CLINICAL RESEARCH IN INFECTIOUS DISEASES

STATISTICAL ANALYSIS PLAN

for

DMID Protocol: 14-0112

Study Title:

A Phase II, Double-Blind, Multicenter, Randomized, Placebo-Controlled Trial to Assess the Safety, Reactogenicity and Immunogenicity of Two Doses of Multimeric-001 (M-001) Followed by Seasonal Quadrivalent Influenza Vaccine

NCT 03058692

Version 1.0

DATE: 09 September 2019

STUDY TITLE

Protocol Number Code:	**DMID Protocol: 14-0112**
Development Phase:	Phase II
Products:	1. M-001 manufactured by BiondVax 2. Licensed seasonal quadrivalent inactivated influenza vaccine (IIV4) 3. Normal saline placebo
Form/Route:	Intramuscular (all products)
Indication Studied:	Influenza
Sponsor:	Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health
Clinical Trial Initiation Date:	9 April 2018
Clinical Trial Completion Date:	Expected April 2020
Date of the Analysis Plan:	09 September 2019
Version Number:	1.0

This study was performed in compliance with Good Clinical Practice.

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AESIs	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C	Celsius
CFR	Code of Federal Regulations
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data and Safety Monitoring Board
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
ER	Emergency Room
F	Fahrenheit
GBS	Guillain-Barre Syndrome
GGT	Gamma Glutamyl Transferase
GMT	Geometric Mean Titer
GMP	Geometric Mean Percentage
GMFR	Geometric Mean Fold Rise
HAI/HI	Hemagglutinin Inhibition
ICH	International Conference on Harmonisation
IIV	Inactivated influenza vaccine
IIV4	Quadrivalent inactivated influenza vaccine
IRB	Institutional Review Board
ITT	Intention to Treat
L	Liter
LLN	Lower Limit of Normal
M-001	Multimeric-001

List of Abbreviations *(continued)*

mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mEq	Milliequivalent
mg	Milligram
mITT	Modified Intent-to-Treat
mL	Milliliter
MAR	Missing at Random
MCAR	Missing Completely at Random
MN	Micro Neutralization (refers to neutralization antibodies)
MNAR	Missing Not at Random
N	Number (typically refers to subjects)
Neut	Neutralization (refers to neutralization antibodies)
NIH	National Institutes of Health
PBS	Phosphate Buffered Saline
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
PT	Preferred Term
RBC	Red Blood Cell
RCD	Reverse Cumulative Distribution
SAE	Serious Adverse Event
SCR	Seroconversion Rate
SD	Standard Deviation
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOC	System Organ Class
SOP	Standard Operating Procedures
U	Units
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

1. PREFACE

This Statistical Analysis Plan (SAP) for DMID Protocol 14-0112, "A Phase II, Double-Blind, Multicenter, Randomized, Placebo-Controlled Trial to Assess the Safety, Reactogenicity and Immunogenicity of Two Doses of Multimeric-001 (M-001) Followed by Seasonal Quadrivalent Influenza Vaccine", 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 (TFLs) planned for the final analyses. Regarding the final analyses and Clinical Study Report (CSR), this SAP follows the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, as indicated in Topic E3 (Structure and Content of Clinical Study Reports), and more generally is consistent with Topic E8 (General Considerations for Clinical Trials) and Topic E9 (Statistical Principles for Clinical Trials). The structure and content of the SAP provide sufficient detail to meet the requirements identified by the FDA and ICH, while all work planned and reported for this SAP will follow internationally accepted guidelines published by the American Statistical Association and the Royal Statistical Society for statistical practice.

This document contains four sections: (1) a review of the study design, (2) general statistical considerations, (3) comprehensive statistical analysis methods for safety and immunogenicity outcomes, and (4) a list of proposed tables, figures, and listings. Within the table, figure, and listing mock-ups (Appendices 1, 2, and 3, respectively), references to CSR sections are included. Any deviation from this SAP will be described and justified in amendments to this SAP 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

Seasonal influenza occurs annually, and in the United States it causes an estimated 100 to 600 thousand hospitalizations annually and up to 50,000 deaths a year [1,2,3]. The continued emergence of novel influenza A viruses in humans—including subtypes H5N1, H3N2v, H7N7, H9N2, 2009 H1N1, and most recently H7N9, underscores the need for focused efforts to prepare for the next influenza pandemic [4-9]. Current licensed inactivated influenza vaccines (IIVs) are good for preventing influenza but are less effective than desired. One approach to improve the effectiveness of IIVs is to prime the immune system with epitope-based vaccines. The M-001 vaccine from BiondVax consists of [redacted] that are [redacted] The epitopes in the vaccine are common to a large majority of influenza virus strains, and the epitopes are recognized by both the *humoral* and *cellular* arms of the immune system [10].

The goal of this clinical trial is to assess in healthy adults the safety, reactogenicity, and immunogenicity of two doses of multimeric-001 (M-001) vaccine followed by the 2018-2019 seasonal quadrivalent IIV (IIV4).

2.1. Purpose of the Analyses

These analyses will assess the safety, reactogenicity, and immunogenicity of two doses of M-001, manufactured by BiondVax, or saline placebo, followed by a single dose of seasonal IIV4 for up to 200 days after the first study vaccination. They will be presented in the CSR, with a subset for compilation in a "topline" report for expedited delivery (exhibits indicated by asterisks in the appendices).

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objectives

Safety

- To assess the safety as measured by vaccine related adverse events, reactogenicity, and laboratory adverse events of two doses of M-001 vaccine, each dose administered approximately 21 days apart

Immunogenicity

- To assess the T cell responses to M-001 component peptides following two doses of M-001

3.1.2. Secondary Objectives

Safety

- To assess all serious adverse events (SAEs) following receipt of each dose of M-001 vaccine or placebo, each dose separated by approximately 21 days, through the end of the study
- To assess all unsolicited non-serious AEs following receipt of each dose of M-001 or placebo, each dose separated by approximately 21 days, through 21 days after each dose of M-001 or placebo

Immunogenicity

- To assess the serum HAI and Neut antibody responses to the 2018-2019 IIV4 vaccine viruses

3.1.3. Exploratory Objectives

Immunogenicity

- To assess the IgG responses to the M-001 vaccine after receipt of placebo or two doses of M-001 vaccine and following receipt of licensed IIV4
- To assess the T cell responses to M-001 component peptides following one dose of M-001 or placebo
- To assess T cell responses to M-001 component peptides following receipt of licensed IIV4
- To assess the T cell cross-reactive responses to current seasonal influenza virus antigens and pandemic influenza virus antigens following each vaccination (M-001 and IIV4)
- To assess the longevity of T cell responses to M-001 peptides, seasonal influenza virus antigens and pandemic influenza virus antigens

3.2. Outcome Measures

3.2.1. 3.2.1 Primary Outcome Measures

Safety

- Occurrence of vaccine-related SAEs from the time of the first study vaccination (M-001 or placebo) through approximately 6 months after the second M-001 study vaccination
- Occurrence of solicited injection site and systemic reactogenicity events on the day of each study vaccination through approximately 7 days after each M-001 vaccination
- Occurrence of clinical safety laboratory adverse events from the time of each study vaccination of M-001 through approximately 7 days after each M-001 vaccination

Immunogenicity

- Geometric Mean Percentage of T cell subsets expressing perforin, CD107a, IFN-γ, TNF-α, and IL2, alone or in combination, in CD4 and CD8 cells after stimulation with M-001 component peptides at baseline (Day 1) and 14 days after the second dose of M-001

3.2.2. Secondary Outcome Measures

Safety

- Occurrence of all SAEs, from the time of receiving the first M-001 or placebo study vaccination through the end of the study
- Occurrence of all unsolicited non-serious AEs from the time of first study vaccination through 21 days after each M-001 vaccination

Immunogenicity

- For HAI and Neuts, the percentage of subjects achieving seroconversion (defined as either a pre-vaccination titer <10 and a post-vaccination titer ≥40 or a pre-vaccination titer ≥10 and a minimum four-fold rise in post-vaccination antibody titer) to IIV4 vaccine viruses from Day 172 to Day 200
- For HAI and Neuts, the percentage of subjects with an antibody titer of 40 or greater and geometric mean titers (GMTs) vs. IIV4 vaccine viruses on Days 1, 43, 172 and 200

3.2.3. Exploratory Outcome Measures

Immunogenicity

- Percentage of subjects achieving seroconversion (defined as a minimum four-fold rise in post-vaccination ELISA antibody titer) and GMTs of ELISA antibody vs. M-001 from Day 1 to Days 22, 43, 78, 172 and 200
- Geometric Mean Percentage of T cell subsets expressing perforin, CD107a, IFN-γ, TNF-α, and IL2, alone or in combination in CD4 and CD8 cells after stimulation with M-001 peptides at baseline (Day 1) and approximately 14 days after one dose of M-001, 56 days following the second dose of M-001, and immediately prior to and 14 and 28 days after IIV4
- Percentage of T cell subsets expressing perforin, CD107a, IFN-γ, TNF-α, and IL2, alone or in combination, in CD4 and CD8 cells after stimulation with other influenza A antigens (including

seasonal and pandemic influenza antigens) at baseline (Day 1), approximately 14 days after each study vaccination, 56 days following the second study vaccination and immediately prior to and approximately 28 days after IIV4

- Percentage of influenza-specific T cell memory subsets expressing discrete memory markers (CCR7, CD45RO, and CD57) at baseline (Day 1), approximately 56 days after the second dose of placebo or M-001 and immediately prior to and approximately 28 days after the IIV4 dose

3.3. Study Definitions and Derived Variables

Geometric mean percentages (GMPs) are calculated as the product of the observed percentages raised to the $1/N^{th}$ root, where N is the number of observed values.

The baseline value for cellular and humoral immunity will be defined as the value obtained on Day 1 prior to M-001 vaccination.

M-001 antibody response after baseline will be summarized by GMTs and the proportion of subjects achieving seroconversion (defined as a minimum four-fold rise in post-vaccination ELISA antibody titer) at each time point, with corresponding 95% confidence intervals.

For individual subjects, fold rise will be calculated as the ratio of: $\frac{post-vaccination\ titer}{pre-vaccination\ titer}$, where pre-vaccination value is always the result obtained at Day 1, prior to the first M-001 dose.

Seroconversion for HAI and Neut assays is defined as either a pre-vaccination titer < 1:10 and a post-vaccination titer ≥ 1:40, or a pre-vaccination titer ≥ 1:10 and a minimum four-fold rise in post-vaccination titer.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

DMID 14-0112 is a Phase II randomized, double-blind, placebo-controlled trial in a sample of 120 males and non-pregnant females, 18 to 49 years old, inclusive, who are in good health and meet all eligibility criteria. This clinical trial is designed to assess the safety, reactogenicity, and immunogenicity of two priming doses of M-001 followed by administration of IIV4.

Subjects are assigned randomly to 1 of 2 study arms (60 subjects per study arm) to receive two doses of the M-001 vaccine or placebo followed by a single dose of IIV4 (see Table 1).

- Group A receives two 1 mg doses of M-001, on Days 1 and 22 followed by a single dose of IIV4 on approximately Day 172 (±30).
- Group B receives saline placebo on both Days 1 and 22, followed by a single dose of IIV4 approximately on Day 172 (±30).

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

This study uses a placebo concurrent control design. Saline was chosen to act as an inactive placebo control as a comparator for the safety, reactogenicity, and immunogenicity of two doses of M-001 vaccine as well as for the downstream immunogenic effects post-seasonal IIV4 vaccination.

4.3. Selection of Study Population

The study population for this clinical trial is 120 males and non-pregnant females, 18-49 years of age, inclusive, who meet all eligibility criteria. Eligibility criteria ensure that subjects are in good health at the time of vaccination and have not received (and do not plan to receive) therapies that would interfere with immune response to the study products, such as non-study vaccines or immunosuppressive therapies. Exact eligibility criteria can be found in the protocol sections 5.1 and 5.2. Subjects are recruited from the general population at the participating Vaccine Trial and Evaluation Unit (VTEU) sites that have substantial experience conducting large influenza vaccine studies.

4.4. Treatments

4.4.1. Treatments Administered

Two doses of either multimeric M-001 vaccine or saline placebo are administered per subject's randomized assignment, followed by administration of seasonal IIV4 vaccine to all subjects.

4.4.2. Identity of Investigational Product(s)

Seasonal Quadrivalent Inactivated Influenza Vaccine (IIV4)

IIV4 for intramuscular injection is indicated for active immunization against influenza disease caused by influenza virus subtypes A and type B present in the vaccine. The 2018-2019 Fluzone Quadrivalent IIV4 used in the study was formulated by Sanofi to contain HA of each of the following four influenza strains recommended for the 2018-2019 Northern Hemisphere influenza season: A/Michigan/45/2015 X-275 (H1N1), A/Singapore/INFIMH-16-0019/2016 IVR-186 (H3N2), B/Maryland/15/2016 BX-69A (a B/Colorado/06/2017-like virus, B Victoria lineage), and B/Phuket/3073/2013 (Yamagata lineage).

M-001

Multimeric-001 (M-001) vaccine developed by BiondVax is [redacted]

Placebo

Sterile normal saline will be used as the placebo.

4.4.3. Method of Assigning Subjects to Study Arms (Randomization)

Enrollment/randomization is done through the enrollment module in the electronic data capture system, maintained by the SDCC.

Eligible subjects are randomized and assigned in a [1:1] ratio to receive two priming doses 21 days apart of either M-001 (Group A) or saline placebo (Group B), followed by seasonal IIV4 vaccination (all groups). Randomization is stratified by prior receipt of the 2017-2018 influenza vaccine and by site. The randomization is based on a variable blocked scheme to provide an approximately balanced allocation to the study arms during the study.

4.4.4. Selection of Doses in the Study

Multiple studies of M-001 have assessed the safety and immunogenicity profile in healthy adults, and their results suggested that immune responses were improved with increasing doses up to 1 mg, with no safety concerns identified. The 1 mg dosage was selected for this trial based on the elevated HAI antibody responses in that study group in the placebo-controlled BVX-006 trial [NCT02293317], where no SAEs or safety concerns were observed.

4.4.5. Selection and Timing of Dose for Each Subject

All subjects receive the assigned vaccination at Day 1 and Day 22 (+2 days), followed by a single dose of IIV4 on approximately Day 172 (±30 days).

4.4.6. Blinding

This trial is double-blinded; subjects, investigators, study personnel performing any study-related assessments following study vaccine administration, and laboratory personnel performing antibody assays are blinded to the treatment assignment.

The randomization scheme was generated by the SDCC and provided to unblinded study personnel (i.e., pharmacists performing study vaccination preparations and unblinded study vaccine administrators) at the participating VTEU sites who are not involved in study-related assessments or have subject contact for data collection following study vaccine administration.

The Data and Safety Monitoring Board (DSMB) receives data in aggregate and presented by group and may request treatment assignment be unblinded for an individual subject if required for safety assessment. The DSMB reviews grouped and unblinded data in the closed session only.

4.4.7. Prior and Concomitant Therapy

Concomitant medications include any medications, therapies, or vaccinations taken in the 60 days prior to Day 1 through approximately 21 days after the last M-001/placebo dose received. Medications reported in the electronic case report form (eCRF) are limited to those taken within 30 days prior to the first study

vaccination through approximately 21 days after the second M-001/placebo dose. In addition, receipt of any non-study vaccines is solicited at each clinic visit or phone call and reported in the eCRF for the entire duration of the study.

