dose, Per Protocol Population

Visit			Group 1 vs Group 2	Group 1 vs Group 4	Group 2 vs Group 4	Group 1+ Group 2 vs Group 4[3]
13	Adjusted GMT Ratio[1]	Estimate				
		95% CI				
		P-value				
	Seroresponse Rate	Difference				
		95% CI				
		P-value[2]				

[1] Pairwise comparison based on Least Squares Means, unadjusted for multiplicity
[2] Fisher Exact 2-tailed test, unadjusted for multiplicity
[3] Additional test provided per outcome if Group 1 vs Group 2 is not significant
Overall F-test on the adjusted GMT ratio: p-value = x.xxxx

Table 19: Comparison of Anti-H1 HA-stalk IgG (serum) Humoral Response: Adjusted GMT ratio and Seroresponse (≥4-fold) Rate, 28 Days Post-Boost Dose, Per Protocol Population

Similar to Comparison of Anti-H1 HA-stalk total IgA (serum) Humoral Response

Table 20: Comparison of Anti-H1 HA-stalk Secretory IgA (Saliva), Mucosal Response: Adjusted GMT Ratio and Seroresponse (≥4-fold) Rate, 28 Days post-Boost Dose, Per Protocol Population

Similar to Comparison of Anti-H1 HA-stalk total IgA (serum) Humoral Response

Table 21: Comparison of Anti-H1 HA-stalk Total IgA (saliva), Mucosal Response: Adjusted GMT Ratio and Seroresponse (≥4-fold) Rate, 28 Days Post-Boost Dose, Per Protocol Population

Similar to Comparison of Anti-H1 HA-stalk total IgA (serum) Humoral Response

Table 22: Comparison of Anti-H1 HA-stalk IgG (saliva), Mucosal Response: Adjusted GMT ratio and Seroresponse (≥4-fold) rate, 28 days post-Boost Dose, Per Protocol Population

Similar to Comparison of Anti-H1 HA-stalk total IgA (serum) Humoral Response

b. MN Assay

Table 23: Summary of MN Assay by Virus Strain, Study Day, Study Group, and Priming Dose, Per Protocol Population

Similar to Summary of ELISA assay but with Virus Strain:
Anti-H1 HA-stalk MN assay
Anti-heterosubtypic HA Group 1 Virus (H5N8)
Anti-heterosubtypic HA Group 1 Virus MN Assay (Pandemic H1N1)
Anti-heterosubtypic HA Group 1 Virus MN Assay (Avian-swine H1N1)

Table 24: Summary of MN Assay by Virus Strain, Study Day, Study Group, and Priming Dose, Per Protocol Population-CCHMC

Similar to Summary of ELISA assay but with Virus Strain:
Anti-H1 HA-stalk MN assay

Table 25: Summary of MN Assay by Virus Strain, Study Day, Study Group, and Priming Dose, Per Protocol Population-DCRI

Similar to Summary of ELISA assay but with Virus Strain:
Anti-H1 HA-stalk MN assay

Table 26: Comparison of Anti-H1 HA-stalk MN Assay: Adjusted GMT Ratio and Seroresponse (≥4-Fold) Rate, 28 Days Post-Boost Dose, Per Protocol Population

Similar to Comparison of Anti-H1 HA-stalk total IgA (serum) Humoral Response

c. HI Assay

Table 27: Summary of HI Assay by Virus Strain, Study Day, Study Group, and Priming Dose, Per Protocol Population

Virus Strain	Visit		Group 1 (N = X)	Group 2 (N = X)	Group 1+ Group 2 (N = X)	Group 3 (N = X)	Group 4 (N = X)	Group 5 (N = X)
cH8/1N1 Virus	02/03	**Number of Observation**	n					
		Mean (SD) log Titer	x (x.xx)					
		Seropositive	n (%)					
		Exact 95% CI	(xx,xx)					
		Seroprotection Rate	n (%)					
		Seroprotection 95% CI	(xx,xx)					
		GMT	x					
		GMT 95% CI	(xx,xx)					
	10	**Number of Observation**						
		Mean (SD) log Titer						
		Seropositive						
		Exact 95% CI						
		Seroconversion Rate						
		Seroconversion 95% CI						
		Seroprotection Rate						
		Seroprotection 95% CI						
		GMT						
		GMT 95% CI						
		MGI						
		MGI 95% CI						
		≥4-Fold Increase						
		≥4-Fold Increase 95% CI						
		≥10-Fold Increase						
		≥10-Fold Increase 95% CI						
		Continue for rest of visits						
cH5/1N1 Virus	…	…						
cH6/1N5 Virus								
H1N1								

Virus Strain	Visit		Group 1 (N = X)	Group 2 (N = X)	Group 1+ Group 2 (N = X)	Group 3 (N = X)	Group 4 (N = X)	Group 5 (N = X)
Avian Swine H1N1								
H5N8								

N= Number of Subjects in the Per-Protocol Population
GMT=Geometric Mean Titer
MGI=Geometric Mean Fold-Rise
Seroprotection Rate=Percentage of vaccinees with serum HI titer ≥ 1:40
Seroconversion Rates = Percentage of vaccinees with a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer ≥ 1:40, or a pre-vaccination HI titer ≥ 1:10 and at least a 4-fold increase in post vaccination HI titer

d. Activity, by antibody-dependent cell-mediated cytotoxic (ADCC)

Table 28: Summary of Serum ADCC Activity by Study Day, Study Group, and Priming Dose, Per Protocol Population

Similar to Summary of Anti-H1 HA-stalk total IgA (serum) Humoral Response

Table 29: Summary of Serum ADCC Activity by Study Day, Study Group, and Priming Dose, Per Protocol Population-CCHMC

Similar to Summary of Anti-H1 HA-stalk total IgA (serum) Humoral Response

Table 30: Summary of Serum ADCC Activity by Study Day, Study Group, and Priming Dose, Per Protocol Population-DCRI

Similar to Summary of Anti-H1 HA-stalk total IgA (serum) Humoral Response

Table 31: Comparison of Serum ADCC Activity: Adjusted Geometric Mean AUC Ratio, 28 Days Post-Boost Dose, Per Protocol Population

Similar to Comparison of Anti-H1 HA-stalk total IgA (serum) Humoral Response

e. Activity, antibody-dependent cellular phagocytosis (ADCP)

Table 32: Summary of Serum ADCP Activity by Study Day, Study Group, and Priming Dose, Per Protocol Population

Similar to Summary of Anti-H1 HA-stalk total IgA (serum) Humoral Response

f. Passive Transfer to Mice

Table 33: Kaplan-Meier Survival Summary and Comparison by Challenge, Study Group, and Time Point

	Post-Challenge		Group 1 (N = X)			Group 2 (N = X)			Group 4 (N = X)			Placebo (N = X)		
Challenge	**Survival Time (Day)**	**Parameter**	**Visit 02**	**Visit 13**	**Visit 15**	**Visit 02**	**Visit 13**	**Visit 15**	**Visit 03**	**Visit 13**	**Visit 15**	**Visit 02/03**	**Visit 13**	**Visit 15**
cH6/1N5	**0**	**n**												
		No. of Living (Death)												
		Prob. Survival (Death)												
	1	**n**												
		No. of Living (Death)												
		Prob. Survival (Death)												
	2	**n**												
		No. of Living (Death)												
		Prob. Survival (Death)												
	3	…												
	4	**…**												
	5	**…**												
	6	**…**												
	7	…												
	8	…												
	9	…												
	10	…												
	11	…												
	12	…												
	13	…												
	14	…												
		Pairwise Comparison[1] Reference = Visit 02		0 xxx	0.xxx		0 xxx	0 xxx		0 xxx	0 xxx		0 xxx	0 xxx
		Reference =Visit 13			0.xxx			0 xxx			0 xxx			0 xxx
		Global Comparison[2]		0 xxx			0 xxx			0.xxx			0.xxx	
H1N1	**…**	…												

N= Number of mice that received serum
n= Number of mice with observation
[1] Pairwise comparison unadjusted for multiplicity will be performed if global comparison is significant at 0.05
[2] Global comparison based on log-rank test

Table 34: Comparison of Survival Time Across Group by Challenge

		Global Comparison[1]	Pairwise Comparison[2]					
Challenge	**Time Point**	**All Groups**	**Group 1 vs Group 2**	**Group 1 vs Group 4**	**Group 2 vs Group 4**	**Group 1 vs Placebo**	**Group 2 vs Placebo**	**Group 4 vs Placebo**
cH6/1N5	**Visit 02/03**	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx
	Visit 13							
	Visit 15							
H1N1	**…**							

[1] Global comparison based on log-rank test
[2] Pairwise comparison unadjusted for multiplicity will be performed if global comparison is significant at 0.05

Table 35: Summary of Weight Change from Baseline and Percent of Initial Body Weight by Challenge, Study Group, and Time Point

Challenge	Post-Challenge (Day)	Parameter	Group 1 (N = X)			Group 2 (N = X)			Group 4 (N = X)			Placebo (N = X)		
			Visit 02	Visit 13	Visit 15	Visit 02	Visit 13	Visit 15	Visit 03	Visit 13	Visit 15	Visit 02/03	Visit 13	Visit 15
cH6/1N5	**0**	**n**												
		Mean (SD)												
		Median												
		Range												
	1	**n**												
		Mean (SD)												
		Median												
		Range												
		Mean % of initial Weight												
	2	**n**												
		Mean (SD)												
		Median												
		Range												
		Mean % of initial Weight												
	3													
	4													
	5													
	6													
	7	…												
	8	…												
	9	…												
	10	…												
	11	…												
	12	…												
	13	…												
	14	…												
		Pairwise Comparison[1] Reference = Visit 02/03		0.xxx	0 xxx		0 xxx	0 xxx		0 xxx	0 xxx		0 xxx	0 xxx

Challenge	Post-Challenge (Day)	Parameter	Group 1 (N = X)			Group 2 (N = X)			Group 4 (N = X)			Placebo (N = X)		
			Visit 02	Visit 13	Visit 15	Visit 02	Visit 13	Visit 15	Visit 03	Visit 13	Visit 15	Visit 02/03	Visit 13	Visit 15
		Reference = Visit 13			0 xxx			0 xxx			0 xxx			0 xxx
		Global Comparison[2]	0 xxx			0 xxx			0 xxx			0.xxx		
H1N1	**…**	…												

N= Number of mice that received serum

n= Number of mice with observation

[1] Pairwise comparison unadjusted for multiplicity will be performed if global comparison is significant at 0.05

[2] Global comparison will be performed based on Gehan's generalization of the Wilcoxon test

Table 36: Comparison of Maximum Percent Weight Loss Across Group by Challenge

Similar to Table on Comparison of Survival Time but will use Gehan's generalization of the Wilcoxon test for global group comparison within time point and pairwise comparison across group unadjusted for multiplicity if global comparison is significant at 0.05

Table 37: Summary of Lung Virus Titer by Challenge, Cohort, Study Group, and Time Point

				Group 1 (N = X)			Group 2 (N = X)			Group 4 (N = X)			Placebo (N = X)		
Challenge	**Cohort**	**Comparison**	**Parameter**	**Visit 02**	**Visit 13**	**Visit 15**	**Visit 02**	**Visit 13**	**Visit 15**	**Visit 03**	**Visit 13**	**Visit 15**	**Visit 02/03**	**Visit 13**	**Visit 15**
cH6/1N5	**Day 3**		n												
			Mean (SD) log Titer												
			GMT												
			95% CI for GMT												
			GMFR												
			95% CI for GMFR												
		Pairwise Comparisons[1]	Reference = Visit 02/03		0 xxxx	0 xxxx		0 xxxx	0 xxxx		0 xxxx	0 xxxx		0.xxxx	0 xxxx
			Reference = Visit 13			0 xxxx			0 xxxx			0 xxxx			0 xxxx
		Global Comparison[2]	P-value		0 xxxx			0 xxxx			0 xxxx			0 xxxx	
	Day 6	**…**	…												
H1N1	**Day 3**	**…**	…												
	Day 6	**…**	…												

N= Number of mice that received serum
n= Number of mice with observation
[1] Pairwise comparison unadjusted for multiplicity will be performed if global comparison is significant at 0.05
[2] Global comparison will be performed based on Kruskal-Wallis Test