Use of new medication should prompt evaluation for the presence of a new diagnosis of chronic medical disease or condition. Medications that might interfere with the evaluation of the investigational product were not to be used unless absolutely necessary. Medications in this category include the prohibited medications per the Subject Exclusion Criteria. In addition, the site PI or appropriate staff may identify other mediations that should not be used due to a risk to subject safety or assessment of reactogenicity and immunogenicity.

4.4.8. Treatment Compliance

All subjects receive two doses of either M-001 or saline placebo followed by seasonal IIV4 administered in the clinic.

4.5. Immunogenicity and Safety Variables

See Table 2 for the schedule of study procedures in DMID protocol 14-0112.

4.5.1. Safety Variables

Safety will be assessed by the frequency and severity of:

1. All SAEs occurring from the time of the first study vaccination through the end of the study
2. Solicited AEs – reactogenicity events occurring on the day of each study vaccination through 7 days after each M-001 study vaccination:
    a) Injection site reactions including pruritus, ecchymosis, erythema, induration/swelling, pain, and tenderness.
    b) Systemic reactions including fever, feverishness, fatigue, malaise, myalgia, arthralgia, headache, and nausea.
3. Unsolicited AEs – non-serious AEs occurring from the time of the first M-001 study vaccination through approximately 21 days after the second M-001 study vaccination.
4. Safety laboratory abnormalities occurring from the time of the first study vaccination through 8 days after the last dose of M-001.
    a) Clinical safety laboratory parameters measured: WBC, hemoglobin, platelets, ALT, total bilirubin, and creatinine

4.5.2. Immunogenicity Variables

Cellular immunogenicity data will be reported by the Baylor College of Medicine. These data will include the frequency of influenza-specific T cells as measured by fluorescence-based flow cytometric assays. The lab at Baylor will also report the percentage of influenza-specific T cells expressing discrete memory markers (CCR7, CD45RO, and CD57), the percentage of CD4 and CD8 T cells expressing perforin, CD107a, IFN-γ, TNF-α, and IL2, alone or in combination, the percentage of CD4+ T cell subsets expressing IL-4 or IL-17, T follicular helper (TFH) cells (CD4+, CXCR5+, PD-1+, IL-21+) , T follicular regulatory (Tfr) cells (CXCR5+, PD-1+, CD25+, CD127+) , and T regulatory cells (Tregs) (CD25+, Foxp3+)as measured by flow cytometry.

Individual HAI and Neut antibody results will be reported for the IIV4 vaccine strain by the central immunology laboratory at St Louis University. Assay results are reported as a reciprocal titer with values of $10*2^k$, where k=0, 1, 2, etc. The lower limit of detection for both the HAI and Neut assays is 1:10; values below the limit of detection are reported as '<10', and for analysis are imputed as one-half the limit of detection (10/2 = 5). For analysis, the geometric mean of repeated results for each sample will be computed and used as the response for all subsequent calculations. The variation arising from multiple measurements for an individual at a single time point will not be used in subsequent calculations. See Section 3.3 for definitions of derived variables for the analysis of HAI and Neut data.

Assays to determine serum levels of antibodies to M-001 will be performed by BiondVax.

5. SAMPLE SIZE CONSIDERATIONS

The study population for this clinical trial was planned to include 120 males and non-pregnant females, 18 to 49 years old, inclusive, who are in good health and meet all eligibility criteria. The subjects were recruited from the general population at the participating VTEU sites that have substantial experience conducting large influenza vaccine studies.

Based on the accrual rate for similar studies, it was expected that the participating VTEUs would be able to enroll this trial in a timely fashion. Prior experience suggests up to 5% of subjects could be excluded from the per protocol analysis for the primary immunogenicity outcome either because they are lost-to-follow-up or otherwise do not have data available following the second study vaccination or because they had a protocol deviation requiring their exclusion from the per protocol analysis.

Table 3 indicates the probability of observing one or more safety events, such as solicited injection site or systemic reactogenicity events or an unsolicited non-serious AE of a particular type, for a single study arm (N=60) and all enrolled subjects (N=120).

Binomial confidence intervals (CI) are widest (have the least precision) when the response rate is 50%. Table 4 is presented to indicate the worst-case scenario for precision of observed exact (Clopper-Pearson) binomial confidence intervals.

With N=60 subjects per arm and assuming the standard deviation of log GMP is 0.75, the study will have 80% power to detect a 2.5-fold increase in the GMP of T cell subsets expressing IFN-γ. Table 5 illustrates a power analysis considering a range of standard deviations for log GMP and a range of GMP fold-change with N=60 subjects per arm, and further includes the power under the conservative assumption of 10% drop out in each study arm. Power is calculated for a two-sided t-test with significance level (alpha) 0.05 using PROC POWER in SAS 9.4. Utilizing different tests instead of those based on Normal approximations could increase the power from what is shown.

While there will be multiple comparisons performed for this primary immunogenicity objective (for each of five parameters alone measured in CD4 and CD8 T cells plus any combinations measured), it is assumed that these analyses are not intended to be confirmatory and thus no adjustment for multiple comparisons is considered. Instead, p-value thresholds of $p<0.001$, $p<0.01$, and $p<0.05$ will be considered as strong, moderate, and weak evidence of differences between study arms. These will be indicated in relevant tables with ***, **, and *, respectively.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. General Principles

All continuous variables, unless otherwise specified, will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, minimum and maximum. Titers will be summarized with geometric means, first across replicates to compute one value for each individual sample and then across subjects within a study group. Percentages of cell types will also be summarized by geometric means within each study group. The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures. In general, all data will be listed, sorted by treatment and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each vaccination group in the order presented in Table 1 and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

If a substantial number of subjects meet eligibility criteria, but had intercurrent infections that might affect the immunoassay results for the vaccine strains, sensitivity analyses will be performed excluding those and qualitative comparisons will be made with the mITT and PP analyses.

6.2. Timing of Analyses

No interim analysis is planned.

The final analysis will be performed after the last subject completes the final visit, and the database is cleaned, monitored, and locked. A topline report will be generated upon receipt and processing of immunogenicity data (T cell responses after stimulation with M-001 peptides and with other Influenza A antigens, and M-001 ELISA responses) through Day 200. Tables and figures to be included have an asterisk following the title.

The CSR will be completed when all primary and secondary endpoint data are available. All available exploratory endpoint data will be included in the CSR, and additional data not available at the time of CSR generation will be included in one or more addendums, depending on the timing of each set of exploratory assays.

6.3. Analysis Populations

A tabular listing of all subjects, visits, and observations excluded from the analysis populations will be provided in Listing 5. In the case of mis-randomization, subjects will be analyzed according to the study product actually received for all analysis populations.

6.3.1. Modified Intent-to-Treat (mITT) Population

The modified intent-to-treat (mITT) population includes all subjects who received at least one dose of study vaccine and contributed at least one post-study vaccination venous blood sample for immunogenicity testing for which valid results were reported.

6.3.2. Per Protocol Population

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

- Data from all available visits for subjects found to be ineligible at baseline
- Data from all visits subsequent to major protocol deviations, such as:
  - Second or third study vaccination not received

- Second or third study vaccination received out of window
- Receipt of non-study licensed live vaccine within 30 days before or 21 days after each study vaccination
- Receipt of non-study licensed inactivated vaccine within 14 days before or 21 days after each study vaccination
- Receipt of non-study seasonal influenza vaccine (live or inactivated) within 30 days before or for the duration of the study
- Receipt of immunosuppressive therapy (e.g., corticosteroids) within 30 days before or after each of the first two study vaccinations (Dose 1 and Dose 2)

- Data from any visit that occurs out of window
  - Visit 03: Day 14 + 2 days post vaccination 1
  - Visit 04: Day 22 + 2 days post vaccination 1
  - Visit 06: Day 14 + 2 days post vaccination 2
  - Visit 07: Day 21 + 7 days post vaccination 2
  - Visit 08: Day 56 + 7 days post vaccination 2
  - Visit 09: Day 150 ± 30 days post vaccination 2
  - Visit 10: Day 14 + 3 days post vaccination 3
  - Visit 11: Day 28 + 7 days post vaccination 3

6.3.3. Safety Analysis Population

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

6.4. Covariates and Subgroups

The protocol does not define any formal subgroup analyses, and the study is not adequately powered to perform subgroup analyses.

6.5. Missing Data

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 judgement 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.

6.6. Interim Analyses and Data Monitoring

Interim safety data is reviewed by the DSMB as described in Protocol Section 9.6.2. Interim summary reports for the DSMB safety review include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, solicited reactogenicity events and unsolicited AE/SAEs. There were no formal interim analyses planned.

6.7. Multicenter Studies

Data will be pooled across all three 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 endpoints.

6.8. Multiple Comparisons/Multiplicity

While there will be multiple comparisons performed for the primary immunogenicity objective (for each of five parameters alone measured in CD4 and CD8 T cells plus any combinations measures), it is assumed that these analyses are not intended to be confirmatory and thus no adjustment for multiple comparisons is considered.

7. STUDY SUBJECTS

7.1. Disposition of Subjects

The disposition of subjects in the study will be tabulated by study arm (Table 13). The table shows the total number of subjects screened, enrolled, received treatment, received all treatment, completed follow-up, completed the final blood draw, and the number completing the study. The composition of analysis populations, including reasons for subject exclusion is presented by study arm in Table 14. The dates of each study vaccination will be summarized by site and study arm in Table 15, and a summary of screening failures will be presented in Table 16.

A flowchart showing the disposition of study subjects, adapted from the Consort Statement [11] will be included (Figure 1). This figure will present the number of subjects screened, enrolled, lost to follow-up, and analyzed, by study arm.

A listing of subjects who discontinued dosing or terminated from study follow-up and the reason will be included in Listing 2. A listing of all subjects receiving investigational product will be given in Listing 1.

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 arm for all subjects (Table 6). Deviations that are considered major deviations that will be reviewed for possible subject exclusion from the per protocol population include: second or third study vaccination not received, second or third study vaccination received out of window, receipt of non-study licensed live vaccine within 30 days before or 21 days after each study vaccination, receipt of non-study licensed inactivated vaccine within 14 days before or 21 days after each study vaccination, receipt of non-study seasonal influenza vaccine (live or inactivated) within 30 days before or for the duration of the study, and receipt of immunosuppressive therapy within 30 days before or after each of the first two study vaccinations. All subject-specific protocol deviations and non-subject specific protocol deviations will be included in Appendix 3 as data listings (Listing 3 and Listing 4, respectively).

8. IMMUNOGENICITY EVALUATION

Analysis of all immune responses will be conducted using the PP population. In addition, for the primary endpoint, analysis conducted with the mITT population will be used as a sensitivity analysis. Percentages of cell subset responses will be measured by flow cytometry as described in Section 4.5.2.

Data listings of HAI and Neut assay results as reported by the central immunogenicity laboratory will be provided in Listing 8, Listing 9, Listing 10, Listing 11, Listing 12, Listing 13, Listing 14, and Listing 15. ELISA assay results will be provided in Listing 16, and flow cytometry results will be provided in Listing 17 and Listing 18.

8.1. Primary Immunogenicity Analysis

The primary immunogenicity objective is to determine whether priming with M-001 improves T cell responses. The cells are sorted via flow cytometry, and the percentages of CD4+ and CD8+ T cells expressing perforin, CD107a, IFNγ, TNF-α, IL-2, or any combination of these are calculated as the number of cells positive for these proteins divided by the total number of T cells counted in each sample. To compare the T cell responses between groups, the following Poisson regression model will be fit for each combination of proteins of interest:

$$\log(E(Y|X)/Z)=\beta_0+ \beta_1*X,$$

where Y is the number of cells expressing a given combination of proteins, X is an indicator variable for Group A, and Z (the offset) is the total number of T cells in each sample. Wald tests will be performed to evaluate whether there are differences in the expression of T cell subsets between the two study arms. As described in Section 6.8, adjustments for multiple comparisons are not planned.

GMPs of CD4+ and CD8+ T cells expressing each combination of proteins and the corresponding 95% bootstrap confidence intervals will also be presented for each study armTable 22Table 23Table 24Table 25. These will be presented in Table 22 , Table 23, Table 24, and Table 25 and summarized visually in boxplots over time in in Figure 2, Figure 3, Figure 4, and Figure 5.

8.2. Secondary Immunogenicity Analyses

Humoral immune responses in terms of strain-specific IIV4 HAI and Neut antibody titers will be summarized by study arm at each time point. Descriptive summary statistics will be provided for all assays and time points including number of subjects with non-missing results, number and percentage of subjects with titers ≥1:40, number and proportion of subjects achieving seroconversion, and GMTs along with corresponding 95% CIs. Clopper-Pearson exact confidence intervals will be presented for proportion endpoints. Summaries of humoral immunogenicity endpoints are presented in Table 30, Table 31, Table 32, Table 33, Table 34, Table 35, Table 36, and Table 37.

HAI and Neut seroconversion by Day 172 or Day 200, the percentage of subjects with titer ≥40, and GMT's against the 2018-2019 IIV4 vaccine strain on Days 1, 43, 182, and 200 will be summarized as described above.

The reverse cumulative distributions of HAI and Neut assays against each strain will be displayed in Figure 10, Figure 11, Figure 12, Figure 13, Figure 14, Figure 15, Figure 16, and Figure 17. The Spearman correlation between HAI, Neut, and M-001 antibody titers will be calculated at each time point over all groups. The correlation will be depicted in scatter plots beginning at Figure 18 and continuing through Figure 29.

8.3. Exploratory Immunogenicity Analyses

ELISA seroconversion and GMTs of the ELISA antibody against M-001 from Day 1 to Days 22, 43, 78, 172, and 200 will be presented in Table 44.

Table 26Table 27Table 28Table 29

These percentages will be summarized visually in box plots over time in Figure 6, Figure 7, Figure 8, and Figure 9, for selected cell subsets.

GMPs of influenza-specific CD4+ T cell subsets expressing discrete memory markers (CCR7, CD45RO, and CD57) will be summarized at baseline (Day 1) and on study days 15, 36, 43, 78, 172, 186, and 200 (Table 38), by study arm. The subject-level percentages corresponding to selected cell subsets will be presented in Figure 30. Analogous summaries will be presented for CD8+ T cells in Table 39and Figure 31.

The percentage of influenza-specific CD4+ cell subsets expressing IL-4 or IL-17, T follicular helper cells (CD4+, CXCR5+, PD-1+, IL-21+), T follicular regulatory (Tfr) cells (CXCR5+, PD-1+, CD25+, CD127+), and Tregs (CD25+, Foxp3+) measured by flow cytometry will be summarized at baseline (Day 1) and on study days 15, 36, 43, 78, 172, 186, and 200 (Table 40, Table 41, Table 42, and Table 43, respectively). Boxplots for these percentages will also be presented in Figure 32, Figure 33, Figure 34, and Figure 35.

9. SAFETY EVALUATION

All summaries and analysis of safety data will be presented for the Safety Analysis population. Safety summaries will be presented overall and by study arm.

Continuous variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation, median, maximum, and minimum. All categorical measures will be summarized by the frequency and percentages of observed levels. The denominator for the percentages may be based on the number of non-missing observations for an assessment or based on the number of subjects in a population. This will be described for each table.

9.1. Demographic and Other Baseline Characteristics

Summaries of age, sex, ethnicity, race, BMI, and prior receipt of seasonal influenza vaccine will be presented by site (Table 17 and Table 18) and by vaccination group (Table 19 and Table 20). Age will be summarized as a continuous as well as categorical variable. Ethnicity is categorized as Hispanic or Latino, not Hispanic, and not Latino, Not Reported, or Unknown. In accordance with NIH reporting policy, subjects may self-designate as belonging to more than one race or may refuse to identify a race, the latter reflected in the eCRF as "No" to each racial option. BMI will be summarized as a continuous and a categorical variable, categorized as (<30, ≥30). Self-reported history of prior receipt of seasonal influenza vaccine will be categorized by influenza season (2016-17 only, 2017-18 only, both 2016-17 & 2017-18, neither, or unknown).

Individual subject listings will be presented for all demographics (Listing 6).

9.1.1. Prior and Concurrent Medical Conditions

All current illnesses and past pre-existing medical conditions will be coded using the Medical Dictionary for regulatory affairs (MedDRA®) coded version 22.0 or higher.

Summaries of subjects' pre-existing medical conditions will be presented by MedDRA System organ class (SOC) and study arm (Table 21).

Individual subject listings will be presented for all medical conditions (Listing 7).

9.2. Measurements of Treatment Compliance

All subjects were to receive three study vaccinations administered in the clinic. The number of study vaccinations administered to subjects will be presented by vaccine group as part of the subject disposition table (Table 13).

9.3. Adverse Events

An overall summary of all adverse events will be presented in Table 45. A summary of adverse events occurring in 5% or more of subjects in any study arm will be presented in Table 46.

9.3.1. Solicited Events and Symptoms

Solicited injection site and systemic reactogenicity events will be documented from the time of each study vaccination (Day 1 (Visit 01) and approximately Day 22 (Visit 04)) through 7 days after each study vaccination. They were graded on a scale of 0 (none), 1 (mild), 2 (moderate), and 3 (severe). Systemic events include fever, feverishness, fatigue, malaise, myalgia, arthralgia, headache, and nausea, and the grading scale for these can be found in Table 7. The grading scale for fever is included in Table 8. Injection site events

include pain, tenderness, pruritus, ecchymosis, erythema, and induration/swelling. Ecchymosis, erythema, and induration are measured by both functional and measurement grading scales defined in Table 9 and Table 10, respectively.

When calculating the incidence of solicited events, each subject will be counted once at the highest severity following the applicable dose, and any repetitions will be ignored. For summaries presented separately for each vaccination, the denominator for percentages will be the number of subjects who received the respective vaccination with non-missing data for the event summarized. For summaries over all vaccinations the denominator will be the number of subjects who received at least one vaccination with non-missing data for the event summarized.

Additionally, solicited AEs will be analyzed by dichotomizing the response into a binary variable (none vs mild, moderate, or severe) and using 95% CIs calculated using Clopper-Pearson methodology from a binomial distribution (SAS Proc Freq with a binomial option) to summarize the proportion of subjects reporting each symptom, any injection site symptom, and any systemic symptom (Table 47). Summaries of solicited AEs will be presented separately for each study vaccination as well as overall study vaccinations by study arm (Table 49, Table 50, Table 51, Table 52, and Table 53). A comparison of the proportion of subjects reporting solicited symptoms by study arm will be shown in Table 48, and the proportion of subjects reporting solicited symptoms between the first and second study vaccinations will be compared using McNemar's test in Table 54.

Listings of systemic and local solicited events will be presented in Listing 19 and Listing 20, respectively.

Listing 18Listing 19Figure 36Figure 37**Unsolicited Adverse Events**

Unsolicited, non-serious AEs were documented from the time of the first study vaccination (Day 1 (Visit 01)) through approximately 21 days after the second M-001 study vaccination (approximately Day 43 (Visit 07)), and SAEs were collected through the entire study duration (Day 200). All AEs will be MedDRA coded by for preferred term (PT) and SOC. Serious unsolicited adverse events will be reported by detailed listings showing the event description, MedDRA PT and SOC, relevant dates (study vaccinations and AE), severity, relatedness, and outcome for each event. Non-serious unsolicited AEs will be summarized as number and percentage of subjects reporting at least one event in each MedDRA PT and SOC, cross tabulated by severity and relationship to study product. Additionally, the proportion of subjects and exact 95% CIs (calculated in the same way as above) of AEs in aggregate and by MedDRA categories will be computed.

Unsolicited adverse events by subject will be presented in Listing 21.

The following summaries for unsolicited adverse events will be presented by MedDRA system organ class, preferred term, vaccination and study arm:

- Subject incidence and total frequency of adverse events over time by dose with 95% CI (Days 1-8, Days 9-22) (Table 55);
- Summary of severity and relationship to study product (Table 56);
- Subject incidence and total frequency of related adverse events over time (Table 57);
- Bar chart of AE incidence by severity and MedDRA system organ class and Study Arm (Figure 38);
- Bar chart of total frequency of AEs by relationship to study product and MedDRA system organ class and study arm (Figure 39);

- Bar chart of AE incidence by relationship to study product and MedDRA system organ class and Study Arm (Figure 40).

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

Serious Adverse Events were documented from the time of the first study vaccination (Day 1 (Visit 01)) through the end of the study.

A listing of death and other serious adverse events will be presented by Subject ID, Age (years) Adverse Event Description, Adverse Event Onset Date/End Date, Last Dose Received/Days Post Dose, Reason Reported as an SAE, Relationship to Treatment, Alternate Etiology if not Related, Outcome, and Duration of Event (days) (Table 58).

9.5. Pregnancies

For any subjects in the Safety population who became pregnant during the study, every attempt will be made to follow these subjects to completion of pregnancy to document the outcome, including information regarding any complications with pregnancy and/or delivery. Pregnancies and outcomes will be presented in Listing 27, Listing 28, Listing 29, Listing 30, and Listing 31.

9.6. Clinical Laboratory Evaluations

Clinical safety laboratory evaluations were performed at baseline and approximately 8 days after Dose 1 and Dose 2 of study vaccination. The grading scale for clinical laboratory evaluations will be presented in Table 12. Subject visits with abnormal laboratory results, Grade 1 severity or higher, will be presented in Table 59 and Table 60 for Chemistry and Hematology parameters, respectively.

The distribution of chemistry results by severity, study day, and vaccination group will be presented in Table 61, Table 62, Table 63, and Table 64. Descriptive statistics including mean, standard deviation, median, minimum, and maximum by study day, will be summarized for each parameter in Table 65, Table 66, and Table 67. Plots illustrating the change from baseline for each chemistry laboratory parameter will be presented in Figure 41.

The distribution of hematology results by severity, study day, and vaccination group will be presented in Table 68, Table 69, Table 70, and Table 71. Descriptive statistics including mean, standard deviation, median, minimum, and maximum by study day, will be summarized for each parameter in Table 72, Table 73, and Table 74. Plots illustrating the change from baseline for each hematology laboratory parameter will be presented in Figure 42.

A complete listing of individual clinical laboratory results will be presented in Listing 22 and Listing 23.

9.7. Vital Signs and Physical Evaluations

Vital sign measurements blood pressure, oral temperature, and pulse. Vital signs were assessed at Day 1, Day 22, and Day 172, and as needed at the other study visits. The grading system for vital signs can be found in Table 11. Vital signs will be tabulated by visit and study arm (Table 75, Table 76, Table 77, Table 78, and Table 79). A listing of vital findings will be presented in Listing 24.

Physical examinations may be conducted at any study visit based on indicated symptoms. A listing of physical exam findings will be presented in Listing 25.

9.8. Concomitant Medications

All current medications and medications taken in the 30 days before Study Day 1 (prescription and over-the-counter drugs) will be recorded in the eCRF, as well as vaccinations, vitamins, and supplements, through 21 days after the second M-001 study injection. All concomitant medications and vaccinations taken within 60 days prior to signing the ICF will be recorded on the appropriate data collection form prior to the first study vaccination. Concomitant medications (vaccines only) will be recorded on the appropriate data collection form after Visit 7 through the end of the study. Assessment of eligibility will also include a review of prohibited medications (per the exclusion criteria).

A by-subject listing of the concomitant medication use will be presented (Listing 26). The use of concomitant medications during the study will be summarized by ATC1, ATC2 code and study arm for the Safety population (Table 80).

10. REPORTING CONVENTIONS

P-values ≥0.001 and ≤0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001" The mean, standard deviation, and other statistics will be reported to 1 decimal place greater than the original data. The minimum and maximum will use the same number of decimal places as the original data. Proportions will be presented as 2 decimal places; values greater than zero but <0.01 will be presented as "<0.01". Percentages will be reported to the nearest whole number; values greater than zero but < 1% will be presented as "<1"; values greater than 99% but less than 100% will be reported as >99%. Estimated parameters, not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

11. TECHNICAL DETAILS

SAS version 9.4 or above and R version 3.6 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

After the data format for the primary analysis was confirmed, the planned analysis was changed from what is described in the protocol. Instead of utilizing a normal approximation, a Poisson regression model will be fit to test for differences between study arms, as described in Section 8.1.

Additionally, the modified Intent-to-Treat population will only be used as a sensitivity analysis for the primary objective. Originally it was also planned for secondary and exploratory objectives involving antibody responses, but these will not be done in the interest of conciseness.

13. REFERENCES

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APPENDICES

APPENDIX 1. TABLE MOCK-UPS

LIST OF TABLES

9.1 Overall Study Design and Plan Description

Table 1: Study Design

Study Arm	Dose 1 Day 1	Dose 2 Day 22	Dose 3 Day 172
A (n=60)	1 mg M-001	1 mg M-001	IIV4
B (n=60)	Placebo	Placebo	IIV4

9.5.1 Efficacy/Immunogenicity and Safety Measurements Assessed and Flow Chart

Table 2: Schedule of Study Procedures

Study Visit (V)	01	02	03	04	05	06	07	08	09	10	11	12
Study Day	**1**	**9**	**15**	**22**	**30**	**36**	**43**	**78**	**172**	**186**	**200**	**200+**
Visit Windows		(+2)	(+2)	(+2)	(+2)	(+2)	(+7)	(+7)	142-202	(+3)	(+7)	(+14)
Sign Consent Form[1]	X											
Assess eligibility	X			X					X			
Collect demographic information	X											
Review Medical History	X		X	X		X	X	X	X	X	X	X
Concomitant meds	X	X	X	X	X	X	X	X[7]	X[7]	X[7]	X[7]	X[7]
Vital signs[2]	X	{X}	{X}	X	{X}	{X}	{X}	{X}	X	{X}	{X}	
Height, Weight	X											
Targeted Physical Exam	{X}	{X}	{X}	{X}	{X}	{X}	{X}	{X}	{X}	{X}	{X}	
Review contraception/ Counseling[3]	X	X	X	X	X	X	X	X	X	X		
Pregnancy Test[2,4]	X			X					X			
Blood - Safety Labs (10 mL)	X	X			X							
Blood – Antibody Assays (10-20 mL)	X			X			X	X	X*		X*	
Blood – PBMCs (40-60 mL)	X=		X			X	X=	X	X	X	X	
Randomization	X											
AE/SAE Assessment[2#]	X	X	X	X	X	X	X	X	X	X	X	X
Vaccination[4]	X[5]			X[5]					X			
Evaluate vaccination site	X	X		X	X							
Postvaccination procedures[6]	X			X								
Review Memory Aid Data		X			X							
Blood volume (mL)	80	10	40	10	10	40	70	50	60	40	60	

{ } required at this visit only if clinically indicated

[1] Consent process completed and form signed before any study-related procedures are conducted.

[2] Vital signs include blood pressure, pulse, and oral temperature. On vaccination visits, these items should be completed prior to vaccination.

[3] Counseling on avoidance of pregnancy for women of childbearing potential.

[4] Urine or serum pregnancy test must be negative and be completed within 24 hours prior to vaccination for women of childbearing potential.

[5] All subjects will be observed for a minimum of 20 minutes following vaccination.

[6] Post-vaccination procedures will include documentation of any reactogenicity during the observation period and any AEs/SAEs post-vaccination, as well as provision of Memory Aid and instructions on completion.

[7] Concomitant medications (vaccines only) will be recorded on the appropriate data collection form after Visit 7 through the end of the study.

[+] Visit 12 will occur as a phone call only if visit 11 occurs prior to Study Day 200.

[*] 20 mL of blood will be collected for antibody assays on these days; 10 mL will be collected on other days of collection for antibody assays

[=] 60 mL of blood will be collected for PBMCs on these days; 40 mL will be collected on other days of PBMC collection

[#] AEs will be limited to SAEs after 21 days after M-001 study vaccinations.

9.7.1 Sample Size

Table 3: Power (%) to Detect Safety Events

Event Frequency	Single Study Arm N=60	Two Study Arms N=120
≥10% Very Common	99.8	>99.9
≥1% Common	45.3	70.1
≥0.1% Uncommon	5.8	11.3
≥0.01% Rare	<1	1.2

Table 4: Precision of Binomial Confidence Intervals

	N	95% CI
Single Study Arm	60	(36.8, 63.2)
Two Study Arms	120	(40.7, 59.3)

Table 5: Power Analysis for Primary Immunogenicity Endpoint

GMP_e/GMT_c {fold-change}	$\log_{10}(GMP_M)-\log_{10}(GMP_c)$ {log-difference}	Std Dev $\log_{10}$ (GMP)	Power (N = 60)	Power (N=54) 10% drop out
1.5	0.18	0.25	97	96
		0.50	49	45
		0.75	26	23
2	0.30	0.25	>99	>99
		0.50	90	87
		0.75	58	54
3	0.48	0.25	>99	>99
		0.50	>99	99
		0.75	93	90
4	0.60	0.25	>99	>99
		0.50	>99	>99
		0.75	99	98

10.2 Protocol Deviations

Table 6: Distribution of Protocol Deviations by Category, Type, and Study Arm (All Enrolled Subjects)

[Implementation Note: Include all deviation types collected in the study, even if not listed here; do not include categories with zero deviations reported for All Subjects.]

Category	Deviation Type	Group A: 1 mg M-001 (N=X)		Group B: Placebo (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
Eligibility/enrollment	Any type						
	Did not meet inclusion criterion	x	x	x	x	x	x
	Met exclusion criterion						
	ICF not signed prior to study procedures						
	Other						
Treatment administration schedule	Any type						
	Out of window visit						
	Missed visit/visit not conducted						
	Missed treatment administration						
	Delayed treatment administration						
	Other						
Follow-up visit schedule	Any type						
	Out of window visit						
	Missed visit/visit not conducted						
	Other						
Protocol procedure/assessment	Any type						
	Incorrect version of ICF signed						
	Blood not collected						
	Too few aliquots obtained						
	Specimen result not obtained						
	Required procedure not conducted						
	Required procedure done incorrectly						
	Study product temperature excursion						
	Specimen temperature excursion						
	Other						

Category	Deviation Type	Group A: 1 mg M-001 (N=X)		Group B: Placebo (N=X)		All Subjects (N=X)	
		No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.	No. of Subj.	No. of Dev.
Treatment administration	Any type						
	Required procedure done incorrectly						
	Study product temperature excursion						
	Other						
Blinding policy/procedure	Any type						
	Treatment unblinded						
	Other						
Note: N=Number of subjects enrolled.							

12.2.2 Displays of Adverse Events

Table 7: Subjective Systemic Reactogenicity Grading

Systemic (Subjective)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Feverishness (Chills/Shivering/Sweating)	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Fatigue	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Malaise	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Myalgia*	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Arthralgia*	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Headache	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity
Nausea	No interference with daily activity	Some interference with daily activity	Significant interference, prevents daily activity

* Not at injection site.

Table 8: Quantitative Systemic Reactogenicity Grading

Systemic (Quantitative)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever* - oral†	38.0°C – 38.4°C 100.4°F – 101.1°F	38.5°C – 38.9°C 101.2°F – 102.0°F	>38.9°C >102.0°F
Note: Oral temperature assessed on Day 1 prior to the first primary series study vaccination will be considered as baseline. * A fever can be considered not related to the study product if an alternative etiology can be documented. † Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.			