Table 38: Comparison of Lung Viral Titer Across Group by Challenge and Cohort

Cohort	Challenge	Pre- to Post-Vaccination Comparison	Parameter	Group 1 vs Group 2	Group 1 vs Group 4	Group 2 vs Group 4	Group 1 vs Placebo	Group 2 vs Placebo	Group 4 vs Placebo
Day 3	**cH6/1N5**	**Visit 02/03 to Visit 13**	Mean Difference[1]						
			95% Confidence Interval[2]						
			P-value (Pairwise)[2]						
			P-value (Global)[3]						
		Visit 02/03 to Visit 15	Mean Difference[1]						
			95% Confidence Interval[2]						
			P-value (Pairwise)[2]						
			P-value (Global)[3]						
	H1N1	**…**	…						
Day 6	**cH6/1N5**	**…**	…						
	H1N1	**…**	…						

[1] In change from pre-vaccination log-titer
[2] t-test and confidence interval
[3] Overall F-test across groups

g. Cell-Mediated Immunity Assessment

Table 39: Summary of Memory B-Cells by Study Day, Study Group, and Priming Dose, Per Protocol Population

Visit		Group 1 (N = X)	Group 2 (N = X)	Group 1+ Group 2 (N = X)	Group 3 (N = X)	Group 4 (N = X)	Group 5 (N = X)
cH6/1 HA IgG							
02/03	**Number of Observations**	n					
	Mean (SD)	x (x.xx)					
	Median	xx					
	95% CI of the Median	(xx.x, xx x)					
10	**Number of Observations**						
	Mean (SD)						
	Median						
	95% CI of the Median						
11	**Number of Observations**						
	Mean (SD)						
	Median						
	95% CI of the Median						
13	**Number of Observations**						
	Mean (SD)						
	Median						
	95% CI of the Median						
15	**Number of Observations**						
	Mean (SD)						
	Median						
	95% CI of the Median						
cH6/1 HA IgA							
LAIV Virus IgG + IgA							
pH1N1 Virus IgG + IgA							
Continue with rest of assays							
N= Number of Subjects in the Per-Protocol Population Units are number of cells per 10^6 PBMC							

Table 40: Summary of Plasmablasts by Study Day, Study Group, and Priming Dose, Per Protocol Population

Similar to Table on Summary of Memory B-Cells

C. SAFETY

a. Solicited Reactions

Table 41: Summary of Vaccination Reactions Within 7 Days Following Any Vaccination by Study Group- Safety Population

		Group 1 (N = X)		Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)		Fisher's Exact Test
	Time Point	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	P-Value
Local Reactions												
Any	60 Min											
	7 Days											
Nasal congestion	60 Min											
	7 Days											
Continue for rest of reactions…	60 Min											
	7 Days											
Systemic Reactions												
Any	60 Min											
	7 Days											
Fever	60 Min											
	7 Days											
Continue for rest of reactions…	60 Min											
	7 Days											

N= Number of Subjects in the safety population
CI= Exact Confidence Interval
Fisher's Exact Test on Group 1 vs Group 2 vs Group 3 vs Group 4 vs Group 5
Events within 7 days after vaccination include events within 60 minutes

Table 42: Summary of Vaccination Reactions Within 7 Days Following Priming Dose by Study Group and Study Product - Safety Population

		Group 1 (N = X)		Group 2 (N = X)		Group 1 + Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)		Fisher's Exact Test
	Time Point	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	P-Value
Local Reactions														
Any	60 Min													
	7 Days													
Nasal congestion	60 Min													
	7 Days													
Rhinorrhea	60 Min													
	7 Days													
Pain	60 Min													
	7 Days													
Redness	60 Min													
	7 Days													
Swelling	60 Min													
	7 Days													
Systemic Reactions														
Any	60 Min													
	7 Days													
Fever	60 Min													
	7 Days													
Shivering	60 Min													
	7 Days													
Fatigue	60 Min													
	7 Days													
Headache	60 Min													
	7 Days													
Myalgia	60 Min													
	7 Days													
Arthralgia	60 Min													
	7 Days													

		Group 1 (N = X)		Group 2 (N = X)		Group 1 + Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)		Fisher's Exact Test
	Time Point	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**P-Value**
Nausea	60 Min													
	7 Days													
Vomiting	60 Min													
	7 Days													
Abdominal Pain	60 Min													
	7 Days													
Diarrhea	60 Min													
	7 Days													
Sore throat	60 Min													
	7 Days													
Cough	60 Min													
	7 Days													
Wheezing	60 Min													
	7 Days													

N= Number of Subjects in the safety population that received priming dose
CI= Exact Confidence Interval
Fisher's Exact Test on Group 3 vs Group 4 vs Group 5 vs Group 1 + Group 2
Events within 7 days after vaccination include events within 60 min

Table 43: Summary of Vaccination Reactions Within 7 Days Following Priming Dose by Study Group and Study Product-Safety Population-CCHMC

Similar to table above

Table 44: Summary of Vaccination Reactions Within 7 Days Following Priming Dose by Study Group and Study Product-Safety Population-DCRI

Similar to table above

Table 45: Summary of Vaccination Reactions Within 7 Days Following Boost Dose by Study Group and Study Product-Safety Population

		Group 1 (N = X)		Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)		Group 1+Group 4 (N = X)		Group 3+Group 5 (N = X)		Fisher's Exact Test
	Time Point	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**P-Value**
Local Reactions																
Any	60 Min															
	7 Days															
Pain	60 Min															
	7 Days															
Redness	60 Min															
	7 Days															
Swelling	60 Min															
	7 Days															
Systemic Reactions																
Any	60 Min															
	7 Days															
Fever	60 Min															
	7 Days															
Shivering	60 Min															
	7 Days															
Fatigue	60 Min															
	7 Days															
Headache	60 Min															
	7 Days															
Myalgia	60 Min															
	7 Days															
Arthralgia	60 Min															
	7 Days															
Nausea	60 Min															
	7 Days															
Vomiting	60 Min															
	7 Days															
	60 Min															

		Group 1 (N = X)		Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)		Group 1+Group 4 (N = X)		Group 3+Group 5 (N = X)		Fisher's Exact Test
	Time Point	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**P-Value**
Abdominal Pain	7 Days															
Diarrhea	60 Min															
	7 Days															
Sore throat	60 Min															
	7 Days															
Cough	60 Min															
	7 Days															
Wheezing	60 Min															
	7 Days															

N= Number of Subjects in the safety population that received boost dose
CI= Exact Confidence Interval
Fisher's Exact Test on Group 2 vs Group 1 + Group 4 vs Group 3 + Group 5
Events within 7 days after vaccination include events within 60 min

Table 46: Summary of Vaccination Reactions Within 7 Days Following Boost Dose by Study Group and Study Product-Safety Population-CCHMC

Similar to Table above

Table 47: Summary of Vaccination Reactions Within 7 Days Following Boost Dose by Study Group and Study Product-Safety Population-DCRI

Similar to Table above

Table 48: Listing of Solicited Adverse Events Ongoing at 7 Days Following Any Vaccination, by Site, Study Group and Vaccination Number.

							Start			Stop			
Subject ID	**Study Group**	**Site**	**Vaccination Number**	**Vaccination Date**	**Reaction Type**	**Reaction**	**Date**	**Day**	**Severity**	**Date**	**Day**	**Severity**	**Max. Severity**
000001				DDMMYYYY			DDMMYYYY			DDMMYYYY			
Day 1=Day of Vaccination													

b. Local Reactions

Table 49: Number and Percentage of Subjects Experiencing Local Vaccination Reactions Following Priming Dose, by Reaction, Study Group, Study Product and Maximum severity- Safety Population

		Group 1 (N = X)		Group 2 (N = X)		Group 1 + Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)		Fisher's Exact Test
Local Reaction	**Severity**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**P-Value**
Nasal congestion	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													
Rhinorrhea	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													
Pain	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													
Redness	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													
Swelling	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													

N=Number of subjects in the safety population that received priming dose
CI= Exact Confidence Interval
Fisher's Exact Test on Group 3 vs Group 4 vs Group 5 vs Group 1 + Group 2
Events within 60 minutes and events within 7 days are combined

Table 50: Number and Percentage of Subjects Experiencing Local Vaccination Reactions Following Boost Dose, by Reaction, Study Group, Study Product and Maximum severity- Safety Population

		Group 1 (N = X)		Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)		Group 1 +Group 4 (N = X)		Group 3 +Group 5 (N = X)		Fisher's Exact Test
Local Reaction	**Severity**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**P-Value**
Pain	Any Severity															
	Mild															
	Moderate															
	Severe															
	Moderate or Severe															
Redness	Any Severity															
	Mild															
	Moderate															
	Severe															
	Moderate or Severe															
Swelling	Any Severity															
	Mild															
	Moderate															
	Severe															
	Moderate or Severe															

N=Number of subjects in the safety population that received boost dose
CI= Exact Confidence Interval
Fisher's Exact Test on Group 2 vs Group 1 + Group 4 vs Group 3 + Group 5
Events within 60 minutes and events within 7 days are combined

Table 51: Local Vaccination Reactions Within 7 Days Following Priming Dose by Maximum Severity, Study Day, Study Group, and Study Product - Safety Population

			Group 1 (N = X)		Group 2 (N = X)		Group 1 + Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)		Fisher's Exact Test
Local Reaction	**Post- Priming Dose**	**Severity**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**P-Value**
Nasal congestion	Day 1	Any Severity													
		Mild													
		Moderate													
		Severe													
	Day 2	Any Severity													
		Mild													
		Moderate													
		Severe													
	Day 3	Any Severity													
		Mild													
		Moderate													
		Severe													
	Day 4	Any Severity													
		Mild													
		Moderate													
		Severe													
	Day 5	Any Severity													
		Mild													
		Moderate													
		Severe													
	Day 6	Any Severity													
		Mild													
		Moderate													
		Severe													
	Day 7	Any Severity													
		Mild													
		Moderate													
		Severe													
Continue for rest of reactions…															

CI=Exact Confidence Interval
N= Number of Subjects in the safety population that received priming dose
Fisher's Exact Test on Group 3 vs Group 4 vs Group 5 vs Group 1 + Group 2
Events within 60 minutes are combined with events in Day 1

Table 52: Local Vaccination Reactions Within 7 Days Following Boost Dose by Maximum Severity, Study Day, Study Group, and Study Product - Safety Population

			Group 1 (N = X)		Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)		Group 1 +Group 4 (N = X)		Group 3 +Group 5 (N = X)		Fisher's Exact Test
Local Reaction	**Post- Priming Dose**	**Severity**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**P-Value**
Redness	Day 1	Any Severity															
		Mild															
		Moderate															
		Severe															
	Day 2	Any Severity															
		Mild															
		Moderate															
		Severe															
	Day 3	Any Severity															
		Mild															
		Moderate															
		Severe															
	Day 4	Any Severity															
		Mild															
		Moderate															
		Severe															
	Day 5	Any Severity															
		Mild															
		Moderate															
		Severe															
	Day 6	Any Severity															
		Mild															
		Moderate															
		Severe															
	Day 7	Any Severity															
		Mild															
		Moderate															
		Severe															
Continue for rest of reaction…																	

CI=Exact Confidence Interval
N= Number of Subjects in the safety population that received boost dose
Fisher's Exact Test on Group 2 vs Group 1 + Group 4 vs Group 3 + Group 5
Events within 60 minutes are combined with events in Day 1

c. Solicited General Reactions

Table 53: Number and Percentage of Subjects Experiencing General Reactions Following Priming Dose, by Reaction, Study Group, Study Product, and Maximum Severity- Safety Population

		Group 1 (N = X)		Group 2 (N = X)		Group 1+ Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)		Fisher's Exact Test
Systemic Reaction	**Severity**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**P-Value**
Fever	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													
Shivering	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													
Fatigue	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													
Headache	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													
Myalgia	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													

		Group 1 (N = X)		Group 2 (N = X)		Group 1+ Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)		Fisher's Exact Test
Systemic Reaction	**Severity**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**P-Value**
Arthralgia	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													
Nausea	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													
Vomiting	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													
Abdominal Pain	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													
Diarrhea	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													
Sore throat	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													

		Group 1 (N = X)		Group 2 (N = X)		Group 1+ Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)		Fisher's Exact Test
Systemic Reaction	**Severity**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**P-Value**
Cough	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													
Wheezing	Any Severity													
	Mild													
	Moderate													
	Severe													
	Moderate or Severe													

CI=Exact Confidence Interval
N= Number of Subjects in the safety population that received priming dose
Fisher's Exact Test on Group 3 vs Group 4 vs Group 5 vs Group 1 + Group 2
Events within 60 minutes and events within 7 days are combined