Table 9: Injection Site Reactogenicity Grading

Injection Site Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain – experienced without touching the injection site (spontaneous discomfort)	Subject is aware of pain, but it does not interfere with daily activity, **and** no pain medication is taken	Subject is aware of pain; there is interference with daily activity **or** it requires repeated use of a non-narcotic pain reliever for >24 hours	Subject is aware of pain, **and** it prevents daily activity or requires any use of a narcotic pain reliever
Tenderness – hurts only when injection site is touched or the arm is moved	The area immediately surrounding the injection site hurts only when touched or with arm motion, **and** it does **not** interfere with daily activity	The area immediately surrounding the injection site hurts when touched or with arm motion, **and** it interferes with daily activity	The area immediately surrounding the injection site hurts when touched or with arm motion, **and** it prevents daily activity
Pruritus	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Ecchymosis*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Erythema*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Induration/Edema*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
*Will be also measured in mm but size will not be used as halting criteria.			

Table 10: Injection Site Reactogenicity Measurements

Injection Site Reaction	Small	Medium	Large
Ecchymosis *	<20 mm	20 mm – 50 mm	>50 mm
Erythema*	<20 mm	20 mm – 50 mm	>50 mm
Induration /Edema*	<20 mm	20 mm – 50 mm	>50 mm
* Will not be used as halting criteria.			

Table 11: Pulse and Blood Pressure Grading

Physiologic Parameter	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Bradycardia - beats per minute	45 – 49	40 – 44	<40
Tachycardia - beats per minute	116 – 130	131 – 155	>155
Hypotension (systolic) mm Hg	80 – 84	75 – 79	<75

12.4.1 Individual Laboratory Measurements and Abnormal Laboratory Values

Table 12: Laboratory Adverse Event Grading Scale

Parameter	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Hematology			
WBC 10^3/µL (Decrease)	2.5 – 3.9	1.5 – 2.4	<1.5
WBC 10^3/µL (Increase)	10.6 – 15.0	15.1 – 20.0	>20.0
Hgb g/dL (Decrease) (Female)	10.1 – 11.4	8.5 – 10	<8.5
Hgb g/dL (Decrease) (Male)	11.0 – 12.4	9.5 – 10.9	<9.5
Platelets 10^3/µL (Decrease)	125 – 139	100 – 124	<100
Platelets 10^3/µL (Increase)	416 – 550	551– 750	>750
Chemistry			
ALT IU/L (Increase) (Female)	44 – 100	101 – 200	>200
ALT IU/L (Increase) (Male)	61 – 138	139 – 275	>275
Total Bilirubin mg/dL (Increase) – when accompanied by any increase in ALT	1.30 – 1.59	1.60 – 1.80	>1.80
Total Bilirubin mg/dL (Increase) – when ALT is normal	1.30 – 1.89	1.90 – 2.40	>2.40
Creatinine mg/dL (Increase) (Female)	1.1 – 1.7	1.8 – 2.0	>2.0
Creatinine mg/dL (Increase) (Male)	1.4 – 1.7	1.8 – 2.0	>2.0
Note: Clinical laboratory evaluations assessed at the enrollment visit (Visit 01) will be considered as baseline.			

14.1 Description of Study Subjects

14.1.1 Disposition of Subjects

Table 13: Subject Disposition by Study Arm

Subject Disposition	Group A: 1 mg M-001 (N=X)		Group B: Placebo (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Screened	--	--	--	--	x	--
Enrolled/Randomized	x	100	x	100	x	100
Received Study Vaccination	x	xx	x	xx	x	xx
Received first 2 doses	x	xx	x	xx	x	xx
Received All Scheduled Study Vaccinations[a]	x	xx	x	xx	x	xx
Completed PBMC Blood Draw at Study Day 43 (Visit 07)	x	xx	x	xx	x	xx
Completed Follow-up (Study Day 200)[a]	x	xx	x	xx	x	xx
Completed Final PBMC Blood Draw (Day 200 / Visit 11)	x	xx	x	xx	x	xx

Note: N=Number of subjects enrolled.
[a] Refer to Listing 2 for reasons subjects discontinued or terminated early.

Table 14: Analysis Populations by Study Arm

Analysis Populations	Reason Subjects Excluded	Group A: 1 mg M-001 (N=X)		Group B: Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	%	n
Safety Analysis Population	Any Reason	x	xx	x	xx	x	xx
	No Study Vaccination Received						
Modified Intent-to-Treat Population	Any Reason						
	No Study Vaccination Received						
	Ineligible at Baseline						
	No Post-Vaccination Results Available						
Per Protocol, Day 9	Any Reason						
	No Study Vaccination Received						
	Ineligible at Baseline						
	No Day 9 Result Reported by Lab						
	Receipt of Non-Study Vaccination						
	Receipt of Immunosuppressive Medication						
	Day 9 Visit Out of Window						
Per Protocol, Day 15	Any Reason						
	No Study Vaccination Received						
	Ineligible at Baseline						
	No Day 15 Result Reported by Lab						
	Receipt of Non-Study Vaccination						
	Receipt of Immunosuppressive Medication						
	Day 15 Visit Out of Window						
Per Protocol, Day 22	Any Reason						
	No Study Vaccination Received						
	Ineligible at Baseline						
	No Day 22 Result Reported by Lab						
	Receipt of Non-Study Vaccination						
	Receipt of Immunosuppressive Medication						
	Day 22 Visit Out of Window						
Per Protocol, Day 30	Any Reason						
	No Study Vaccination Received						
	Study Vaccination 2 Not Received						
	Study Vaccination 2 Out of Window						
	Ineligible at Baseline						
	No Day 30 Result Reported by Lab						
	Receipt of Non-Study Vaccination						

Table 14: Analysis Populations by Study Arm (Continued)

Analysis Populations	Reason Subjects Excluded	Group A: 1 mg M-001 (N=X)		Group B: Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	%	n
	Receipt of Immunosuppressive Medication						
	Day 30 Visit Out of Window						
Per Protocol, Day 36 **(Primary Endpoint)**	Any Reason						
	No Study Vaccination Received						
	Study Vaccination 2 Not Received						
	Study Vaccination 2 Out of Window						
	Ineligible at Baseline						
	No Day 36 Result Reported by Lab						
	Receipt of Non-Study Vaccination						
	Receipt of Immunosuppressive Medication						
	Day 36 Visit Out of Window						
Per Protocol, Day 43	Any Reason						
	No Study Vaccination Received						
	Study Vaccination 2 Not Received						
	Study Vaccination 2 Out of Window						
	Ineligible at Baseline						
	No Day 43 Result Reported by Lab						
	Receipt of Non-Study Vaccination						
	Receipt of Immunosuppressive Medication						
	Day 43 Visit Out of Window						
Per Protocol, Day 78	Any Reason						
	No Study Vaccination Received						
	Study Vaccination 2 Not Received						
	Study Vaccination 2 Out of Window						
	Ineligible at Baseline						
	No Day 78 Result Reported by Lab						
	Receipt of Non-Study Vaccination						
	Receipt of Immunosuppressive Medication						
	Day 78 Visit Out of Window						
Per Protocol, Day 172	Any Reason						
	No Study Vaccination Received						
	Study Vaccination 2 Not Received						
	Study Vaccination 2 Out of Window						

Table 14: Analysis Populations by Study Arm (Continued)

Analysis Populations	Reason Subjects Excluded	Group A: 1 mg M-001 (N=X)		Group B: Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	%	n
	Ineligible at Baseline						
	No Day 172 Result Reported by Lab						
	Receipt of Non-Study Vaccination						
	Receipt of Immunosuppressive Medication						
	Day 172 Visit Out of Window						
Per Protocol, Day 186	Any Reason						
	No Study Vaccination Received						
	Study Vaccination 3 Not Received						
	Study Vaccination 3 Out of Window						
	Study Vaccination 2 Not Received						
	Study Vaccination 2 Out of Window						
	Ineligible at Baseline						
	No Day 186 Result Reported by Lab						
	Receipt of Non-Study Vaccination						
	Receipt of Immunosuppressive Medication						
	Day 186 Visit Out of Window						
Per Protocol, Day 200	Any Reason						
	No Study Vaccination Received						
	Study Vaccination 3 Not Received						
	Study Vaccination 3 Out of Window						
	Study Vaccination 2 Not Received						
	Study Vaccination 2 Out of Window						
	Ineligible at Baseline						
	No Day 200 Result Reported by Lab						
	Receipt of Non-Study Vaccination						
	Receipt of Immunosuppressive Medication						
	Day 200 Visit Out of Window						

Note: N=Number of subjects enrolled.

Table 15: Dates of First Vaccination by Site and Study Arm

[Implementation Note: Weekly intervals for dosing date should be displayed. The earliest date should be the FSFV over all sites.]

	Site 1: BCM		Site 2: Iowa		Site 3: CCHMC	
Dates of Dosing	**Group A: 1 mg M-001 (N=X)**	**Group B: Placebo (N=X)**	**Group A: 1 mg M-001 (N=X)**	**Group B: Placebo (N=X)**	**Group A: 1 mg M-001 (N=X)**	**Group B: Placebo (N=X)**
Dose 1						
Total (Entire period of enrollment)						
DDMMMYYYY-DDMMMYYYY	x	x	x	x	x	x
Dose 2						
Total (Entire period of enrollment)						
DDMMMYYYY-DDMMMYYYY	x	x	x	x	x	x
Dose 3						
Total (Entire period of enrollment)						
DDMMMYYYY-DDMMMYYYY	x	x	x	x	x	x

Notes: N=Number of subjects enrolled.
BCM=Baylor College of Medicine, Iowa=University of Iowa, CCHMC=Cincinnati Children's Hospital Medical Center

Table 16: Ineligibility Summary of Screen Failures

Inclusion/Exclusion Category	Inclusion/Exclusion Criterion	n[a]	%[b]
Inclusion and Exclusion	Number of subjects failing any eligibility criterion	x	100
Inclusion	Any inclusion criterion	x	xx
	Systolic blood pressure is within the per protocol range	x	xx
	Diastolic blood pressure is within the per protocol range	x	xx
	Are able to understand and comply with planned study procedures and be available for all study visits	x	xx
	Are in good health	x	xx
	Women of childbearing potential must use an acceptable method of contraception from 30 days prior to vaccination until 60 days after the second dose of M-001 or placebo	x	xx
	Women of childbearing potential must use an acceptable method of contraception from 30 days prior to receipt of IIV vaccination, and must plan to use until 28 days after the IIV	x	xx
Exclusion	Any exclusion criterion	x	xx
	Have any medical disease or condition that, in the opinion of the site PI or appropriate sub-investigator, is a contraindication to study participation	x	xx
	Have an acute illness, as determined by the site PI or appropriate sub-investigator, within 72 hours prior to study vaccination	x	xx
	Have signs or symptoms that could confound or confuse assessment of study vaccine reactogenicity	x	xx
	Plan to travel outside the U.S. (continental U.S., Hawaii, and Alaska) in the time between the first study vaccination and 21 days after the last study vaccination	x	xx
	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	x	xx
	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	x	xx

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

14.1.2 Demographic Data by Study Group

Table 17: Summary of Categorical Demographic and Baseline Characteristics by Site

Variable	Characteristic	Site 1: BCM (N=X)		Site 2: Iowa (N=X)		Site 3: CCHMC (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%	n	%
Sex	Male	x	xx	x	xx	x	xx	x	xx
	Female								
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx	x	xx
	Hispanic or Latino								
	Not Reported								
	Unknown								
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx	x	xx
	Asian								
	Native Hawaiian or Other Pacific Islander								
	Black or African American								
	White								
	Multi-Racial								
	Unknown								
Prior Seasonal Influenza Vaccination	2016-17 only								
	2017-18 only								
	Both								
	Neither								
	Unknown								
Age	18-29								
	30-39								
	40-49								
BMI	<30								
	≥30								

Notes: N=Number of subjects enrolled.
BCM=Baylor College of Medicine, Iowa=University of Iowa, CCHMC=Cincinnati Children's Hospital Medical Center

Table 18: Summary of Continuous Demographic and Baseline Characteristics by Site

Variable	Statistic	Site 1: BCM (N=X)	Site 2: Iowa (N=X)	Site 3: CCHMC (N=X)	All Subjects (N=X)
Age (Years)	Mean	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx
	Median	xx	xx	xx	xx
	Minimum	x	x	x	x
	Maximum	x	x	x	x
BMI	Mean	xx	xx	xx	xx
	Standard Deviation	xx	xx	xx	xx
	Median	xx	xx	xx	xx
	Minimum	x	x	x	x
	Maximum	x	x	x	x

Notes: N=Number of subjects enrolled.
BCM=Baylor College of Medicine, Iowa=University of Iowa, CCHMC=Cincinnati Children's Hospital Medical Center

Table 19: Summary of Categorical Demographic and Baseline Characteristics by Study Arm, All Enrolled Subjects

Variable	Characteristic	Group A: 1 mg M-001 (N=X)		Group B: Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Sex	Male	x	xx	x	xx	x	xx
	Female						
Ethnicity	Not Hispanic or Latino	x	xx	x	xx	x	xx
	Hispanic or Latino						
	Not Reported						
	Unknown						
Race	American Indian or Alaska Native	x	xx	x	xx	x	xx
	Asian						
	Native Hawaiian or Other Pacific Islander						
	Black or African American						
	White						
	Multi-Racial						
	Unknown						
Prior Seasonal Influenza Vaccination (2017-2018)	2016-17 only						
	2017-18 only						
	Both						
	Neither						
	Unknown						
Age	18-29						
	30-39						
	40-49						
BMI	<30						
	≥30						
Note: N=Number of subjects enrolled.							

Table 20: Summary of Continuous Demographic and Baseline Characteristics by Study Arm, All Enrolled Subjects

Variable	Statistic	Group A: 1 mg M-001 (N=X)	Group B: Placebo (N=X)	All Subjects (N=X)
Age (years)	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
BMI	Mean	xx	xx	xx
	Standard Deviation	xx	xx	xx
	Median	x	x	x
	Minimum	x	x	x
	Maximum	x	x	x
Note: N=Number of subjects enrolled.				

14.1.3 Prior and Concurrent Medical Conditions

Table 21: Summary of Subjects with Pre-Existing Medical Conditions by MedDRA System Organ Class and Study Arm

MedDRA System Organ Class	Group A: 1 mg M-001 (N=X)		Group B: Placebo (N=X)		All Subjects (N=X)	
	n	%	n	%	n	%
Any SOC	x	xx	x	xx	x	xx
[SOC 1]						
[SOC 2]						

Notes: N=Number of subjects enrolled
n = Number of subjects reporting medical history within the specified SOC. A subject is only counted once per SOC.

14.2 Efficacy/Immunogenicity Data

Table 22: Geometric Mean Percentage (GMP) of CD4+ T Cell Subsets Expressing Markers Alone or in Combination After M-001 Stimulation with 95% Confidence Intervals by Study Day and Study Arm, Per Protocol Population*

Study Day	Perforin	CD107a	IFN-γ	TNF-α	IL2	Group A: 1 mg M-001			Group B: Placebo			p-value[x]
						n	GMP	95% CI	n	GMP	95% CI	
Primary Endpoint												
Day 36	+	+	+	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+	+	+	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+	+	+	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+	+	+	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+	+	-	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+	+	-	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+	+	-	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+	+	-	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+	-	+	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+	-	+	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+	-	+	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+	-	+	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+	-	-	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+	-	-	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+	-	-	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+	-	-	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	-	+	+	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	-	+	+	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	-	+	+	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	-	+	+	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	-	+	-	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	-	+	-	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	-	+	-	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	-	+	-	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	-	-	+	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	-	-	+	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	-	-	+	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	-	-	+	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	-	-	-	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	-	-	-	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	-	-	-	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	

Study Day	Perforin	CD107a	IFN-γ	TNF-α	IL2	Group A: 1 mg M-001			Group B: Placebo			p-value[x]
						n	GMP	95% CI	n	GMP	95% CI	
	-	-	-	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+	+/-	+/-	+/-	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+/-	+	+/-	+/-	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+/-	+/-	+	+/-	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+/-	+/-	+/-	+	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
	+/-	+/-	+/-	+/-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x	
Exploratory Endpoints												
Repeat for Baseline, Day 15, Day 43, Day 78, Day 172, Day 186, and Day 200 without p-value column.												
Notes: N = number of subjects in Per Protocol population. [x]Wald test from Poisson regression used to compare groups. 95% CIs calculated via 10,000 bootstrap samples.												

Tables with similar format:

[Implementation Note: Do not include p-value column for Tables 28-31, and only include it for Day 36 for Tables 25-27. Include rows for any perforin, any CD107a, any IFN-γ, any TNF-α, and any IL2.]

Table 23: Geometric Mean Percentage (GMP) of CD8+ T Cell Subsets Expressing Markers Alone or in Combination After M-001 Stimulation with 95% Confidence Intervals by Study Day and Study Arm, Per Protocol Population*

Table 24: Geometric Mean Percentage (GMP) of CD4+ T Cell Subsets Expressing Markers Alone or in Combination After M-001 Stimulation with 95% Confidence Intervals by Study Day and Study Arm, Modified Intent-to-Treat Population*

Table 25: Geometric Mean Percentage (GMP) Of CD8+ T Cell Subsets Expressing Markers Alone or in Combination After M-001 Stimulation with 95% Confidence Intervals by Study Day and Study Arm, Modified Intent-to-Treat Population*

Table 26: Percentage of CD4+ T Cell Subsets Expressing Markers Alone or in Combination After Seasonal Influenza A Antigen Stimulation with 95% Confidence Intervals by Study Day and Study Arm, Per Protocol Population

Table 27: Percentage of CD8+ T Cell Subsets Expressing Markers Alone or in Combination After Seasonal Influenza A Antigen Stimulation with 95% Confidence Intervals by Study Day and Study Arm, Per Protocol Population

Table 28: Percentage of CD4+ T Cell Subsets Expressing Markers Alone or in Combination After Pandemic Influenza A Antigen Stimulation with 95% Confidence Intervals by Study Day and Study Arm, Per Protocol Population

Table 29: Percentage of CD8+ T Cell Subsets Expressing Markers Alone or in Combination After Pandemic Influenza A Antigen Stimulation with 95% Confidence Intervals by Study Day and Study Arm, Per Protocol Population

Table 30: Summaries of Hemagglutination Inhibition Antibody Against A/Michigan/45/2015 X-275 (H1N1) by Study Day and Study Arm, Per Protocol Population

	Group A: 1 mg M-001 (N=X)	Group B: Placebo (N=X)
Day 1		
n	x	x
GMT (95% CI)	xxx.x(xxx.x,xxx.x)	xxx.x(xxx.x,xxx.x)
Titer ≥ 1:40 - %(95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
Day 22		
n	x	x
GMT (95% CI)	xxx.x(xxx.x,xxx.x)	xxx.x(xxx.x,xxx.x)
Seroconversion - %(95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
Titer ≥ 1:40 - %(95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
Day 43		
n	x	x
GMT (95% CI)	xxx.x(xxx.x,xxx.x)	xxx.x(xxx.x,xxx.x)
Seroconversion - %(95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
Titer ≥ 1:40 - %(95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
Day 172		
n	x	x
GMT (95% CI)	xxx.x(xxx.x,xxx.x)	xxx.x(xxx.x,xxx.x)
Seroconversion - %(95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
Titer ≥ 1:40 - %(95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
Day 200		
n	x	x
GMT (95% CI)	xxx.x(xxx.x,xxx.x)	xxx.x(xxx.x,xxx.x)
Seroconversion - %(95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
Titer ≥ 1:40 - %(95% CI)	x.x (x.x, x.x)	x.x (x.x, x.x)
Note: N=Number of subjects in Per Protocol population.		

Tables with similar format:

Table 31: Summaries of Hemagglutination Inhibition Antibody Against A/Singapore/INFIMH-16-0019/2016 NIB-104(H3N2)-Guinea RBC by Study Day and Study Arm, Per Protocol Population

Table 32: Summaries of Hemagglutination Inhibition Antibody Against B/Colorado/6/2017 (B Victoria Lineage) by Study Day and Study Arm, Per Protocol Population

Table 33: Summaries of Hemagglutination Inhibition Antibody Against B/Phuket/3073/2013 (B Yamagata Lineage) by Study Day and Study Arm, Per Protocol Population

Table 34: Summaries of Neutralizing Antibody Against A/Michigan/45/2015 X-275 (H1N1) by Study Day and Study Arm, Per Protocol Population

Table 35: Summaries of Neutralizing Antibody Against A/Singapore/INFIMH-16-0019/2016 NIB-104(H3N2) by Study Day and Study Arm, Per Protocol Population

Table 36: Summaries of Neutralizing Antibody Against B/Colorado/6/2017 (B Victoria Lineage) by Study Day and Study Arm, Per Protocol Population

Table 37: Summaries of Neutralizing Antibody Against B/Phuket/3073/2013 (B Yamagata Lineage) by Study Day and Study Arm, Per Protocol Population

Table 38: Percentage of Influenza-Specific CD4+ Cell Subsets Expressing Discrete Memory Markers (CCR7, CD45RO, and CD57) by Study Arm and Study Day, Per Protocol Population

Study Day	CCR7	CD45RO	CD57	Group A: 1 mg M-001			Group B: Placebo		
				n	GMP	95% CI	n	GMP	95% CI
Baseline	+	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	+/-	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+/-	+	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+/-	+/-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Day 15	+	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	+/-	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+/-	+	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+/-	+/-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Day 36	+	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	+/-	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+/-	+	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+/-	+/-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x

Table 38: Percentage of Influenza-Specific CD4+ Cell Subsets Expressing Discrete Memory Markers (CCR7, CD45RO, and CD57) by Study Arm and Study Day, Per Protocol Population (Continued)

Study Day	CCR7	CD45RO	CD57	Group A: 1 mg M-001			Group B: Placebo		
				n	GMP	95% CI	n	GMP	95% CI
Day 43	+	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	+/-	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+/-	+	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+/-	+/-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Day 78	+	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	+/-	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+/-	+	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+/-	+/-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Day 172	+	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	+/-	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+/-	+	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+/-	+/-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Day 186	+	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x

Table 38: Percentage of Influenza-Specific CD4+ Cell Subsets Expressing Discrete Memory Markers (CCR7, CD45RO, and CD57) by Study Arm and Study Day, Per Protocol Population (Continued)

Study Day	CCR7	CD45RO	CD57	Group A: 1 mg M-001			Group B: Placebo		
				n	GMP	95% CI	n	GMP	95% CI
	+	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	+/-	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+/-	+	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+/-	+/-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
Day 200	+	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	+	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	+	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	-	-	-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+	+/-	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+/-	+	+/-	x	x.x	x.x, x.x	x	x.x	x.x, x.x
	+/-	+/-	+	x	x.x	x.x, x.x	x	x.x	x.x, x.x

Note: N = number of subjects in Per Protocol population.

Tables with similar format:

Table 39: Percentage of Influenza-Specific CD8+ Cell Subsets Expressing Discrete Memory Markers (CCR7, CD45RO, and CD57) by Study Arm and Study Day, Per Protocol Population

Table 40: Percentage of Influenza-Specific CD4+ Cell Subsets expressing IL-4 or IL-17 by Study Arm and Study Day, Per Protocol Population

Table 41: Percentage of Influenza-Specific CD4+ Cell Subsets expressing T Follicular Helper Cells (CD4+, CXCR5+, PD-1+, IL-21+) by Study Arm and Study Day, Per Protocol Population

Table 42: Percentage of Influenza-Specific CD4+ Cell Subsets expressing T Follicular Regulatory Cells (CXCR5+, PD-1+, CD25+, CD127+) by Study Arm and Study Day, Per Protocol Population

Table 43: Percentage of Influenza-Specific CD4+ Cell Subsets expressing Tregs (CD25+, Foxp3+) by Study Arm and Study Day, Per Protocol Population

Table 44: Summaries of ELISA Antibody Against M-001 by Study Day and Study Arm, Per Protocol Population

	Group A: 1 mg M-001			Group B: Placebo		
Study Day	N	GMT (95% CI)	Seroconversion % (95% CI)	N	GMT (95% CI)	Seroconversion % (95% CI)
Baseline	x	x.x (x.x, x.x)	NA	x	x.x (x.x, x.x)	NA
Day 22	x	x.x (x.x, x.x)	xx (xx, xx)	x	x.x (x.x, x.x)	xx (xx, xx)
Day 43	x	x.x (x.x, x.x)	xx (xx, xx)	x	x.x (x.x, x.x)	xx (xx, xx)
Day 78	x	x.x (x.x, x.x)	xx (xx, xx)	x	x.x (x.x, x.x)	xx (xx, xx)
Day 172	x	x.x (x.x, x.x)	xx (xx, xx)	x	x.x (x.x, x.x)	xx (xx, xx)
Day 200	x	x.x (x.x, x.x)	xx (xx, xx)	x	x.x (x.x, x.x)	xx (xx, xx)

Notes: N=Number of subjects in Per Protocol population.
Seroconversion is defined as either a pre-vaccination titer <10 and a post-vaccination titer ≥ 40 or a pre-vaccination titer ≥ 10 and a minimum four-fold rise in post-vaccination antibody titer.

14.3 Safety Data

14.3.1 Displays of Adverse Events

Table 45: Overall Summary of Adverse Events*

	Group A: 1 mg M-001 (N = xx)		Group B: Placebo (N = xx)		All Subjects (N = xx)	
Subjects[a] with	n	%	n	%	n	%
At least one local solicited adverse event	x	x	x	x	x	x
Mild (Grade 1)	x	x	x	x	x	x
Moderate (Grade 2)	x	x	x	x	x	x
Severe (Grade 3)	x	x	x	x	x	x
At least one systemic solicited adverse event	x	x	x	x	x	x
Mild (Grade 1)	x	x	x	x	x	x
Moderate (Grade 2)	x	x	x	x	x	x
Severe (Grade 3)	x	x	x	x	x	x
At least one unsolicited adverse event	x	x	x	x	x	x
At least one related unsolicited adverse event	x	x	x	x	x	x
Mild (Grade 1)	x	x	x	x	x	x
Moderate (Grade 2)	x	x	x	x	x	x
Severe (Grade 3)	x	x	x	x	x	x
Not yet assessed						
At least one severe (Grade 3) unsolicited adverse event	x	x	x	x	x	x
Related	x	x	x	x	x	x
Unrelated	x	x	x	x	x	x
At least one unsolicited non-serious Adverse Event from first study vaccination through 21 days after each M-001 vaccination	x	x	x	x	x	x
At least one serious adverse event[b]	x	x	x	x	x	x
At least one related, serious adverse event	x	x	x	x	x	x
At least one adverse event leading to early termination[c]	x	x	x	x	x	x
At least one clinical safety laboratory adverse event	x	x	x	x	x	x
Mild (Grade 1)	x	x	x	x	x	x

	Group A: 1 mg M-001 (N = xx)		**Group B: Placebo (N = xx)**		**All Subjects (N = xx)**	
Subjects[a] with	n	%	n	%	n	%
Moderate (Grade 2)	x	x	x	x	x	x
Severe (Grade 3)	x	x	x	x	x	x
Not yet assessed						

Notes: N=Number of subjects in Safety Analysis population.
[a] Subjects are counted once for each category regardless of the number of events.
[b] A listing of Serious Adverse Events is included in Table 58.
[c] As reported on the Adverse Event eCRF.

Table 46: Adverse Events Occurring in 5% of Subjects in Any Study Arm by MedDRA System Organ Class and Preferred Term, and Study Arm

MedDRA System Organ Class	Preferred Term	Group A: 1 mg M-001 (N=X)			Group B: Placebo (N=X)			All Subjects (N=X)		
		n	%	Events	n	%	Events	n	%	Events
Serious Adverse Events										
All	All	x	x	x	x	x	x	x	x	x
SOC1	PT1	x	x	x	x	x	x	x	x	x
Etc.	Etc.									
Other (Non-serious) Adverse Events										
All	All	x	x	x	x	x	x	x	x	x
SOC1	PT1	x	x	x	x	x	x	x	x	x
Etc	Etc									

Notes: N=Number of subjects in Safety Analysis population
n= number of subjects reporting event. Events= total frequency of events reported.

14.3.1.1 Solicited Adverse Events

Table 47: Number and Percentage of Subjects Experiencing Solicited Events with 95% Confidence Intervals by Symptom, Dose, and Study Arm*

Symptom	Post Dose 1 Group A: 1 mg M-001 (N=X)			Post Dose 1 Group B: Placebo (N=X)			Post Dose 2 Group A: 1 mg M-001 (N=X)			Post Dose 2 Group B: Placebo (N=X)			Post Any Dose Group A: 1 mg M-001 (N=X)			Post Any Dose Group B: Placebo (N=X)		
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
Any Systemic Symptom																		
Fever																		
Feverishness																		
Fatigue																		
Malaise																		
Myalgia																		
Arthralgia																		
Headache																		
Nausea																		
Any Local Symptom																		
Pain																		
Tenderness																		
Ecchymosis																		
Ecchymosis (measurement)																		
Erythema																		
Erythema (measurement)																		
Induration/Swelling																		
Induration/Swelling (measurement)																		

Note: N=Number of subjects in Safety Analysis population.

Table 48: Comparison of the Proportion of Subjects Experiencing Solicited Events by Study Arm

Symptom	Statistic	Group A: 1 mg M-001 Post Either Dose (N=X)	Group B: Placebo Post Either Dose (N=X)
Any Symptom	Proportion	x.xx	x.xx
	95% CI (for proportion)	x.xx, x.xx	x.xx, x.xx
	Difference		x.xx
	95% CI (for difference)		x.xx, x.xx
[Symptom 1]	Proportion		
	95% CI (for proportion)		
	Difference		
	95% CI (for difference)		
[Repeat for all solicited events]			
Note: N=Number of subjects in Safety Analysis population.			