Table 54: Number and Percentage of Subjects Experiencing General Reactions Following Boost Dose, by Reaction, Study Group, Study Product, and Maximum severity- Safety Population

		Group 1 (N = X)		Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)		Group 1 +Group 4 (N = X)		Group 3 +Group 5 (N = X)		Fisher's Exact Test
Systemic Reaction	**Severity**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**P-Value**
Fever	Any Severity															
	Mild															
	Moderate															
	Severe															
	Moderate or Severe															
Shivering	Any Severity															
	Mild															
	Moderate															
	Severe															
	Moderate or Severe															
Continue for rest of reactions																

CI=Exact Confidence Interval
N= Number of Subjects in the safety population that received boost dose
Fisher's Exact Test on Group 2 vs Group 1 + Group 4 vs Group 3 + Group 5
Events within 60 minutes and events within 7 days are combined

Table 55: General Reactions Within 7 Days Following Priming Dose by Maximum Severity, Study Day, and Study Product Safety Population

			Group 1 (N = X)		Group 2 (N = X)		Group 1 + Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)		Fisher's Exact Test
Systemic Reaction	**Post- Priming Dose**	**Severity**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**P-Value**
Fever	Day 1	Any Severity													
		Mild													
		Moderate													
		Severe													
	Day 2	Any Severity													
		Mild													
		Moderate													
		Severe													
	Day 3	Any Severity													
		Mild													
		Moderate													
		Severe													
	Day 4	Any Severity													
		Mild													
		Moderate													
		Severe													
	Day 5	Any Severity													
		Mild													
		Moderate													
		Severe													
	Day 6	Any Severity													
		Mild													
		Moderate													
		Severe													
	Day 7	Any Severity													
		Mild													
		Moderate													
		Severe													
Continue for rest of reaction															

CI=Exact Confidence Interval
N= Number of Subjects in the safety population that received priming dose
Fisher's Exact Test on Group 3 vs Group 4 vs Group 5 vs Group 1 + Group 2
Events within 60 minutes are combined with events in Day 1

Table 56: General Reactions by Within 7 Days Following Boost Dose by Maximum Severity, Study Day, and Study Product -Safety Population

			Group 1 (N = X)		Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)		Group 1 +Group 4 (N = X)		Group 3 +Group 5 (N = X)		Fisher's Exact Test
Systemic Reaction	**Post- Priming Dose**	**Severity**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**n(%)**	**95% CI**	**P-Value**
Fever	Day 1	Any Severity															
		Mild															
		Moderate															
		Severe															
	Day 2	Any Severity															
		Mild															
		Moderate															
		Severe															
	Day 3	Any Severity															
		Mild															
		Moderate															
		Severe															
	Day 4	Any Severity															
		Mild															
		Moderate															
		Severe															
	Day 5	Any Severity															
		Mild															
		Moderate															
		Severe															
	Day 6	Any Severity															
		Mild															
		Moderate															
		Severe															
	Day 7	Any Severity															
		Mild															
		Moderate															
		Severe															
Continue for rest of reaction																	

CI=Exact Confidence Interval
N= Number of Subjects in the safety population that received boost dose
Fisher's Exact Test on Group 2 vs Group 1 + Group 4 vs Group 3 + Group 5
Events within 60 minutes are combined with events in Day 1

d. Unsolicited Adverse Events

Table 57: Summary of Unsolicited Adverse Events During the Entire Study Period by Study Group, - Safety Population

	Group 1 (N = X)		Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)	
	n(%)	95%CI	n(%)	95%CI	n(%)	95%CI	n(%)	95%CI	n(%)	95%CI
AE										
Any										
Mild										
Moderate										
Severe										
Any SAE										
Any MAE										
Any pIMD										
Any LC-ILI										
Any Grade 2 or greater AE										
Any AE related to Product[1]										
Any Grade 2 or greater AE related to product										
AE that lead to study withdrawal[1]										
Any										
Mild										
Moderate										
Severe										

N=Number of subjects in the Safety Population
[1]Includes SAE
CI=Exact Confidence Interval

Table 58: Summary of Unsolicited Adverse Events During the Entire Study Period by Study Group - Safety Population-CCHMC

Similar to Table above

Table 59: Summary of Unsolicited Adverse Events During the Entire Study Period by Study Group - Safety Population-DCRI

Similar to Table above

Table 60: Number and Percentage of Subjects Experiencing SAE During the Entire Study Period by Study Group, MedDRA® System Organ Class, Preferred Term and Maximum Severity- Safety Population

			Group 1 (N = X)		Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)	
MedDRA System Organ Class	**MedDRA Preferred Term**	**Severity**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
SAE												
Any System Organ Class	Any Preferred Term	Any Severity	x (xx x)	(xx,xx)	x (xx x)	(xx,xx)	x (xx.x)	(xx,xx)	x (xx x)	(xx,xx)	x (xx x)	(xx,xx)
		Mild										
		Moderate										
		Severe										
SOC 1	Any Preferred Term	Any Severity										
		Mild										
		Moderate										
		Severe										
	PT 1	Any Severity										
		Mild										
		Moderate										
		Severe										
	PT 2	Any Severity										
		Mild										
		Moderate										
		Severe										

N= Number of subjects in the safety population
CI: Exact Confidence Interval

Table 61: Number and Percentage of Subjects Experiencing MAE During the Entire Study Period by Study Group, MedDRA® System Organ Class, Preferred Term and Maximum Severity- Safety Population

Similar to Table above

Table 62: Number and Percentage of Subjects Experiencing pIMD During the Entire Study Period by Study Group, MedDRA® System Organ Class, Preferred Term and Maximum Severity- Safety Population

Similar to Table above

Table 63: Summary of ILI Test Results by Study Group

		Group 1 (N = X)		Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)	
Test Conducted	**Strain/Result**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**	**n (%)**	**95% CI**
Any	-	x (xx.x)	(xx,xx)	x (xx.x)	(xx,xx)	x (xx x)	(xx,xx)	x (xx.x)	(xx,xx)	x (xx x)	(xx,xx)
Positive for influenza	Any										
	Influenza A										
	Influenza A H1										
	Influenza A H3										
	Influenza B										
Positive for non-influenza pathogens	Yes										
	No										

N= Number of subjects in the safety population
CI: Exact Confidence Interval
Subject can contribute to multiple influenza type/strain

Table 64: Listing for ILI Test Results

Study Group	Subject ID	Specimen Collection Date	Study Day of Specimen Collection	Last Dose Received	Study Day of Last Dose Received	Positive Test Result	Positive Results	Positive for Non-Influenza Pathogens	Specify
	000001	DDMMMYYYY	x	LAIV/IIV/ Placebo	x	Y/N	Strain 1/ Strain 2/ Strain 3	Y/N	

Programming Note: Sort by Flu Y/N, Group, Subject ID, Study day of specimen collection

Table 65: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events Within 28 Days Following Any Vaccination, by Study Group, Relationship, MedDRA® System Organ Class, Preferred Term and Maximum Severity- Safety Population

MedDRA System Organ Class	MedDRA Preferred Term	Severity	Relation-ship	Group 1 (N = X)		Group 2 (N = X)		Group 3 (N = X)		Group 4 (N = X)		Group 5 (N = X)	
				n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Any System Organ Class	Any Preferred Term	Any Severity	Any										
			Related										
		Mild	Any										
			Related										
		Moderate	Any										
			Related										
		Severe	Any										
			Related										
SOC 1	Any Preferred Term	Any Severity	Any										
			Related										
		Mild	Any										
			Related										
		Moderate	Any										
			Related										
		Severe	Any										
			Related										
	PT 1	Any Severity	Any										
			Related										
		Mild	Any										
			Related										
		Moderate	Any										
			Related										
		Severe	Any										
			Related										

N= Number of subjects in the safety population
CI: Exact Confidence Interval

Table 66: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events Within 28 Days Following Priming Dose by Study Group, Study Product, Relationship, MedDRA® System Organ Class, Preferred Term and Maximum Severity– Safety Population

Similar to Table above with additional column for Group 1+ Group 2

Table 67: Number and Percentage of Subjects Experiencing Unsolicited Adverse Events Within 28 Days Following Boost Dose by Site, Study Group, Study Product, Relationship, MedDRA® System Organ Class, Preferred Term and Maximum Severity– Safety Population

Similar to Table above with additional columns for Group 1+ Group 4, Group 3 + Group 5

Table 68: Frequency of Unsolicited Adverse Events Within 28 Days Following Any Vaccination by Study Group, MedDRA® System Organ Class, Preferred Term, Relationship, and Severity– Safety Population

				Group 1 (N = X)	Group 2 (N = X)	Group 3 (N = X)	Group 4 (N = X)	Group 5 (N = X)
MedDRA System Organ Class	**MedDRA Preferred Term**	**Severity**	**Relationship**	**Events (X=)**	**Events (X=)**	**Events (X=)**	**Events (X=)**	**Events (X=)**
Any System Organ Class	Any Preferred Term	Any Severity	Any	x=	x=	x=	x=	x=
			Related					
		Mild	Any					
			Related					
		Moderate	Any					
			Related					
		Severe	Any					
			Related					
SOC 1	Any Preferred Term	Any Severity	Any					
			Related					
		Mild	Any					
			Related					
		Moderate	Any					
			Related					
		Severe	Any					
			Related					
	PT 1	Any Severity	Any					
			Related					
		Mild	Any					
			Related					
		Moderate	Any					
			Related					
		Severe	Any					
			Related					

N= Number of subjects in the safety population
CI: Exact Confidence Interval

Table 69: Frequency of Unsolicited Adverse Events Within 28 Days Following Priming Dose by Study Group, Study Product, MedDRA® System Organ Class, Preferred Term, Relationship, and Severity– Safety Population

Similar to Table above with additional column for Group 1+ Group 2

Table 70: Frequency of Unsolicited Adverse Events Within 28 Days Following Boost Dose by Study Group, Study Product, MedDRA® System Organ Class, Preferred Term, Relationship, and Severity– Safety Population

Similar to Table above with additional columns for Group 1+ Group 4 and Group 3 + Group 5

Table 71: Listing of Grade 2 or Greater Non-Serious Adverse Events

Subject ID	Study Group	Adverse Event	Associated with Dose No.	Onset Day (Duration)	Severity	SAE	MAE	pIMD	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
Comment:															

Table 72: Listing of Serious Adverse Events

Subject ID	Study Group	Last Vaccination Number	Date of Vaccination	Onset Date/Stop Date	Duration	Max. Severity	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
000001			DDMMYYYY										
Comment:													

Table 73: Listing of Medically Attended Events

Subject ID	Study Group	Associated with Treatment Number	Date of Associated Treatment Number	Onset Date/Stop Date	Duration	Max. Severity	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	SAE
000001		1/2	DDMMYYYY											Y/N
Comment:														

Table 74: Listing of Potential Immune-Mediated Disease Events

Subject ID	Study Group	Associated with Treatment Number	Date of Associated Treatment Number	Onset Date/Stop Date	Duration	Max. Severity	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	SAE
000001		1/2	DDMMYYYY											Y/N
Comment:														

e. Abnormal Lab

Table 75: Listing of All Hematology in Subjects with Any Grade 2 or Greater Severity at Any Time Point– Safety Population

				HEMATOLOGY								
				Leukocytes (WBC)	Neutrophils	Lymphocytes	Eosinophils	Hemoglobin	Platelets	Basophils	Monocytes	Erythrocytes
Subject ID	Age	Visit	Visit Date DDMMYYYY	Cell/mm^3	Cell/mm^3	Cell/mm^3	Cell/mm^3	gm/dL	Cell/mm^3	K/mcL	K/mcL	M/mcL
Study Group: xx												
000001	xx	Screening										
		Visit 02										
		Visit 09										
		Visit 10										
		Visit 11										
		Visit 12										
		Visit 13										
		Visit 14										
		Visit 15										
000002	xx	Screening										
		Visit 02										
		Visit 09										
		…										
000003	xx	Screening										
		Visit 02										
		…										
Study Group: xx												

Green=Outside the Reference Range, Yellow=Grade 1, Orange=Grade 2, Red=Grade 3, Purple=Grade 4
All visits for a subject with a Grade 2 or greater hematology abnormality will be listed

Table 76: Listing of All Biochemistry in Subjects with Any Grade 2 or Greater Severity at Any Time Point– Safety Population