Table 49: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Study Arm*

Symptom	Severity	Post Dose 1 Group A: 1 mg M-001 (N=X)			Post Dose 1 Group B: Placebo (N=X)			Post Dose 2 Group A: 1 mg M-001 (N=X)			Post Dose 2 Group B: Placebo (N=X)			Post Any Dose Group A: 1 mg M-001 (N=X)			Post Any Dose Group B: Placebo (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Any Symptom	None	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
	Mild																		
	Moderate																		
	Severe																		
Systemic Symptoms																			
Any Systemic Symptom	None	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x	x	xx	x.x, x.x
	Mild																		
	Moderate																		
	Severe																		
Fever	None																		
	Mild																		
	Moderate																		
	Severe																		
Feverishness	None																		
	Mild																		
	Moderate																		
	Severe																		
Fatigue	None																		
	Mild																		
	Moderate																		
	Severe																		
Malaise	None																		

Table 49: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Study Arm* (Continued)

Symptom	Severity	Post Dose 1 Group A: 1 mg M-001 (N=X)			Post Dose 1 Group B: Placebo (N=X)			Post Dose 2 Group A: 1 mg M-001 (N=X)			Post Dose 2 Group B: Placebo (N=X)			Post Any Dose Group A: 1 mg M-001 (N=X)			Post Any Dose Group B: Placebo (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
	Mild																		
	Moderate																		
	Severe																		
Myalgia	None																		
	Mild																		
	Moderate																		
	Severe																		
Arthralgia	None																		
	Mild																		
	Moderate																		
	Severe																		
Headache	None																		
	Mild																		
	Moderate																		
	Severe																		
Nausea	None																		
	Mild																		
	Moderate																		
	Severe																		
Local Symptoms																			
Any Local Symptom	None	x	xx		x	xx		x	xx		x	xx		x	xx		x	xx	
	Mild																		

Table 49: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Study Arm* (Continued)

Symptom	Severity	Post Dose 1 Group A: 1 mg M-001 (N=X)			Post Dose 1 Group B: Placebo (N=X)			Post Dose 2 Group A: 1 mg M-001 (N=X)			Post Dose 2 Group B: Placebo (N=X)			Post Any Dose Group A: 1 mg M-001 (N=X)			Post Any Dose Group B: Placebo (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
	Moderate																		
	Severe																		
Pain	None																		
	Mild																		
	Moderate																		
	Severe																		
Tenderness	None																		
	Mild																		
	Moderate																		
	Severe																		
Pruritus	None																		
	Mild																		
	Moderate																		
	Severe																		
Ecchymosis	None																		
	Mild																		
	Moderate																		
	Severe																		
Ecchymosis (measurement)	None																		
	Mild																		
	Moderate																		
	Severe																		

Table 49: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Maximum Severity, Dose, and Study Arm* (Continued)

Symptom	Severity	Post Dose 1 Group A: 1 mg M-001 (N=X)			Post Dose 1 Group B: Placebo (N=X)			Post Dose 2 Group A: 1 mg M-001 (N=X)			Post Dose 2 Group B: Placebo (N=X)			Post Any Dose Group A: 1 mg M-001 (N=X)			Post Any Dose Group B: Placebo (N=X)		
		n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI
Erythema	None																		
	Mild																		
	Moderate																		
	Severe																		
Erythema (measurement)	None																		
	Mild																		
	Moderate																		
	Severe																		
Induration/Swelling	None																		
	Mild																		
	Moderate																		
	Severe																		
Induration/Swelling (measurement)	None																		
	Mild																		
	Moderate																		
	Severe																		

Notes: N=Number of subjects in Safety Analysis population who received the specified dose.
Severity is the maximum severity reported over all solicited symptoms post dosing for each subject.

Table 50: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing, Group A: 1 mg M-001, Post First Vaccination

Group A: 1 mg M-001, Post Dose 1 (N=X)																					
		Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8	
Symptom	Severity	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any Symptom	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Systemic Symptoms																					
Any Systemic Symptom	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Fever	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Feverishness	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				

Table 50: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing, Group A: 1 mg M-001, Post First Vaccination (Continued)

Group A: 1 mg M-001, Post Dose 1 (N=X)																					
		Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8	
Symptom	Severity	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Fatigue	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Malaise	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Arthralgia	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Headache	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Nausea	None																				
	Mild																				
	Moderate																				

Table 50: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing, Group A: 1 mg M-001, Post First Vaccination (Continued)

Group A: 1 mg M-001, Post Dose 1 (N=X)																					
		Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8	
Symptom	Severity	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Severe																				
	Not Reported																				
Local Symptoms																					
Any Local Symptom	None	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Pain	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Tenderness	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Pruritis	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				

Table 50: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing, Group A: 1 mg M-001, Post First Vaccination (Continued)

Group A: 1 mg M-001, Post Dose 1 (N=X)																					
		Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8	
Symptom	Severity	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Ecchymosis	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Ecchymosis (measurement)	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Erythema	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Erythema (measurement)	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Induration/Swelling	None																				
	Mild																				
	Moderate																				

Table 50: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing, Group A: 1 mg M-001, Post First Vaccination (Continued)

Group A: 1 mg M-001, Post Dose 1 (N=X)																					
		Pre-Dose		Post-Dose		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8	
Symptom	Severity	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
	Severe																				
	Not Reported																				
Induration/Swelling (measurement)	None																				
	Mild																				
	Moderate																				
	Severe																				
	Not Reported																				
Notes: N=Number of subjects in Safety Analysis population who received the specified dose. Severity is the maximum severity reported post dosing for each subject for each day.																					

Tables with similar format:

Table 51: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing, Group A: 1 mg M-001, Post Second Vaccination

Table 52: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing, Group B: Placebo, Post First Vaccination

Table 53: Number and Percentage of Subjects Experiencing Solicited Events by Symptom, Severity, and Day Post Dosing, Group B: Placebo, Post Second Vaccination

Table 54: Number and Percentage of Subjects Experiencing Solicited Events for Dose 1 Compared with Dose 2 by Study Arm

Study Arm		Dose 2 – Subjects with No Symptoms	Dose 2 – Subjects with Mild or Greater Symptoms	Dose 2 – Total Number of Subjects	McNemar's Test Result (p-value)
Systemic Symptoms					
Group A: 1 mg M-001	Dose 1 Subject with No Symptoms	x (%)	x (%)	x (%)	
	Dose 1 Subjects with Mild or Greater Symptoms	x (%)	x (%)	x (%)	
	Dose 1 Total Number of Subjects	x (%)	x (%)	x (100%)	
Group B: Placebo	Subject with No Symptoms				
	Subjects with Mild or Greater Symptoms				
	Total Number of Subjects				
Local Symptoms					
Group A: 1 mg M-001	Dose 1 Subjects with No Symptoms	x (%)	x (%)	x (%)	
	Dose 1 Subjects with Mild or Greater Symptoms	x (%)	x (%)	x (%)	
	Dose 1Total Number of Subjects	x (%)	x (%)	x (100%)	
Group B: Placebo	Dose 1 Subjects with No Symptoms				
	Dose 1Subjects with Mild or Greater Symptoms				
	Dose Total Number of Subjects				

Notes: N=Number of subjects in Safety Analysis population who received the first and second dose.
[x] subjects did not get the second dose and are not included in this table.

14.3.1.2 Unsolicited Adverse Events

Table 55: Summary of Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Dose Number, and Study Arm

MedDRA System Organ Class	MedDRA Preferred Term	Day 1-8 Post Dose 1 (N=X)				Day 9-22 Post Dose 1 (N=X)				Day 1-8 Post Dose 2 (N=X)				Day 9-22 Post Dose 2 (N=X)				Any Time Post Any Dose (N=X)			
		n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events	n	%	95% CI	Events
Group A: 1 mg M-001																					
Any SOC	Any PT	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x
[SOC 1]	Any PT																				
	[PT 1]																				
	[PT 2]																				
[SOC 2]	Any PT																				
	[PT 1]																				
	[PT 2]																				
Group B: Placebo																					
Any SOC	Any PT	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x	x	xx	xx, xx	x
[SOC 1]	Any PT																				
	[PT 1]																				
	[PT 2]																				
[SOC 2]	Any PT																				
	[PT 1]																				
	[PT 2]																				

Notes: N=Number of subjects in Safety Analysis population who received the specified dose.
This table presents number and percentage of subjects.
A subject is only counted once per PT/time point.

Table 56: Unsolicited Adverse Events by MedDRA System Organ Class and Preferred Term, Maximum Severity, Relationship, and Study Arm*

MedDRA System Organ Class	Preferred Term	Severity	Group A: 1 mg M-001 (N = X)						Group B: Placebo (N = X)					
			Related		Not Related		Total		Related		Not Related		Total	
			n	%	n	%	n	%	n	%	n	%	n	%
Any SOC	Any PT	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
SOC 1	PT 1	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	PT 2	Any Severity	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Mild	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Moderate	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
		Severe	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

Note: N=Number of subjects in Safety Analysis population.

Table 57: Related Unsolicited Adverse Events Within 21 Days Post Dosing by MedDRA System Organ Class and Preferred Term, Dose, and Study Arm

		Day 1-22 Post Dose 1			Day 1-22 Post Dose 2			Within 21 Days Post Either Dose		
MedDRA System Organ Class	**MedDRA Preferred Term**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**
Group A: 1 mg M-001										
Any SOC	Any PT	x	xx	x	x	xx	x	x	xx	x
[SOC 1]	Any PT									
	[PT 1]									
	[PT 2]									
[SOC 2]	Any PT									
	[PT 1]									
	[PT 2]									
Group B: Placebo										
Any SOC	Any PT									
[SOC 1]	Any PT									
	[PT 1]									
	[PT 2]									
[SOC 2]	Any PT									
	[PT 1]									
	[PT 2]									

Notes: N=Number of subjects in Safety Analysis population.
This table presents number and percentage of subjects.
For each time point, a subject is only counted once per PT.

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Table 58: Listing of Serious Adverse Events*

Adverse Event	Associated with Dose No.	No. of Days Post Associated Dose (Duration)	No. of Days Post Dose the Event Became Serious	Reason Reported as an SAE	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
Subject ID: , Study Arm: , AE Number:												
Comments:												
Subject ID: , Study Arm: , AE Number:												
Comments:												

14.3.3 Narratives of Deaths, Other Serious and Significant Adverse Events

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

14.3.4 Abnormal Laboratory Value Listings (by Subject)

Table 59: Listing of Abnormal Laboratory Results - Chemistry

Subject ID	Study Arm	Sex	Age (years)	Planned Study Day	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Subject Discontinued Due to Result?

Table 60: Listing of Abnormal Laboratory Results - Hematology

Subject ID	Study Arm	Sex	Age (years)	Planned Study Day	Actual Study Day	Laboratory Parameter (Units)	Result (Severity)	Relationship to Treatment	If Not Related, Alternate Etiology	Action Taken with Study Treatment	Subject Discontinued Due to Result?

14.3.5 Displays of Laboratory Results

14.3.5.1 Chemistry Results

Table 61: Laboratory Results by Parameter, Maximum Severity, Study Day, and Study Arm – Any Chemistry Parameter

Study Day	Study Arm	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Group A: 1 mg M-001	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Group B: Placebo											
Day 9	Group A: 1 mg M-001											
	Group B: Placebo											
Day 30	Group A: 1 mg M-001											
	Group B: Placebo											
Max Severity Post Baseline	Group A: 1 mg M-001											
	Group B: Placebo											

Notes: N=number of subjects in Safety Analysis population.
The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

Table 62: Laboratory Results by Parameter, Study Day, and Study Arm – Alanine Aminotransferase

Study Day	Study Arm	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Group A: 1 mg M-001	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Group B: Placebo																	
Day 9	Group A: 1 mg M-001																	
	Group B: Placebo																	
Day 30	Group A: 1 mg M-001																	
	Group B: Placebo																	
Max Severity Post Baseline	Group A: 1 mg M-001																	
	Group B: Placebo																	

Notes: N=number of subjects in Safety Analysis population.
The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

Tables with similar format:

Table 63: Laboratory Results by Parameter, Study Day, and Study Arm – Total Bilirubin

Table 64: Laboratory Results by Parameter, Study Day, and Study Arm – Creatinine

Table 65: Laboratory Summary Statistics by Parameter, Study Day, and Study Arm – Alanine Aminotransferase*

Study Day	Study Arm	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Group A: 1 mg M-001	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Group B: Placebo					
Day 9	Group A: 1 mg M-001					
	Group B: Placebo					
Day 30	Group A: 1 mg M-001					
	Group B: Placebo					
Max Severity Post Baseline	Group A: 1 mg M-001					
	Group B: Placebo					
Note: N=number of subjects in Safety Analysis population.						

Tables with similar format:

Table 66: Laboratory Summary Statistics by Parameter, Study Day, and Study Arm – Total Bilirubin*

Table 67: Laboratory Summary Statistics by Parameter, Study Day, and Study Arm – Creatinine*

14.3.5.2 Hematology Results

Table 68: Laboratory Results by Parameter, Maximum Severity, Study Day, and Study Arm – Any Hematology Parameter

Study Day	Study Arm	N	None		Mild / Grade 1		Moderate/ Grade 2		Severe/ Grade 3		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Group A: 1 mg M-001	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Group B: Placebo											
Day 9	Group A: 1 mg M-001											
	Group B: Placebo											
Day 30	Group A: 1 mg M-001											
	Group B: Placebo											
Max Severity Post Baseline	Group A: 1 mg M-001											
	Group B: Placebo											

Notes: N=number of subjects in Safety Analysis population.
The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

Table 69: Laboratory Results by Parameter, Maximum Severity, Study Day, and Study Arm – White Blood Cells

Study Day	Study Arm	N	None		Mild/ Grade 1 (Low)		Mild/ Grade 1 (High)		Moderate/ Grade 2 (Low)		Moderate/ Grade 2 (High)		Severe/ Grade 3 (Low)		Severe/ Grade 3 (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Group A: 1 mg M-001	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Group B: Placebo																	
Day 9	Group A: 1 mg M-001																	
	Group B: Placebo																	
Day 30	Group A: 1 mg M-001																	
	Group B: Placebo																	
Max Severity Post Baseline	Group A: 1 mg M-001																	
	Group B: Placebo																	

Notes: N=number of subjects in Safety Analysis population.
The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

Tables with similar format:

Table 70: Laboratory Results by Parameter, Maximum Severity, Study Day, and Study Arm – Hemoglobin

Table 71: Laboratory Results by Parameter, Maximum Severity, Study Day, and Study Arm – Platelets

Table 72: Laboratory Summary Statistics by Parameter, Study Day, and Study Arm – White Blood Cells*

Study Day	Study Arm	N	Mean	Standard Deviation	Median	Min, Max
Baseline	Group A: 1 mg M-001	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Group B: Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x
Day 9	Group A: 1 mg M-001	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Group B: Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x
Day 30	Group A: 1 mg M-001	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Group B: Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x
Max Severity Post Baseline	Group A: 1 mg M-001	x	xx.x	xx.x	xx.x	xx.x, xx.x
	Group B: Placebo	x	xx.x	xx.x	xx.x	xx.x, xx.x
Note: N=number of subjects in Safety Analysis population.						

Tables with similar format:

Table 73: Laboratory Summary Statistics by Parameter, Study Day, and Study Arm – Hemoglobin*

Table 74: Laboratory Summary Statistics by Parameter, Study Day, and Study Arm – Platelets*

14.3.6 Displays of Vital Signs

Table 75: Vital Signs by Assessment, Maximum Severity, Study Day, and Study Arm – Any Assessment

Study Day	Study Arm	N	None		Mild		Moderate		Severe		Missing	
			n	%	n	%	n	%	n	%	n	%
Baseline	Group A: 1 mg M-001	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Group B: Placebo	x	x	xx	x	xx	x	xx	x	xx	x	xx
Day 22	Group A: 1 mg M-001	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Group B: Placebo	x	x	xx	x	xx	x	xx	x	xx	x	xx
Day 172	Group A: 1 mg M-001	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Group B: Placebo	x	x	xx	x	xx	x	xx	x	xx	x	xx
Max Severity Post Baseline	Group A: 1 mg M-001	x	x	xx	x	xx	x	xx	x	xx	x	xx
	Group B: Placebo	x	x	xx	x	xx	x	xx	x	xx	x	xx

Notes: N=number of subjects in Safety Analysis population.
The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

Table 76: Vital Signs by Assessment, Maximum Severity, Study Day, and Study Arm – Systolic Blood Pressure

Study Day	Study Arm	N	None		Mild (Low)		Mild (High)		Moderate (Low)		Moderate (High)		Severe (Low)		Severe (High)		Missing	
			n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Baseline	Group A: 1 mg M-001	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Group B: Placebo	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Day 22	Group A: 1 mg M-001	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Group B: Placebo	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Day 172	Group A: 1 mg M-001	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Group B: Placebo	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
Max Severity Post Baseline	Group A: 1 mg M-001	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx
	Group B: Placebo	x	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx	x	xx

Notes: N=number of subjects in Safety Analysis population.
The "Max Post Baseline" rows indicate the maximum severity experienced by each subject at any time point post baseline, including unscheduled assessments.