				Biochemistry			
				ALT	AST	Creatinine	BUN
Subject ID	Age	Visit	Visit Date DDMMYYYY	U/L	U/L	mg/dL	mg/dL
Study Group: xx							
000001	xx	Screening					
		Visit 02					
		Visit 09					
		Visit 10					
		Visit 11					
		Visit 12					
		Visit 13					
		Visit 14					
		Visit 15					
000002	xx	Screening					
		Visit 02					
		Visit 09					
000003	xx	Screening					
		Visit 02					
Study Group: xx							
Green=Outside the Reference Range, Yellow=Grade 1, Orange=Grade 2, Red=Grade 3, Purple=Grade 4							

Table 77: Summary of Hematology by Parameter, Maximum Severity, Study Day, Study Group, Priming Dose– Safety Population

			Statistics			Severity				
			Mean (SD)	Median (IQR)	Min/Max	Above Normal Range	Below Normal Range	Mild	Moderate	Severe
Parameter	**Visit**	**Study Group**				**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Leukocytes (WBC) Cell/mm^3	Screening	Group 1								
		Group 2								
		Group 1 + Group 2								
		Group 3								
		Group 4								
		Group 5								
	Visit 02	Group 1								
		Group 2								
		Group 1 + Group 2								
		Group 3								
	Visit 03	Group 4								
		Group 5								
	Visit 09	Group 1								
		Group 2								
		Group 1 + Group 2								
		Group 3								
		Group 4								
		Group 5								
	Visit 10	Group 1								
		Group 2								
		Group 1 + Group 2								
		Group 3								
		Group 4								
		Group 5								
	Visit 11	Group 1								

			Statistics			Severity				
			Mean (SD)	Median (IQR)	Min/Max	Above Normal Range	Below Normal Range	Mild	Moderate	Severe
Parameter	**Visit**	**Study Group**				**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
		Group 2								
		Group 3								
		Group 4								
		Group 5								
	Visit 12	Group 1								
		Group 2								
		Group 3								
		Group 4								
		Group 5								
	Visit 13	Group 1								
		Group 2								
		Group 3								
		Group 4								
		Group 5								
	Visit 14	Group 1								
		Group 2								
		Group 3								
		Group 4								
		Group 5								
	Visit 15	Group 1								
		Group 2								
		Group 3								
		Group 4								
		Group 5								
Neutrophils Cell/mm^3	Screening	Group 1								
	Etc.	Group 2								
	Visit 02	Group 1								
	Etc.	Group 2								

			Statistics			Severity				
			Mean (SD)	Median (IQR)	Min/Max	Above Normal Range	Below Normal Range	Mild	Moderate	Severe
Parameter	**Visit**	**Study Group**				**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Lymphocytes Cell/mm^3	Screening	Group 1								
	Etc.	Group 2								
	Visit 02	Group 1								
	Etc.	Group 2								
Eosinophils Cell/mm^3	Screening	Group 1								
	Etc.	Group 2								
	Visit 02	Group 1								
	Etc.	Group 2								
Hemoglobin-Male gm/dL	Screening	Group 1								
	Etc.	Group 2								
	Visit 02	Group 1								
	Etc.	Group 2								
Hemoglobin-Female gm/dL	Screening	Group 1								
	Etc.	Group 2								
	Visit 02	Group 1								
	Etc.	Group 2								
Platelets Cell/mm^3	Screening	Group 1								
	Etc.	Group 1								
	Visit 02	Group 2								
	Etc.	Group 1								
Basophils K/mcL										
Monocytes K/mcL										
Erythrocytes M/mcL										

Statistics for hemoglobin will use Change from baseline (Screening)
Basophils, Monocytes, Eosinophils, and Erythrocytes will not be graded Programming note: Page break for each parameter.

Table 78: Summary of Biochemistry by Parameter, Maximum Severity, Study Day, Study Group, Priming Dose– Safety Population

			Statistics			Severity				
			Mean (SD)	Median	Min/Max	Above Normal Range	Below Normal Range	Mild	Moderate	Severe
Parameter	Visit	Study Group				n(%)	n(%)	n(%)	n(%)	n(%)
ALT	Screening	Group 1								
		Group 2								
		Group 1 + Group 2								
		Group 3								
		Group 4								
		Group 5								
	Visit 02	Group 1								
		Group 2								
		Group 1 + Group 2								
		Group 3								
	Visit 03	Group 4								
		Group 5								
	Visit 09	Group 1								
		Group 2								
		Group 1 + Group 2								
		Group 3								
		Group 4								
		Group 5								
	Visit 10	Group 1								
		Group 2								
		Group 1 + Group 2								
		Group 3								
		Group 4								
		Group 5								
	Visit 11	Group 1								
		Group 2								
		Group 3								
		Group 4								
		Group 5								
	Visit 12	Group 1								

			Statistics			Severity				
			Mean (SD)	Median	Min/Max	Above Normal Range	Below Normal Range	Mild	Moderate	Severe
Parameter	**Visit**	**Study Group**				**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
		Group 2								
		Group 3								
		Group 4								
		Group 5								
	Visit 13	Group 1								
		Group 2								
		Group 3								
		Group 4								
		Group 5								
	Visit 14	Group 1								
		Group 2								
		Group 3								
		Group 4								
		Group 5								
	Visit 15	Group 1								
		Group 2								
		Group 3								
		Group 4								
		Group 5								
AST	Screening	Group 1								
	Etc.	Group 2								
	Visit 02	Group 1								
	Etc.	Group 2								
Creatinine mg/dL	Screening	Group 1								
	Etc.	Group 2								
	Visit 02									
	Etc.									
BUN mg/dL										
BUN to Creatinine Ratio										

BUN and BUN to Creatinine ratio will not be graded Programming note: Page break after each parameter

Table 79: Hematology Shift from Baseline by Parameter, Study Day, Study Group, and Priming Dose– Safety Population

Parameter	Visit	Baseline	Shift Category	Group 1 (N = X)	Group 2 (N = X)	Group 1+ Group 2 (N = X)	Group 3 (N = X)	Group 4 (N = X)	Group 5 (N = X)
Leukocytes (WBC)	Visit 09	Normal (n=)	Normal	x/x (xx x)	x/x (xx x)	x/x (xx.x)	x/x (xx x)	x/x (xx x)	x/x (xx x)
			Mild						
			Moderate						
			Severe						
		Mild (n=)	Normal						
			Mild						
			Moderate						
			Severe						
		Moderate (n=)	Normal						
			Mild						
			Moderate						
			Severe						
		Severe (n=)	Normal						
			Mild						
			Moderate						
			Severe						
	Visit 10	Normal (n=)	Normal						
	Visit 11	…	…						
Continue for all Lab	Continue for all Study Visits	…	…						

N=Number of subjects in the safety population
n = Number of subjects with the observed case
Basophils, Monocytes, Eosinophils, and Erythrocytes will not be graded

Table 80: Biochemistry Shift from Baseline by Parameter, Study Day, Study Group, and Priming Dose– Safety Population

Parameter	Visit	Baseline	Shift Category	Group 1 (N = X)	Group 2 (N = X)	Group 1+ Group 2 (N = X)	Group 3 (N = X)	Group 4 (N = X)	Group 5 (N = X)
ALT	Visit 09	Normal (n=)	Normal	x/x (xx.x)	x/x (xx.x)	x/x (xx.x)	x/x (xx x)	x/x (xx x)	x/x (xx.x)
			Mild						
			Moderate						
			Severe						
		Mild (n=)	Normal						
			Mild						
			Moderate						
			Severe						
		Moderate (n=)	Normal						
			Mild						
			Moderate						
			Severe						
		Severe (n=)	Normal						
			Mild						
			Moderate						
			Severe						
	Visit 10	Normal (n=)	Normal						
	Visit 11	…	…						
Continue for all parameter	Continue for all Study Visits	…	…						

N=Number of subjects in the safety population
n = Number of subjects with the observed case
BUN will not be graded

Table 81: Summary of HIV Antibody Results by Study Group and Priming Dose– Safety Population

		Group 1 (N = X)	Group 2 (N = X)	Group 1+ Group 2 (N = X)	Group 3 (N = X)	Group 4 (N = X)	Group 5 (N = X)
Antibody	**Results**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
HIV	Positive	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)	x (xx x)
	Negative						
N=Number of subjects in the safety population n = Number of subjects with the observed case							

Table 82: Listing of Subjects with Positive HIV Antibody Results

Study Group	Subject ID	HIV
		Positive/Negative

f. Vital Signs

Table 83: Summary of Vital Signs by Parameter, Maximum Severity, Study Day, and Study Product – Safety Population

			Statistics		
			Mean (SD)	**Median**	**Min/Max**
Parameter	**Visit**	**Study Groups**			
Systolic Blood Pressure	Screening	Group 1			
		Group 2			
		Group 3			
		Group 4			
		Group 5			
	Visit 03	Group 1			
		Group 2			
		Group 1 + Group 2			
		Group 3			
		Group 4			
		Group 5			
	Visit 11	Group 1			
		Group 2			
		Group 3			
		Group 4			
		Group 5			
Diastolic Blood Pressure	Screening	Group 1			
	…	…			
Temperature	Screening	Group 1			
	…	…			
Respiratory	Screening	Group 1			
	…	…			
Heart Rate	Screening	Group 1			
	…	…			

g. Physical Exam

Table 84: Summary of Abnormal Physical Exam Findings by Study Day, Study Group, and Study Product – Safety Population

Visit	Body System	Group 1 (N = X)	Group 2 (N = X)	Group 3 (N = X)	Group 4 (N = X)	Group 5 (N = X)
		n(%)	n(%)	n(%)	n(%)	n(%)
Screening	Any					
	Abdomen					
	Cardiovascular / heart					
	Extremities					
	General appearance					
	HEENT					
	Continue for other Body System					

N=Number of subjects in the safety population
Targeted PE will be presented in Listing 16, Appendix 3

h. Other Safety Measures

Table 85: Summary of Nasal/Oropharyngeal Shedding of Vaccine Virus by Study Day, Study Group, and Study Product- Inpatient Day- Safety Population

		Pooled				CCHMC				DCRI			
Visit	**Summary**	**Group 1 (N = X)**	**Group 2 (N = X)**	**Group 1+ Group 2 (N = X)**	**Group 3 (N = X)**	**Group 1 (N = X)**	**Group 2 (N = X)**	**Group 1+ Group 2 (N = X)**	**Group 3 (N = X)**	**Group 1 (N = X)**	**Group 2 (N = X)**	**Group 1+ Group 2 (N = X)**	**Group 3 (N = X)**
Any	PCR Positive	x/n(%)											
	MDCK Positive	x/n(%)											
Visit 02	PCR Positive												
	PCR Positive (95% CI)												
	MDCK Positive												
	MDCK Positive (95% CI)												
	Mean (SD) log FFA												
	GMT												
	GMT 95% CI												
Visit 03	…												
Visit 04	…												
Visit 05	…												
Visit 06	…												
Visit 07	…												
Visit 08	…												

N=number of subject in the safety population
GMT=Geometric Mean Titer
x= Number of subjects with the observed case
n= Number of subjects with evaluable samples

D. CONCOMITANT MEDICATIONS

Table 86: Number and Percentage of Subjects with Prior Medications by WHO Drug Classification and Study Group-Safety Population

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Group 1 (N=X)		Group 2 (N=X)		Group 3 (N=X)		Group 4 (N=X)		Group 5 (N=X)	
		n	%	n	%	n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	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 reporting taking at least one medication in the specific WHO Drug Class. N =Number of subjects in the Safety Population											

Table 87: Number and Percentage of Subjects with Ongoing/Concomitant Medications Throughout the Study Period by WHO Drug Classification and Study Group-Safety Population

Similar to Table above excluding Medication Stop Date column

Table 88: Summary of Influenza Vaccination History by Study Group- Safety Population

Year	Vaccine Type	Group 1 (N=X)		Group 2 (N=X)		Group 3 (N=X)		Group 4 (N=X)		Group 5 (N=X)	
		n	%	n	%	n	%	n	%	n	%
2014-2015	Inactivated	x	xx	x	xx	x	xx	x	xx	x	xx
	LAIV										
2015-2016	Inactivated										
	LAIV										
2016-2017	Inactivated										
	LAIV										

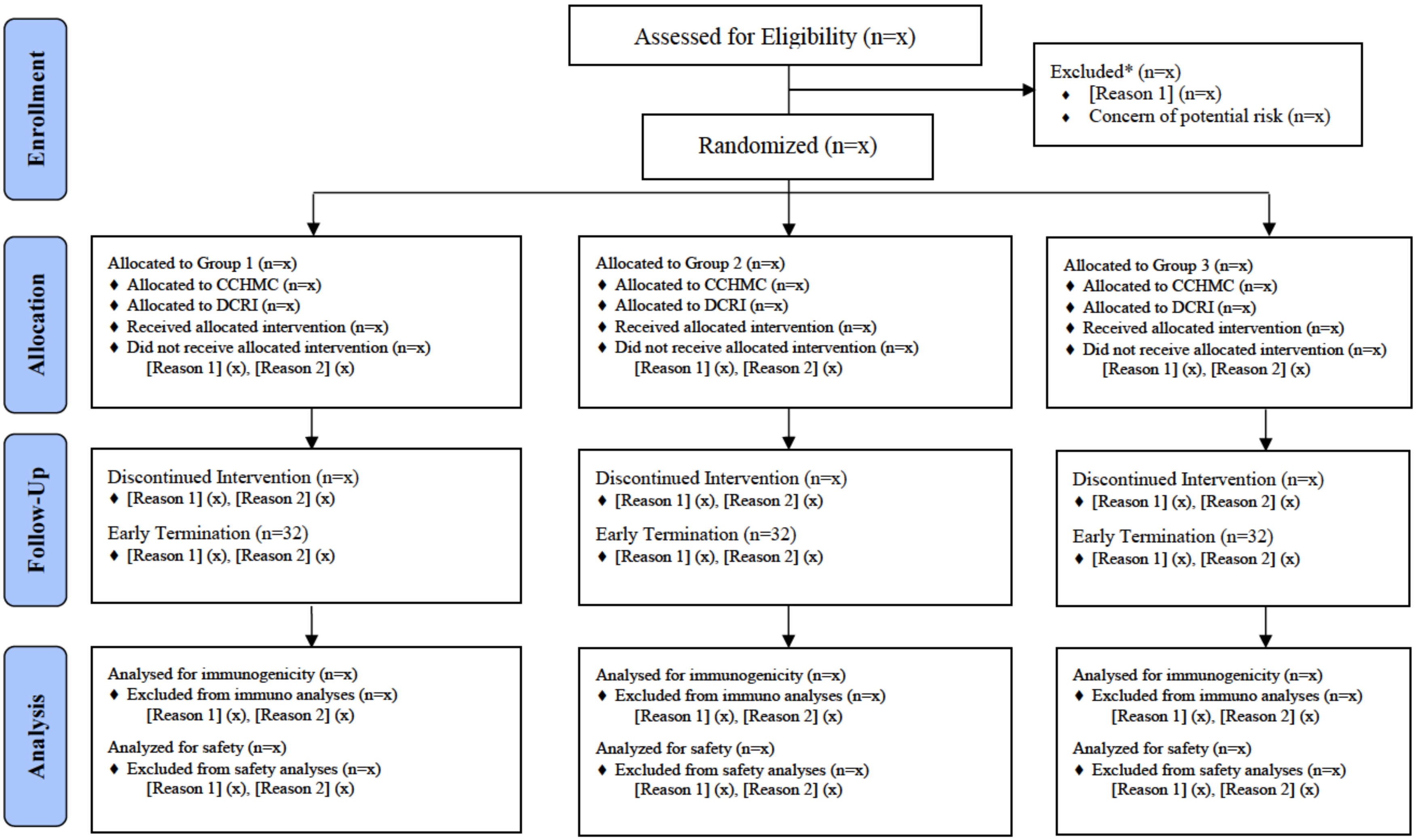
N =Number of subjects in the Safety Population
n=Number of subjects that received seasonal influenza vaccine

APPENDIX 2. FIGURES

LIST OF FIGURES

A. DEMOGRAPHICS

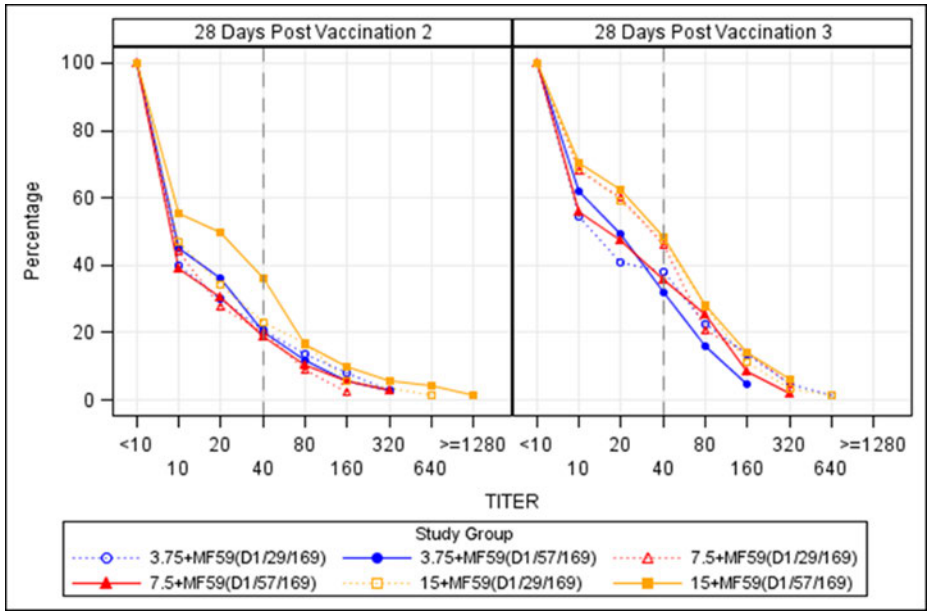
Figure 1: CONSORT Flow Diagram



Implementation Note: A generic sample consort diagram is shown above. The diagram will have one column for each study group.

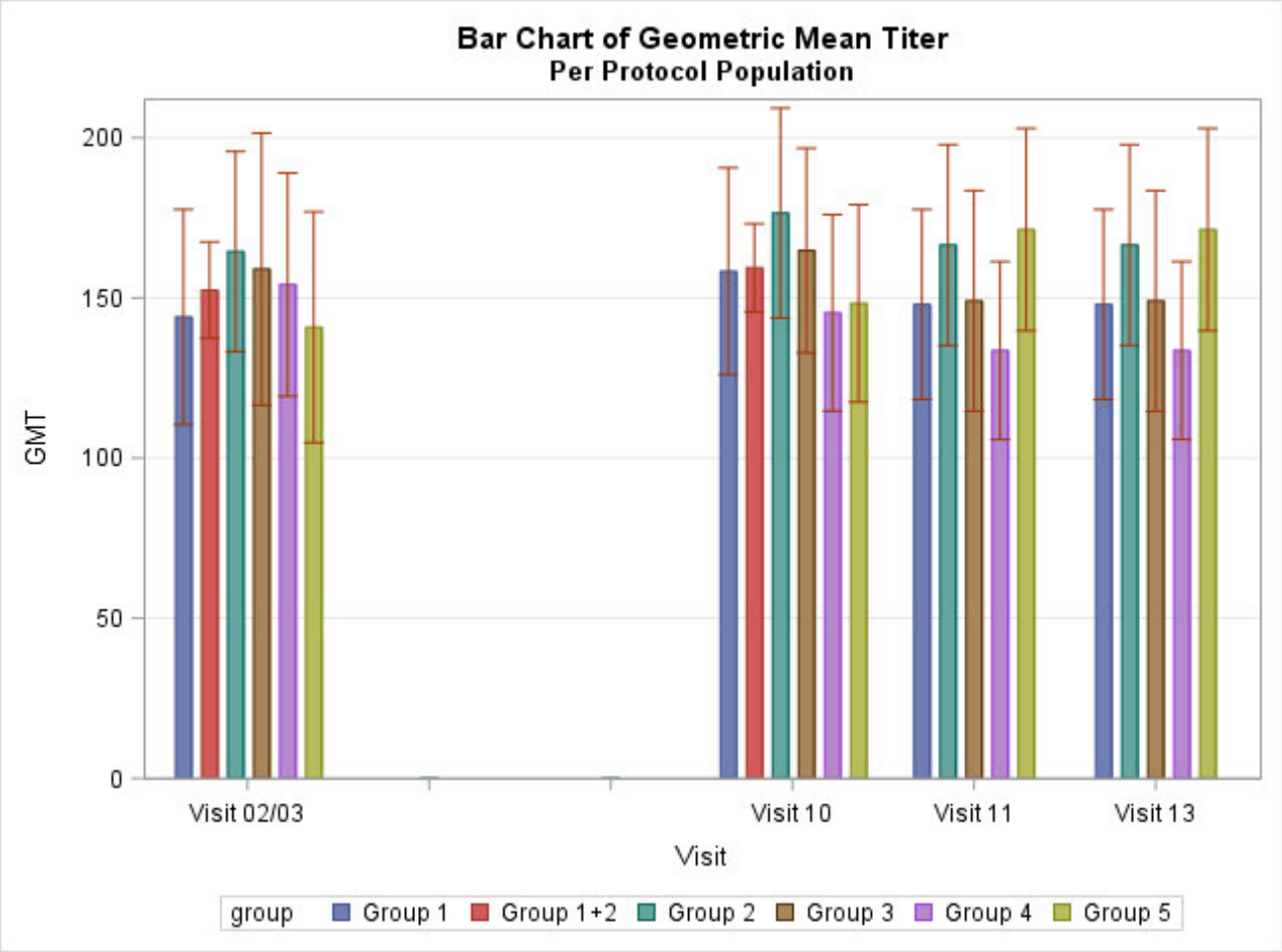
B. IMMUNOGENICITY

Figure 2: Anti-H1 HA-stalk total IgA (serum) Humoral Response: Distribution of Antibody Titers Using Reverse Distribution Curves, Per Protocol Population



Implementation Note: A generic sample figure is shown above. The RCD curves should be presented in a single figure with separate panels for each time point (Visit 02, 10, 11, 13, 14, 15). Visit labels will be included in the panel headers. Within each panel, individual curves will be used for each Study Group. Additional pooled groups (Group 1 and Group 2) will be shown up to Visit 10. Curves will be plotted with different colors. A legend will be included to indicate the Study Groups with the following labels for each Study Groups, including "(N=X)", where N = the number of subjects in the applicable study population and visit.

Figure 3: Anti-H1 HA-stalk total IgA (serum) Humoral Response: Geometric Mean and 95% CI - Per Protocol Population



Implementation Note: A generic sample figure is shown above. The x-axis will be relative study visits and will be scaled appropriately, Titer is plotting on the y-axis on the log-10 scale. For each study group, GMT should be plotted as overlaid jittered data points at each visit with upper and lower error bars for the 95% using the same color. Plot will have only one panels that shows all five study groups with additional pooled groups (Group 1 + Group 2) up to Visit 10. A legend should be included to indicate the study groups.