Tables with similar format:

Table 77: Vital Signs by Assessment, Maximum Severity, Study Day, and Study Arm – Diastolic Blood Pressure

Table 78: Vital Signs by Assessment, Maximum Severity, Study Day, and Study Arm – Oral Temperature

Table 79: Vital Signs by Assessment, Maximum Severity, Study Day, and Study Arm – Pulse

14.4 Summary of Concomitant Medications

Table 80: Number and Percentage of Subjects with Prior and Concurrent Medications by WHO Drug Classification and Study Arm

WHO Drug Code Level 1, Anatomic Group	WHO Drug Code Level 2, Therapeutic Subgroup	Group A: 1 mg M-001 (N=X)		Group B: Placebo (N=X)		All Subjects (N=X)	
		n	%	n	%	n	%
Any Level 1 Codes	Any Level 2 Codes	x	xx	x	xx	x	xx
[ATC Level 1 - 1]	Any [ATC 1 – 1]	x	xx	x	xx	x	xx
	[ATC 2 - 1]	x	xx	x	xx	x	xx
	[ATC 2 - 2]	x	xx	x	xx	x	xx
	[ATC 2 - 3]	x	xx	x	xx	x	xx
[ATC Level 1 – 2]	[ATC 2 - 1]	x	xx	x	xx	x	xx
	[ATC 2 - 2]	x	xx	x	xx	x	xx
	[ATC 2 - 3]	x	xx	x	xx	x	xx

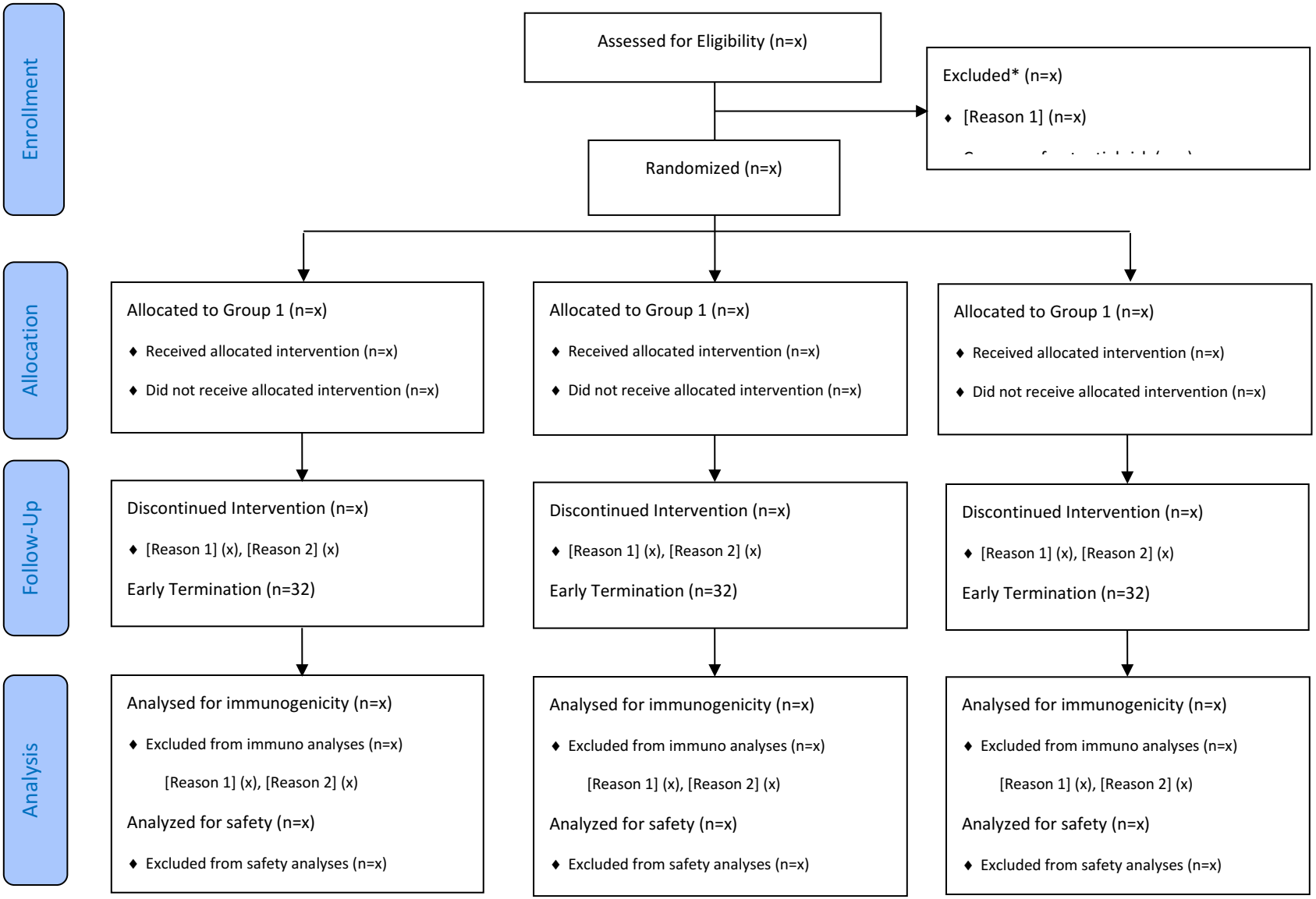
Notes: N=number of subjects in Safety Analysis population.
n=Number of subjects reporting taking at least one medication in the specific WHO Drug Class.

APPENDIX 2. FIGURE MOCK-UPS

LIST OF FIGURES

10.1 Disposition of Subjects

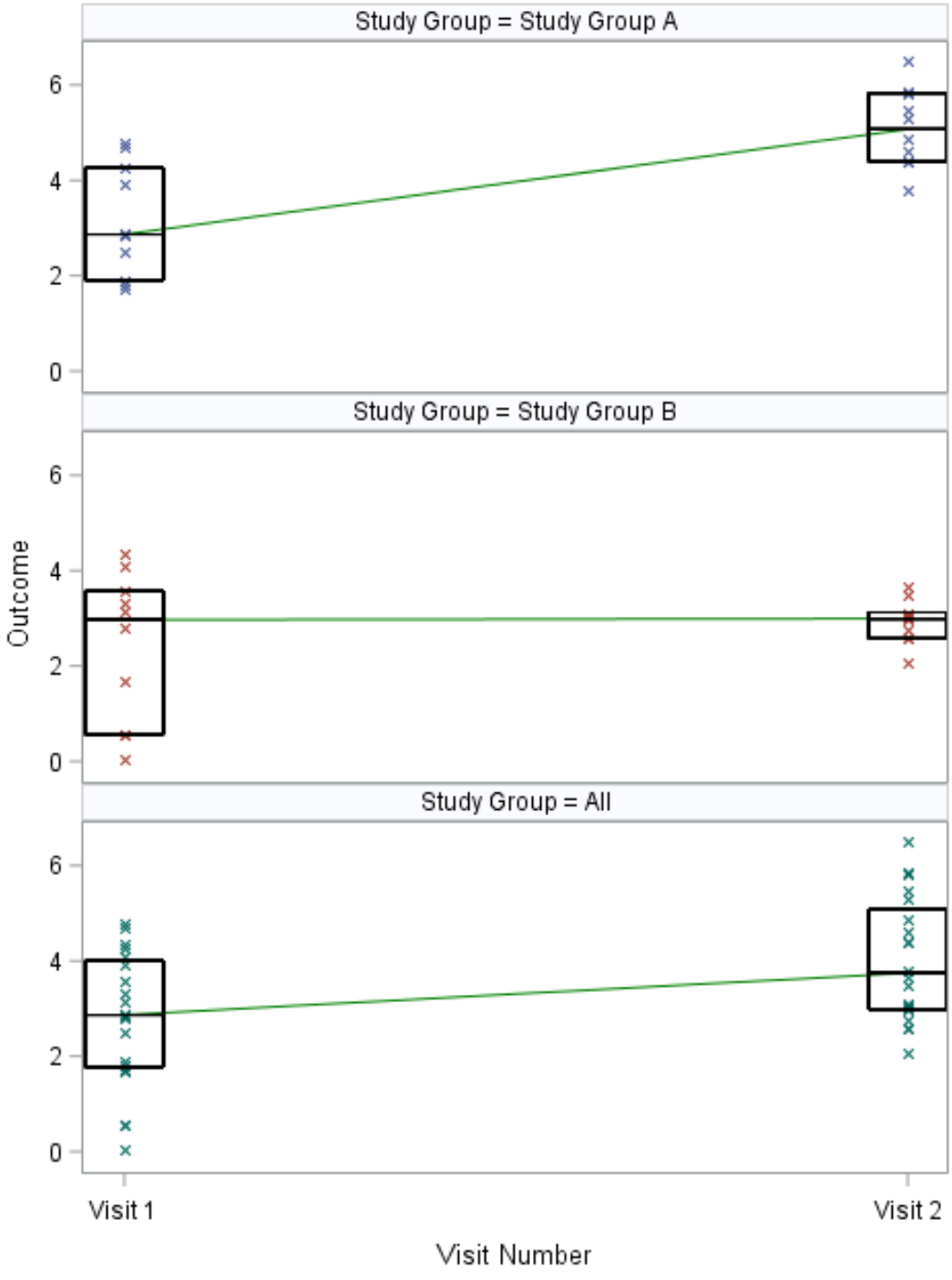
Figure 1: CONSORT Flow Diagram



14.2.2 Efficacy/Immunogenicity Response Figures by Measure, Vaccination, and Study Day

Figure 2: Box Plots of Percentage of Selected CD4+ T Cell Subsets Expressing Markers After M-001 Stimulation by Study Arm and Study Day, Per Protocol Population*

[Implementation Note: The 5 combinations of markers with the highest GMP should be displayed in separate panels of one image file (2 rows, 5 columns). The x-axis should be study day (Baseline, Day 15, Day 36, Day 43, Day 78, Day 172, Day 186, and Day 200), and the y-axis should be percentage. Do not include an "All Subjects" panel.]



Figures with similar format:

Figure 3: Box Plots of Percentage of Selected CD4+ T Cell Subsets Expressing Markers After M-001 Stimulation by Study Arm and Study Day, Modified Intent-to-Treat Population*

Figure 4: Box Plots of Percentage of Selected CD8+ T Cell Subsets Expressing Markers After M-001 Stimulation by Study Arm and Study Day, Per Protocol Population*

Figure 5: Box Plots of Percentage of Selected CD8+ T Cell Subsets Expressing Markers After M-001 Stimulation by Study Arm and Study Day, Modified Intent-to-Treat Population*

Figure 6: Box Plots of Percentage of Selected CD4+ T Cell Subsets Expressing Markers After Seasonal Influenza A Antigen Stimulation by Study Arm and Study Day, Per Protocol Population

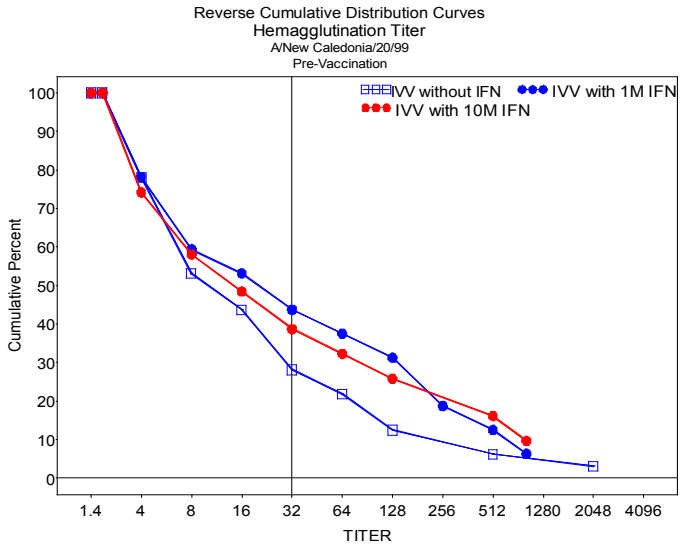
Figure 7: Box Plots of Percentage of Selected CD4+ T Cell Subsets Expressing Markers After Pandemic Influenza A Antigen Stimulation by Study Arm and Study Day, Per Protocol Population

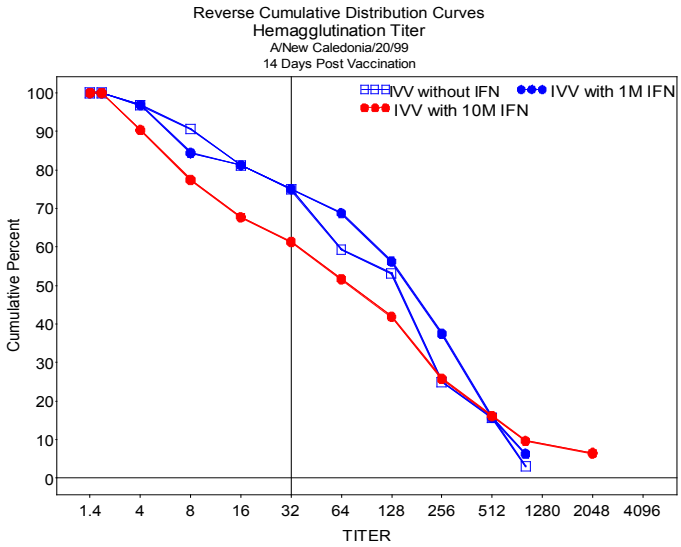
Figure 8: Box Plots of Percentage of Selected CD8+ T Cell Subsets Expressing Markers After Seasonal Influenza A Antigen Stimulation by Study Arm and Study Day, Per Protocol Population

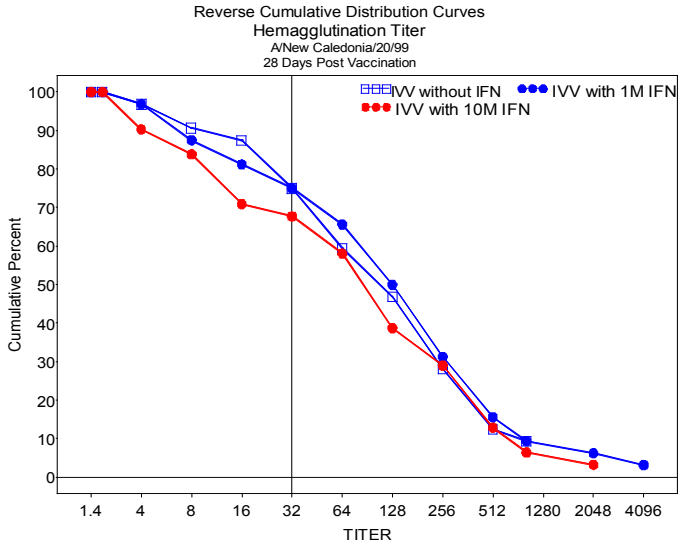
Figure 9: Box Plots of Percentage of Selected CD8+ T Cell Subsets Expressing Markers After Pandemic Influenza A Antigen Stimulation by Study Arm and Study Day, Per Protocol Population

Figure 10: Reverse Cumulative Distribution of Hemagglutination Inhibition Antibody Against A/Michigan/45/2015 X-275 (H1N1) by Study Day and Study Arm, Per Protocol Population

[Implementation Note: Plot each time point in a separate panel, with the 2 study arms in different colors and/or line types.]