Figure 4: Anti-H1 HA-stalk total IgA (serum) Humoral Response: Mean Geometric Increase From Day 1, and 95% CI - Per Protocol Population

Figure 5: Anti-H1 HA-stalk total IgG (serum) Humoral Response: Distribution of Antibody Titers Using Reverse Distribution Curves, Per Protocol Population

Figure 6: Anti-H1 HA-stalk total IgG (serum) Humoral Response: Geometric Mean and 95% CI - Per Protocol Population

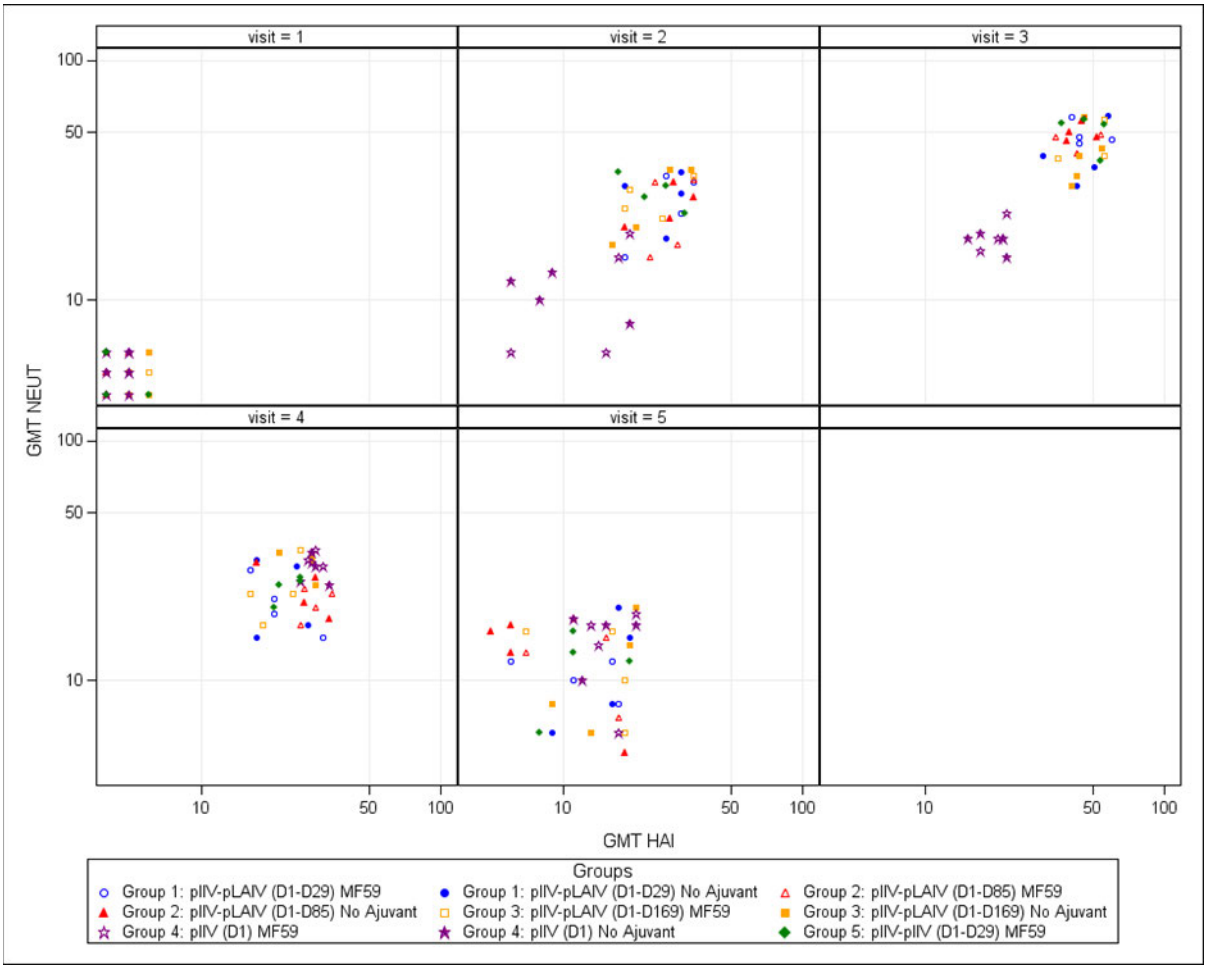
Figure 7: Anti-H1 HA-stalk total IgG (serum) Humoral Response: Mean Geometric Increase From Day 1, and 95% CI - Per Protocol Population

Figure 8: Anti-H1 HA-stalk Secretory IgA (saliva), Mucosal Response: Distribution of Antibody Titers Using Reverse Distribution Curves, Per Protocol Population

Figure 66: Serum ADCP Activity: Geometric Mean and 95% CI - Per Protocol Population

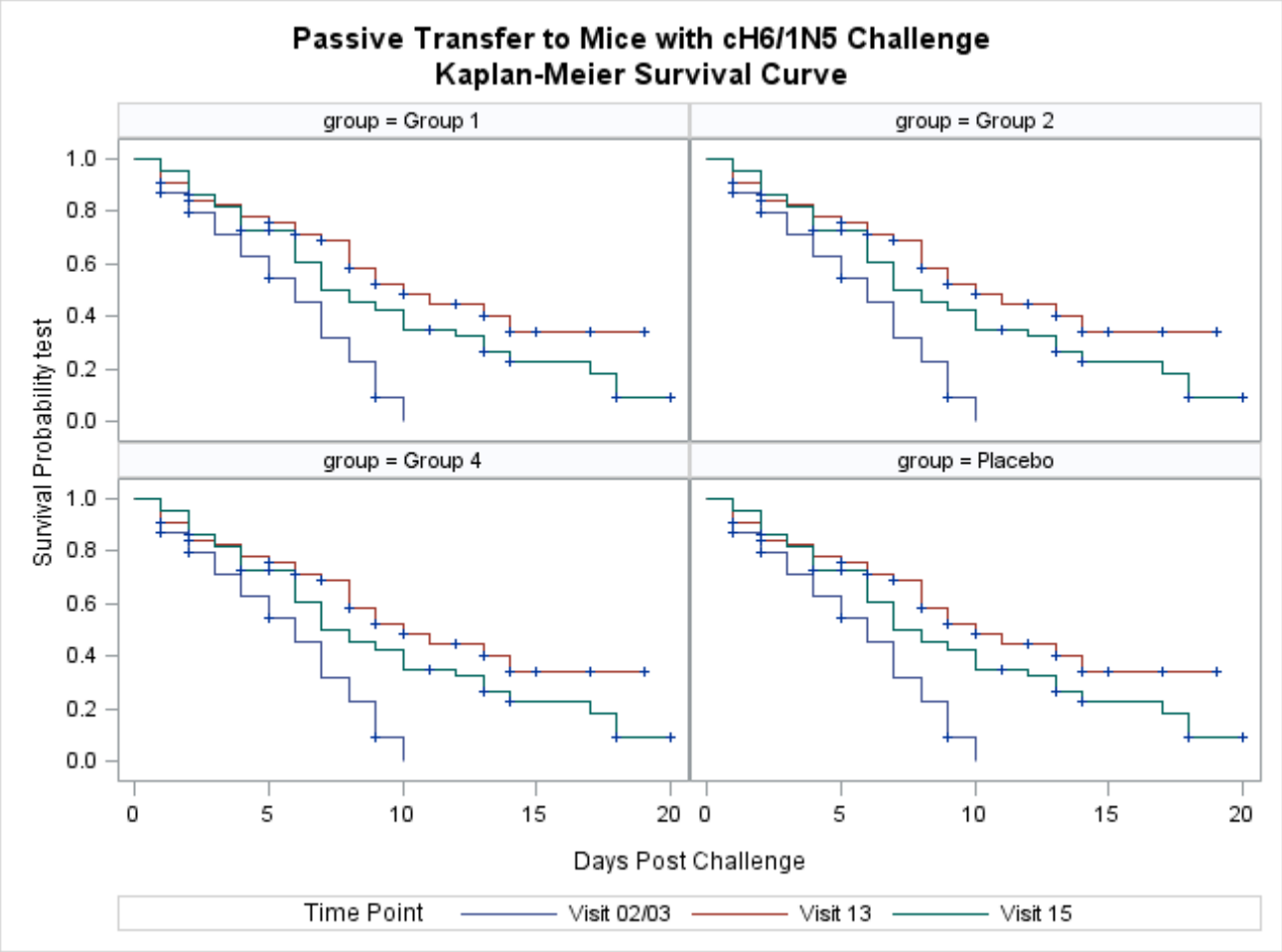
Figure 67: Serum ADCP Activity: Mean Geometric Increase From Day 1, and 95% CI - Per Protocol Population

Figure 68: Correlation Between Anti-H1 Stalk Serum IgG ELISA and Anti-H1 HA-Stalk MN Assay, Per Protocol Population



Implementation Note: A generic sample figure is shown above. Actual figure will reflect the assay that are being compared. The scatter plots should be presented in a single figure with separate panels for each time point. Visit labels should be included in the panel header. Within each panel distinct marker types and colors should be used to indicate the Study Groups (Including pooled group (Group 1+ Group 2) up to Visit 10 and (Group 1+ Group 4, Group 3+ Group 5) after Visit 10). An additional table will be included below the plot/or annotated within each panel on the Spearman correlation between the two assay by group and overall within each visit.

Figure 69: Passive transfer to mice with cH6/1N5 challenge: Kaplan-Meier Survival Curve by Time Point Panel by Study Group

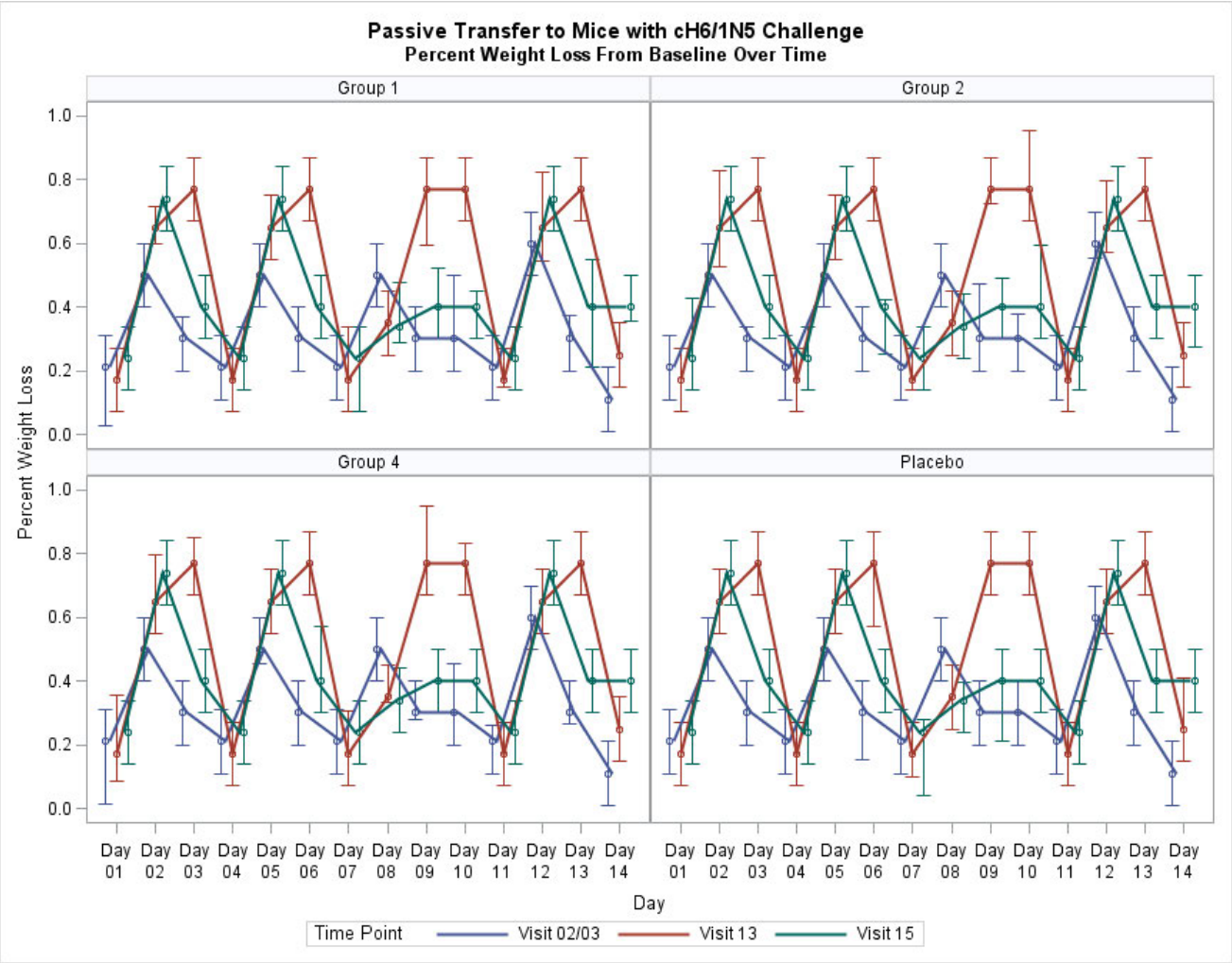


Implementation Note: A sample figure is shown above. There will be four survival curve plot (one for each group) and each plot will contain three survival curves (one for each visit). Appropriate legend displaying study group and visit number will be included. Figures will also include 95% confidence interval either as text or shaded regions as well as annotated log-rank test for the differences among visits within group in the figures. Group 1 and Group 2 will have Visit 02, 13, and 15 mice cohorts; Group 4 will have Visit 03, 13, and 15 mice cohorts; Placebo group will have Visit 02/03, 13, 15 mice cohorts. There will be one plot per study group.

Figure 70: Passive transfer to mice with cH6/1N5 challenge: Kaplan-Meier Survival Curve by Study Group Panel by Time Point

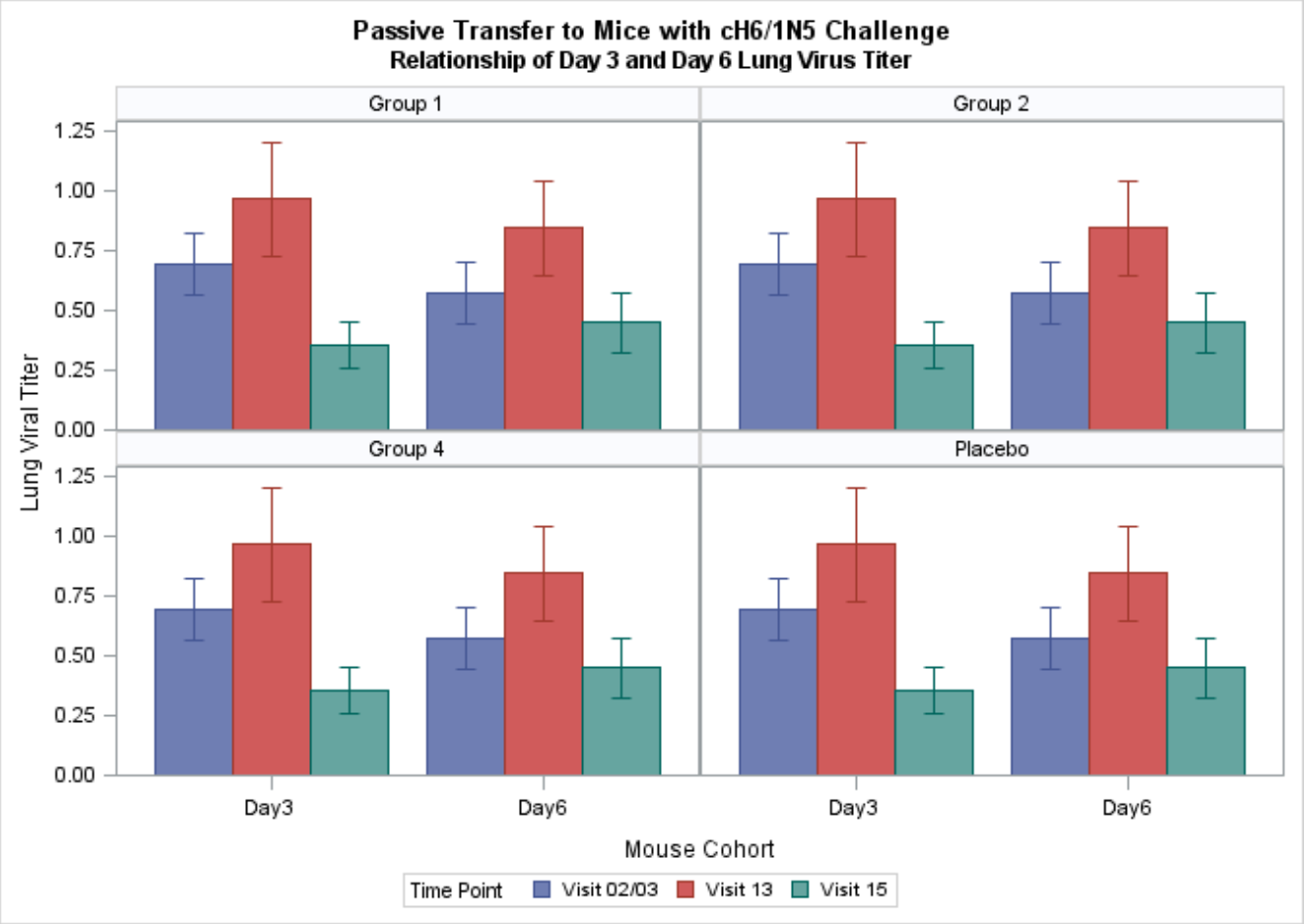
Similar to Figure above. Figures will be paneled by time point and will include annotated log-rank test for the differences among groups within visit in the figures

Figure 71: Passive transfer to mice with cH6/1N5 challenge: Percent Weight Loss from Baseline Over Time with 95% Confidence Interval by Study Group Panel by Time Point



Implementation Note: A generic sample figure is shown above. Percent weight loss will be plotted at each post-challenge day with corresponding 95% confidence interval vis the bootstrap method. Group 1 and Group 2 will have Visits 02, 13, and 15 mice cohorts; Group 4 will have Visit 03, 13, and 15 mice cohorts; Placebo group will have Visit 02/03, 13, 15 mice cohorts. There will be one plot per study groups.

Figure 72: Passive transfer to mice with cH6/1N5 challenge: Lung Virus GMT and 95% CI by Time Points panel by Study Group- Day 3/Day 6 Post-Challenge Cohort



Implementation Note: A sample figure is shown above. Figure will reflect actual data. 95% confidence intervals can be added as text below the legend. Additional overlaid horizontal line for GMT for each visit in each panel as well as x-jittered data points will be plotted. Group 1 and Group 2 will have Visit 02, 13, and 15 mice cohorts; Group 4 will have Visit 03, 13, and 15 mice cohorts; Placebo group will have Visit 02/03, 13, 15 mice cohorts. The y-axis will be on the log 10 scale. There will be one plot per study group.

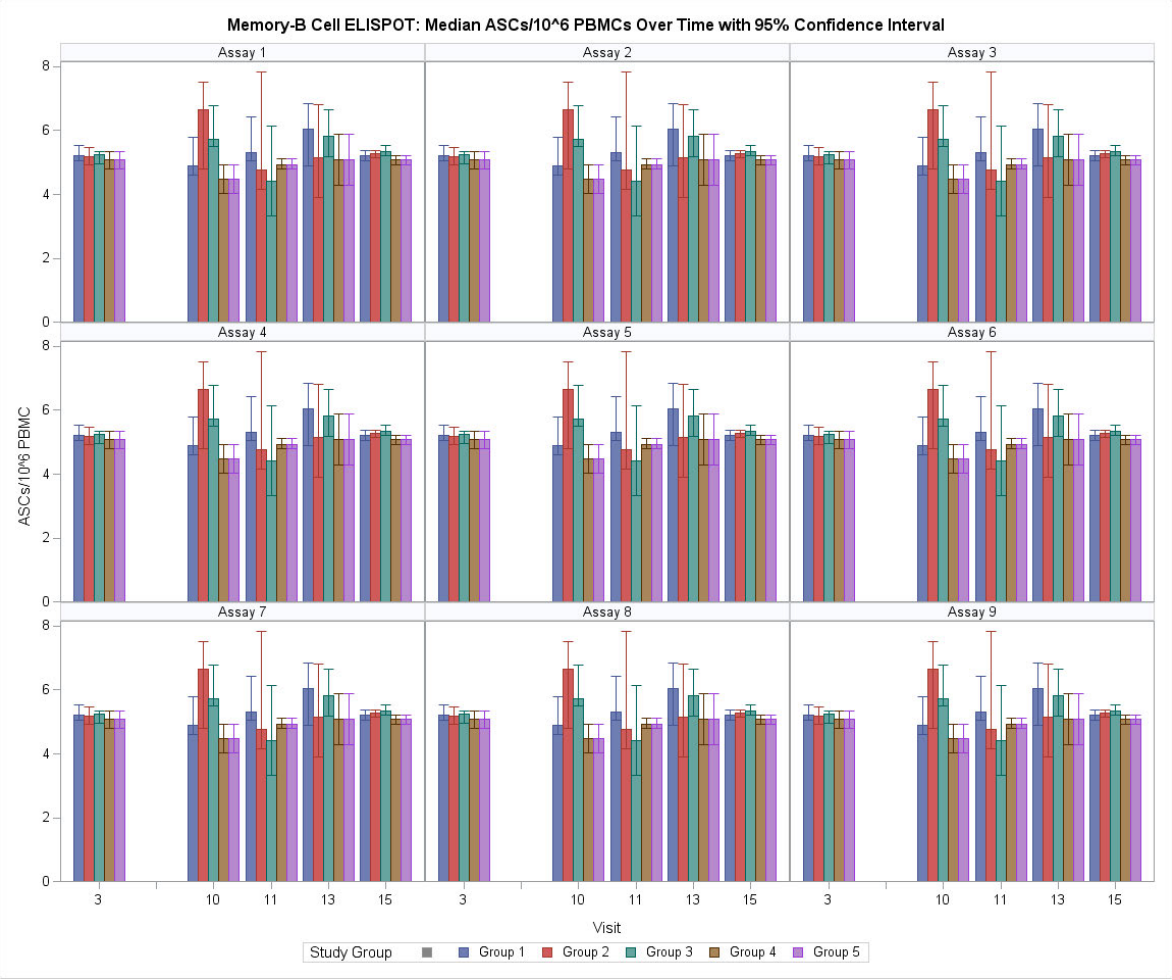
Figure 73: Passive transfer to mice with H1N1 challenge: Kaplan-Meier Survival Curve by Time Point Panel by Study Group

Figure 74: Passive transfer to mice with H1N1 challenge: Kaplan-Meier Survival Curve by Study Group Panel by Time Point

Figure 75: Passive transfer to mice with H1N1 challenge: Percent Weight Loss from Baseline Over Time with 95% Confidence Interval by Study Group Panel by Time Point

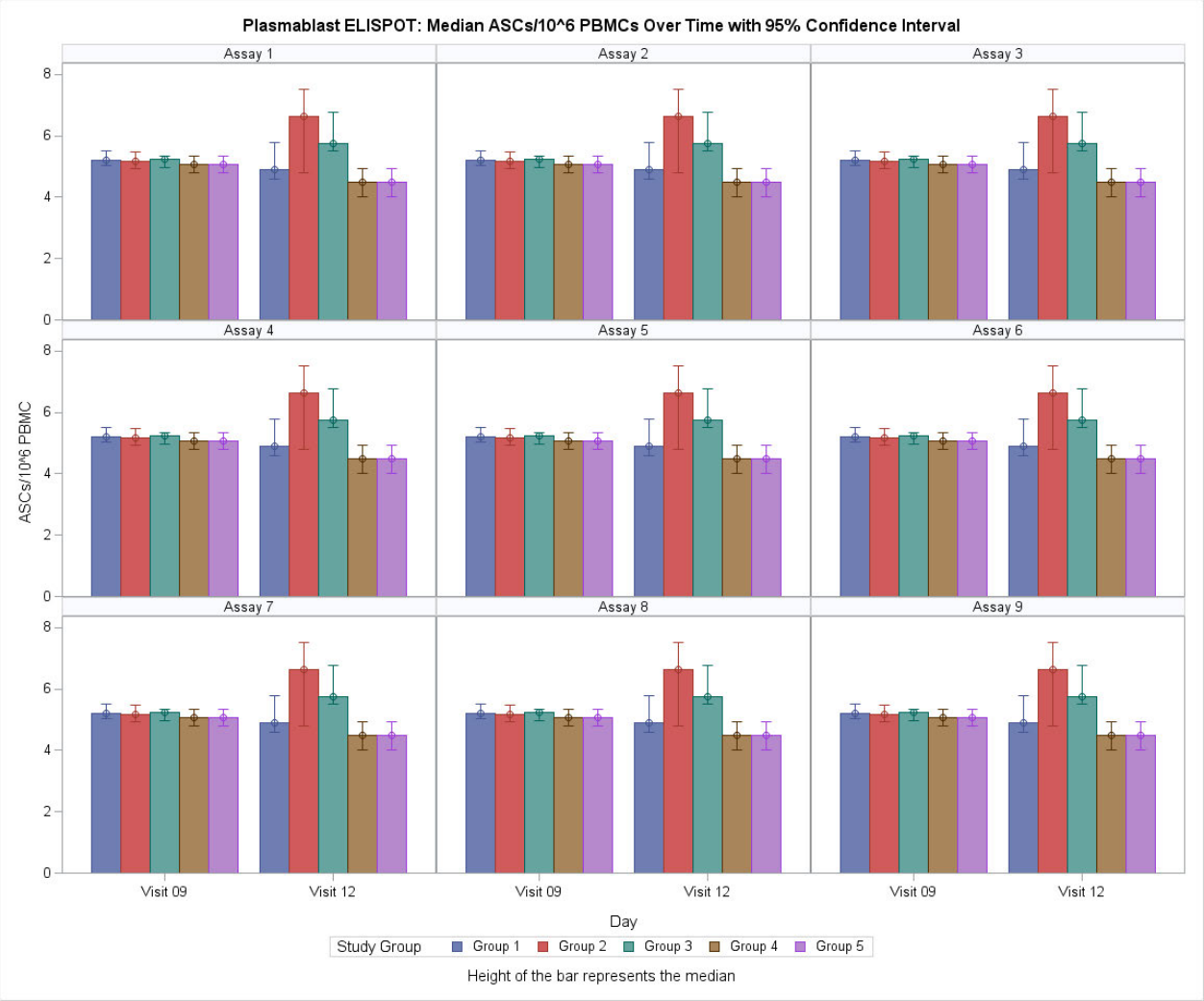
Figure 76: Passive transfer to mice with H1N1 challenge: Lung Virus GMT and 95% CI by Time Points Panel by Study Group- Day 3/Day 6 Post-Challenge Cohort

Figure 77: Memory B-Cell ELISPOT: Median ASCs/10^6 PBMCs Over Time with 95% Confidence Interval by Study Group and Priming Dose - cH6/1 HA IgG



Implementation Note: A generic sample figure is shown above. The x-axis will be relative study visits, which will be scaled appropriately, and y-axis will be the median ASC count. Median ASC count will be plotted at each visit with upper and lower error bars for the 95% confidence interval using the bootstrap method for each study group as well as overlay jitter data. “Assay X” will take the values from the University of Chicago analytical plan. Additional pooled group (Group 1 and Group 2) up to Visit 10 will be included.

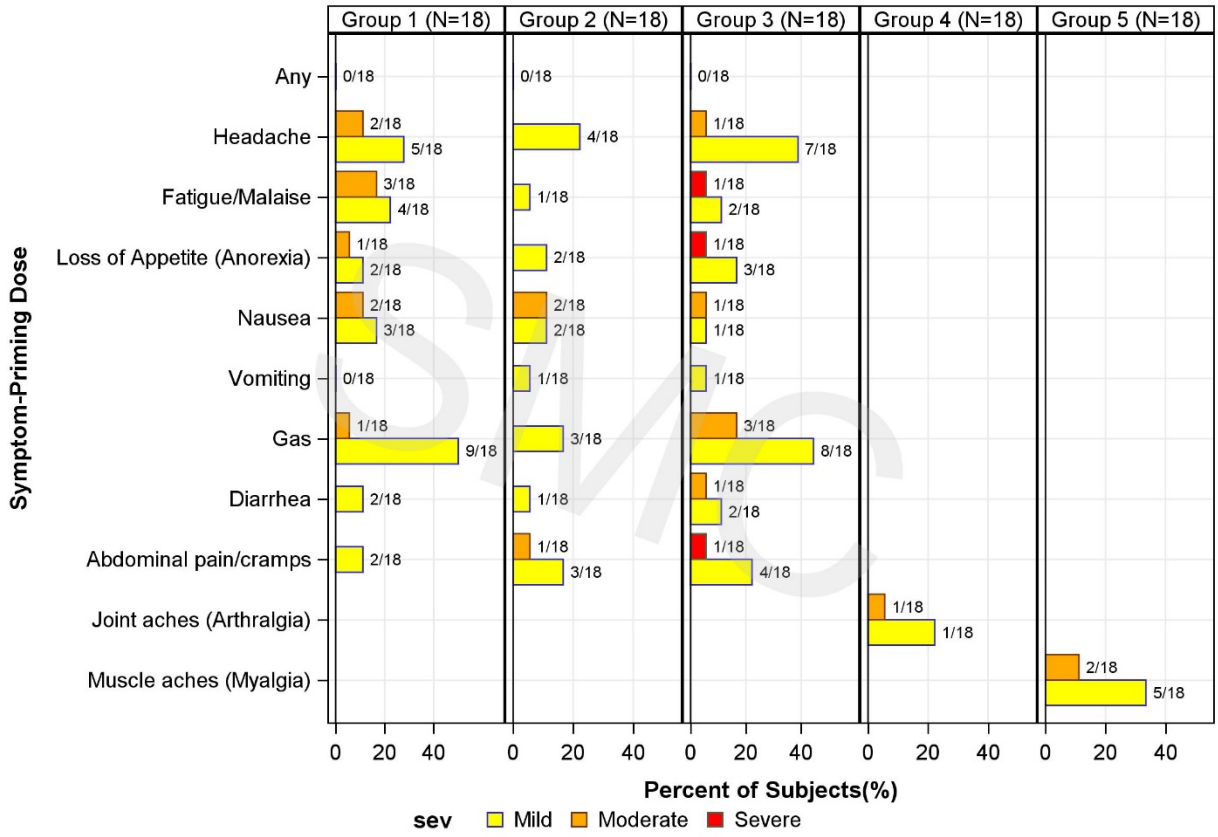
Figure 78: Plasmablast ELISPOT: Median ASCs/10^6 PBMCs Over Time with 95% Confidence Interval by Study Group and Priming Dose - cH6/1 HA IgG



Implementation Note: A generic sample figure is shown above. The x-axis will be relative study visits, which will be scaled appropriately, and y-axis will be the median ASC count. Median ASC count will be plotted at each visit with upper and lower error bars for the 95% confidence interval using the bootstrap method for each study group as well as overlay jitter data. “Assay X” will take the values from the University of Chicago analytical plan. Additional pooled group (Group 1 and Group 2) at Visit 9 will be included.

C. SAFETY

Figure 79: Maximum Severity of All Local Vaccination Reactions Within 7 days Following Priming Dose by Study Group and Study Product



Implementation Note: A Generic figure is shown above. A horizontal bar chart should be presented in a single figure with separate panels for each Study Group. Additional panel for pooled group (Group 1 + Group 2) will also be presented.

Figure 80: Maximum Severity of All General Vaccination Reactions Within 7 days Following Priming Dose by Study Group and Study Product

Figure 81: Maximum Severity of All Local Vaccination Reactions Within 7 days Following Boost Dose by Study Group and Study Product

Implementation Note: Similar figure will be presented. A horizontal bar chart should be presented in a single figure with separate panels for each Study Group. Additional panel for pooled group (Group 1 + Group 4 and Group 3 + Group 5) will also be presented.

Figure 82: Maximum Severity of All General Vaccination Reactions Within 7 days Following Boost Dose by Study Group and Study Product

Figure 83: Percentage of Unsolicited Adverse Events Within 28 Days Following Priming Dose, by MedDRA System Organ Class, Study Group, Study Product, and Maximum Severity

Implementation Note: Figure will be similar to the figure shown above. A vertical bar chart should be presented in a single figure with separate panels for each Study Group. Additional panel for pooled group (Group 1 and Group 2) will also be presented. The SOCs should be sorted in descending frequency.

Figure 84: Percentage of Unsolicited Adverse Events Within 28 Days Following Boost Dose, by MedDRA System Organ Class, Study Group, Study Product, and Maximum Severity

Implementation Note: Figure will be similar to the figure shown above. A vertical bar chart should be presented in a single figure with separate panels for each Study Group. Additional panels for pooled groups (Group 1 + Group 4 and Group 3 + Group 5) will also be presented. The SOCs should be sorted in descending frequency.

Figure 85: Percentage of Related Unsolicited Adverse Events Within 28 Days Following Priming Dose, by MedDRA System Organ Class, Study Group, Study Product, and Maximum Severity

Figure 86: Percentage of Related Unsolicited Adverse Events Within 28 Days Following Boost Dose, by MedDRA System Organ Class, Study Group, Study Product, and Maximum Severity

APPENDIX 3. LISTINGS

LIST OF LISTINGS

Listing 1 Discontinued Subjects

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

Listing 2 Subject Specific Protocol Deviation

Site	Study Group	Subject ID	DV Number	Deviation	Deviation Category	Study Visit	Reason for Deviation	Deviation Resulted in AE?	Deviation Resulted in Subject Termination?	Deviation Affected Product Stability?	Deviation Resolution	Excluded from PPP	Major/ Minor
Comment:													

Listing 3 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

Listing 4 Demographics

Study Group	Subject ID	Site	Sex	Age at Enrollment (years)	Height (cm)	Weight (kg)	Ethnicity	Race

Listing 5 Pre-Existing Conditions

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

Listing 6 Treatment Compliance

Study Group	Subject ID	Dose Number	Dose Assigned	Dose Administered

Listing 7 Immunogenicity Listing-ELISA

			Baseline	Visit 10		Visit 11		Visit 13		Visit 15	
Study Group	Subject ID	Antibody/Antigen	Titer	Titer	Fold Rise	Titer	Fold Rise	Titer	Fold Rise	Titer	Fold Rise

Listing 8 Immunogenicity Listing- CMI

Study Group	Subject ID	Assay type	Visit	Antigen/Virus	Results ASCs/106 PBMCs

Listing 9 Immunogenicity Listing- MN

			Baseline	Visit 10		Visit 11		Visit 13		Visit 15	
Study Group	Subject ID	Virus Strain	Result	Result	Fold Rise	Result	Fold Rise	Result	Fold Rise	Result	Fold Rise

Listing 10 Immunogenicity Listing- HI

			Baseline	Visit 10		Visit 11		Visit 13		Visit 15	
Study Group	Subject ID	Virus Strain	Result	Result	Fold Rise	Result	Fold Rise	Result	Fold Rise	Result	Fold Rise

Listing 11 Local and General Solicited Adverse Events

Study Group	Subject ID	Dose Number	Post Dose Window/Day	Type	Symptom	Severity	Ongoing at 7 Days
			60min/Day 1/Day 2,,,				

Listing 12 Unsolicited Adverse Events

Study Group	Subject ID	Adverse Event	Associated with Dose No.	Onset Day (Duration)	Severity	SAE	MAE	pIMD	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
Comment:															

Listing 13 Clinical Lab Values – Hematology

Study Group	Subject ID	Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Change from Baseline	Result (Severity Grade)	Reference Range Low	Reference Range High

Listing 14 Clinical Lab Values – Chemistry

Study Group	Subject ID	Time Point	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Change from Baseline	Result (Severity Grade)	Reference Range Low	Reference Range High

Listing 15 Vital Signs

Study Group	Subject ID	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 16 Physical Exam Findings

Study Group	Subject ID	Exam Visit	Any Abnormalities	Body System	Abnormal Finding	Reported as an AE? (AE Description; Number)	Targeted Physical Exam Performed
		Screening	(Y/N)				(Y/N)

Listing 17 Nasal/Oropharyngeal Shedding of Vaccine Virus Listing

Study Group	Subject ID	Component	Visit 02	Visit 04	Visit 05	Visit 06	Visit 07	Visit 08
		RT-PCR (Positivity)						
		MDCK (Positivity)						
		MDCK (FFA Result)						

Listing 18 Concomitant Medications

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

Listing 19 Pregnancy Report - Maternal Information

Study Group	Subject ID	Reported Pregnancy Date	Pregnancy Test Date	Pregnancy Status	Estimated Date of Delivery	Number of Fetuses	Actual Date of Delivery	Maternal Complications	Action Taken with Study Product	Study Status	Comments

Listing 20 Pregnancy Report - Gravida and Para

				Live Births												
Study Group	Subject ID	Pregnancy Number	Gravida	Extremely PB[a]	Very Early PB[a]	Early PB[a]	Late PB[a]	Early TB[b]	Full TB[b]	Late TB[b]	Post TB[b]	Still Births	Spontaneous Abortion/ Miscarriage	Elective Abortions	Therapeutic Abortions	Major Congenital Anomaly with Previous Pregnancy?

Note: Gravida includes the current pregnancy, para events do not.

[a] Preterm Birth

[b] Term Birth

Listing 21 Pregnancy Report - Live Birth Outcomes

Study Group	Subject ID	Pregnancy Number	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Live Birth	Size for Gestational Age	Apgar Score, 1 minute	Apgar Score, 5 minutes	Cord pH	Congenital Anomalies?	Illnesses/ Hospitalizations within 1 Month of Birth?

Note: Congenital Anomalies are included in the Adverse Event listing.

Listing 22 Pregnancy Report - Still Birth Outcomes

Study Group	Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Fetal Distress During Labor and Delivery?	Delivery Method	Gestational Age at Still Birth	Size for Gestational Age	Cord pH	Congenital Anomalies?	Autopsy Performed?	If Autopsy, Etiology for Still Birth Identified?

Listing 23 Pregnancy Report - Spontaneous, Elective, or Therapeutic Abortion Outcomes

Study Group	Subject ID	Date of Initial Report	Fetus Number	Pregnancy Outcome (for this Fetus)	Gestational Age at Termination	Abnormality in Product of Conception?	Reason for Therapeutic Abortion