Figures with similar format:

Figure 11: Reverse Cumulative Distribution of Hemagglutination Inhibition Antibody Against A/Singapore/INFIMH-16-0019/2016 NIB-104 (H3N2)-Guinea RBC by Study Day and Study Arm, Per Protocol Population

Figure 12: Reverse Cumulative Distribution of Hemagglutination Inhibition Antibody Against B/Colorado/6/2017 (B Victoria Lineage) by Study Day and Study Arm, Per Protocol Population

Figure 13: Reverse Cumulative Distribution of Hemagglutination Inhibition Antibody Against B/Phuket/3073/2013 (B Yamagata Lineage) by Study Day and Study Arm, Per Protocol Population

Figure 14: Reverse Cumulative Distribution of Neutralizing Antibody Against A/Michigan/45/2015 X-275 (H1N1) by Study Day and Study Arm, Per Protocol Population

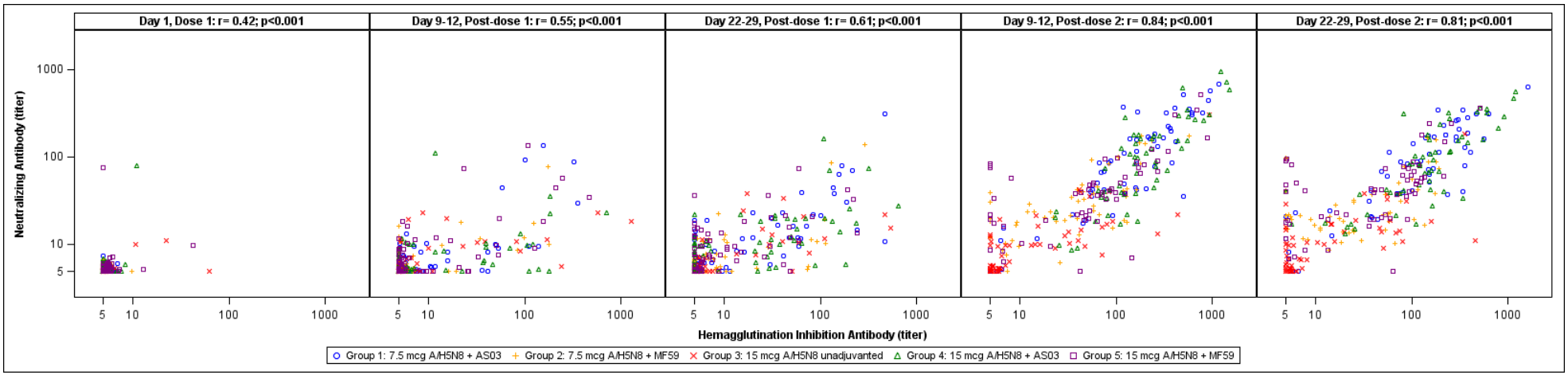
Figure 15: Reverse Cumulative Distribution of Neutralizing Antibody Against A/Singapore/INFIMH-16-0019/2016 NIB-104(H3N2) by Study Day and Study Arm, Per Protocol Population

Figure 16: Reverse Cumulative Distribution of Neutralizing Antibody Against B/Colorado/6/2017 (B Victoria Lineage) by Study Day and Study Arm, Per Protocol Population

Figure 17: Reverse Cumulative Distribution of Neutralizing Antibody Against B/Phuket/3073/2013 (B Yamagata Lineage) by Study Day and Study Arm, Per Protocol Population

Figure 18: Correlation of Hemagglutination Inhibition Antibody and Neutralizing Antibody Against A/H1N1 by Study Day and Study Arm, Per Protocol Population

[Implementation Note: A generic sample figure is shown below. The scatter plots should be presented in a single figure with separate panels for each visit. Visit labels should be included in the panel header. Within each panel distinct marker types and colors should be used to indicate the 2 vaccination groups, with vaccination group labels included in a legend. The spearman correlation should be calculated over all subjects and annotated within each panel header after the visit label as "r=0.xx, p=0.xx". The x-axis should be labeled by "Hemagglutination Inhibition Antibody (Titer)" and the y-axis by "Neutralizing Antibody (Titer)".]



Figures with similar format:

Figure 19: Correlation of Hemagglutination Inhibition Antibody and M-001 Antibody Against A/H1N1 by Study Day and Study Arm, Per Protocol Population

Figure 20: Correlation of Neutralizing Antibody and M-001 Antibody Against A/H1N1 by Study Day and Study Arm, Per Protocol Population

Figure 21: Correlation of Hemagglutination Inhibition Antibody and Neutralizing Antibody against A/H3N2 by Study Day and Study Arm, Per Protocol Population

Figure 22: Correlation of Hemagglutination Inhibition Antibody and M-001 Antibody Against A/H3N2 by Study Day and Study Arm, Per Protocol Population

Figure 23: Correlation of Neutralizing Antibody and M-001 Antibody Against A/H3N2 by Study Day and Study Arm, Per Protocol Population

Figure 24: Correlation of Hemagglutination Inhibition Antibody and Neutralizing Antibody Against B/Colorado/6/2017 (B Victoria Lineage) by Study Day and Study Arm, Per Protocol Population

Figure 25: Correlation of Hemagglutination Inhibition Antibody and M-001 Antibody Against B/Colorado/6/2017 (B Victoria Lineage) by Study Day and Study Arm, Per Protocol Population

Figure 26: Correlation of Neutralizing Antibody and M-001 Antibody Against B/Colorado/6/2017 (B Victoria Lineage) by Study Day and Study Arm, Per Protocol Population

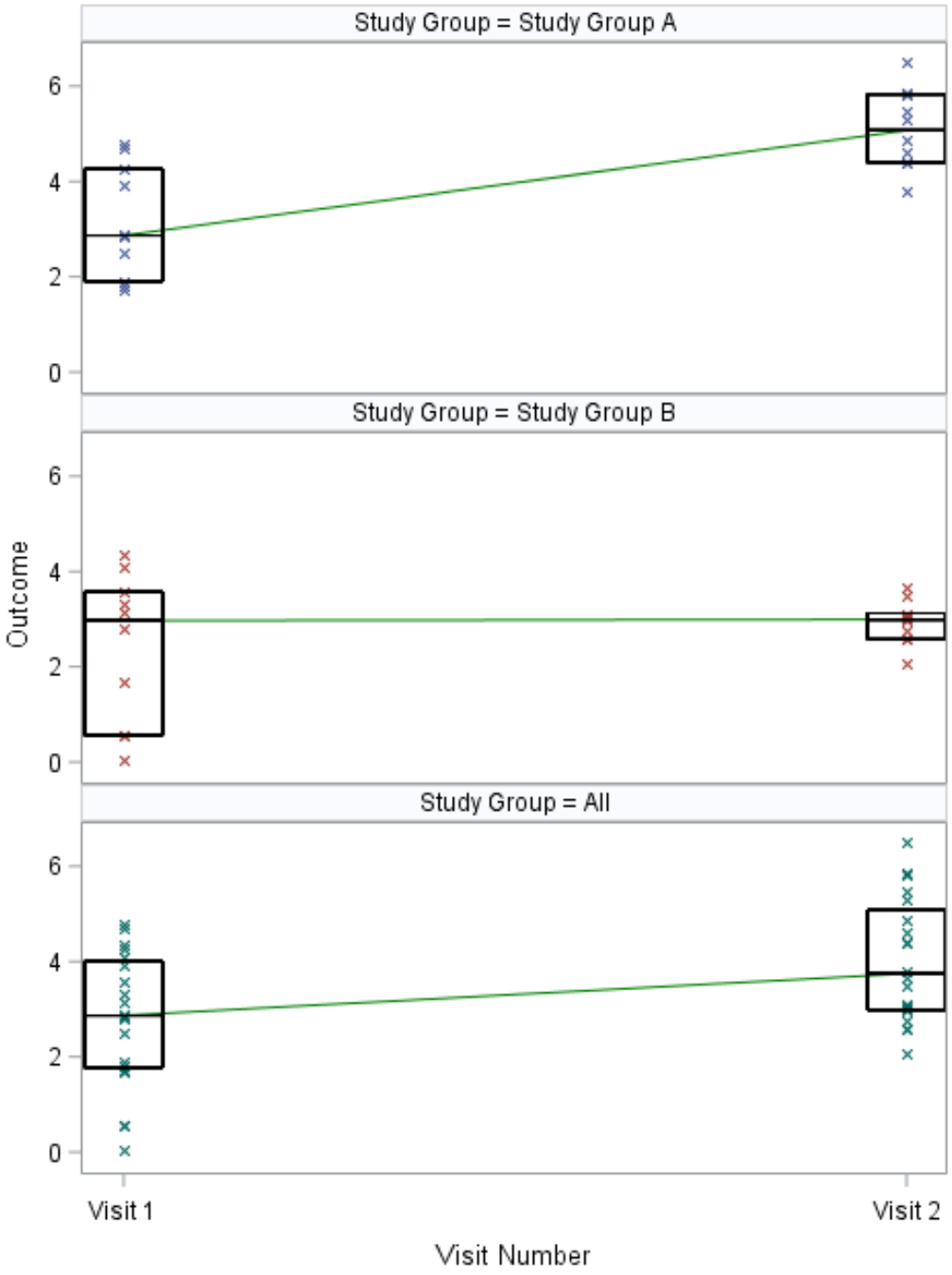
Figure 27: Correlation of Hemagglutination Inhibition Antibody and Neutralizing Antibody Against B/Phuket/3073/2013 (B Yamagata Lineage) by Study Day and Study Arm, Per Protocol Population

Figure 28: Correlation of Hemagglutination Inhibition Antibody and M-001 Antibody Against B/Phuket/3073/2013 (B Yamagata Lineage) by Study Day and Study Arm, Per Protocol Population

Figure 29: Correlation of Neutralizing Antibody and M-001 Antibody Against B/Phuket/3073/2013 (B Yamagata Lineage) by Study Day and Study Arm, Per Protocol Population

Figure 30: Box Plots of Percentage of Influenza-Specific CD4+ T Cell Subsets Expressing Discrete Memory Markers (CCR7, CD45RO, CD57) by Study Arm and Study Day, Per Protocol Population

[Implementation Note: The x-axis should be study day (Baseline, Day 15, Day 36, Day 43, Day 78, Day 172, Day 186, and Day 200), and the y-axis should be percentage.]



Figures with similar format:

Figure 31: Box Plots of Percentage of Influenza-Specific CD8+ T Cell Subsets Expressing Discrete Memory Markers (CCR7, CD45RO, CD57) by Study Arm and Study Day, Per Protocol Population

Figure 32: Box Plots of Percentage of Influenza-Specific CD4+ T Cell Subsets Expressing IL-4 or IL-17 by Study Arm and Study Day, Per Protocol Population

Figure 33: Box Plots of Percentage of Influenza-Specific CD4+ T Cell Subsets Expressing Blood T Follicular Helper Cells (T_{FH} CD4+CXCR5+PD-1+IL-21+) by Study Arm and Study Day, Per Protocol Population

Figure 34: Box Plots of Percentage of Influenza-Specific CD4+ T Cell Subsets Expressing Blood T Follicular Regulatory Cells (T_{FR} CXCR5+PD-1+CD25+CD127+) by Study Arm and Study Day, Per Protocol Population

Figure 35: Box Plots of Percentage of Influenza-Specific CD4+ T Cell Subsets Expressing Blood Tregs (CD25+Foxp3+) by Study Arm and Study Day, Per Protocol Population

14.3.1.1 Solicited Adverse Events

Figure 36: Maximum Severity of Solicited Systemic Symptoms per Subject by Day Post Vaccination

[Implementation Note: The figure can be shaded with the default coloring instead of the patterns.]

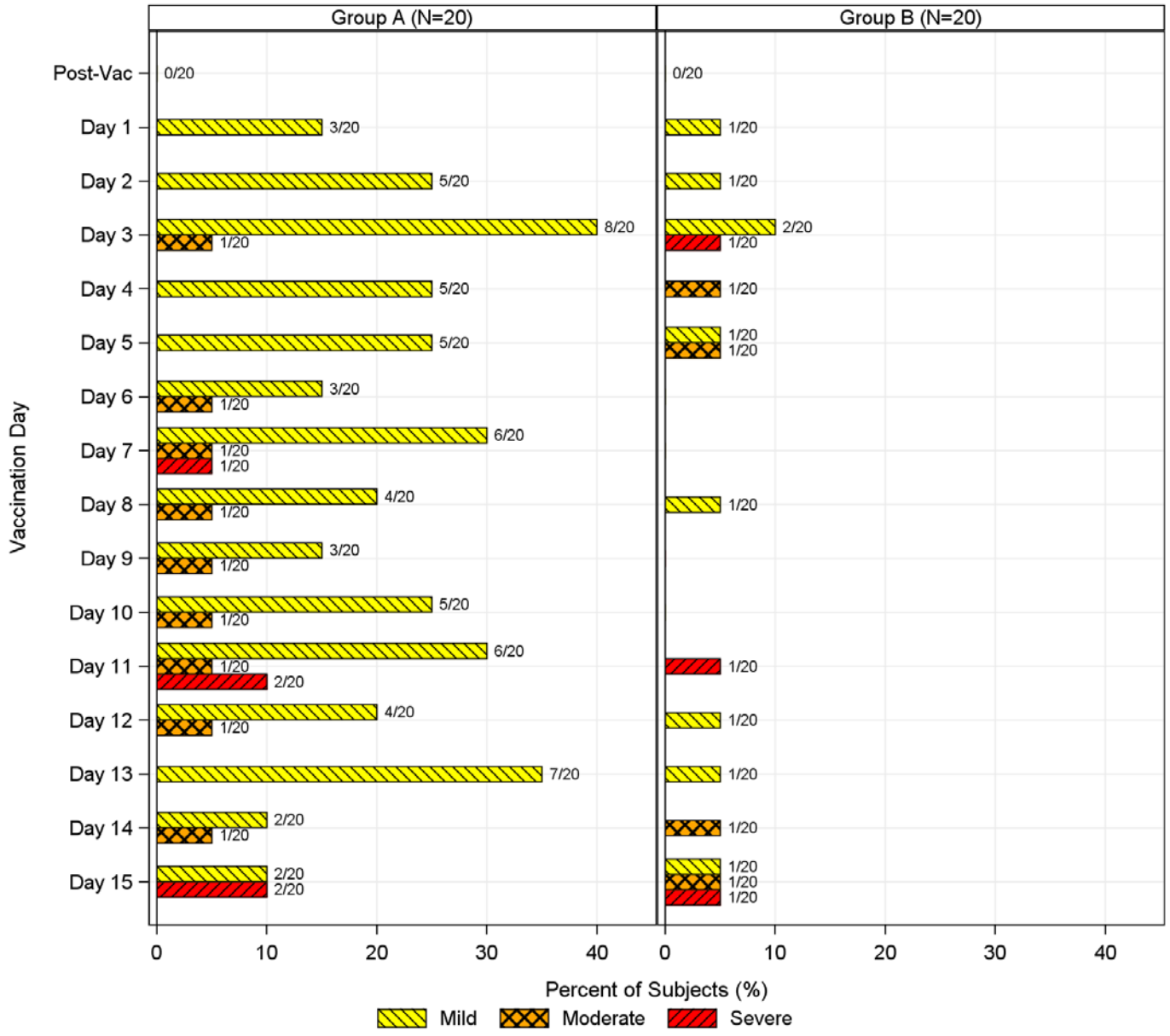
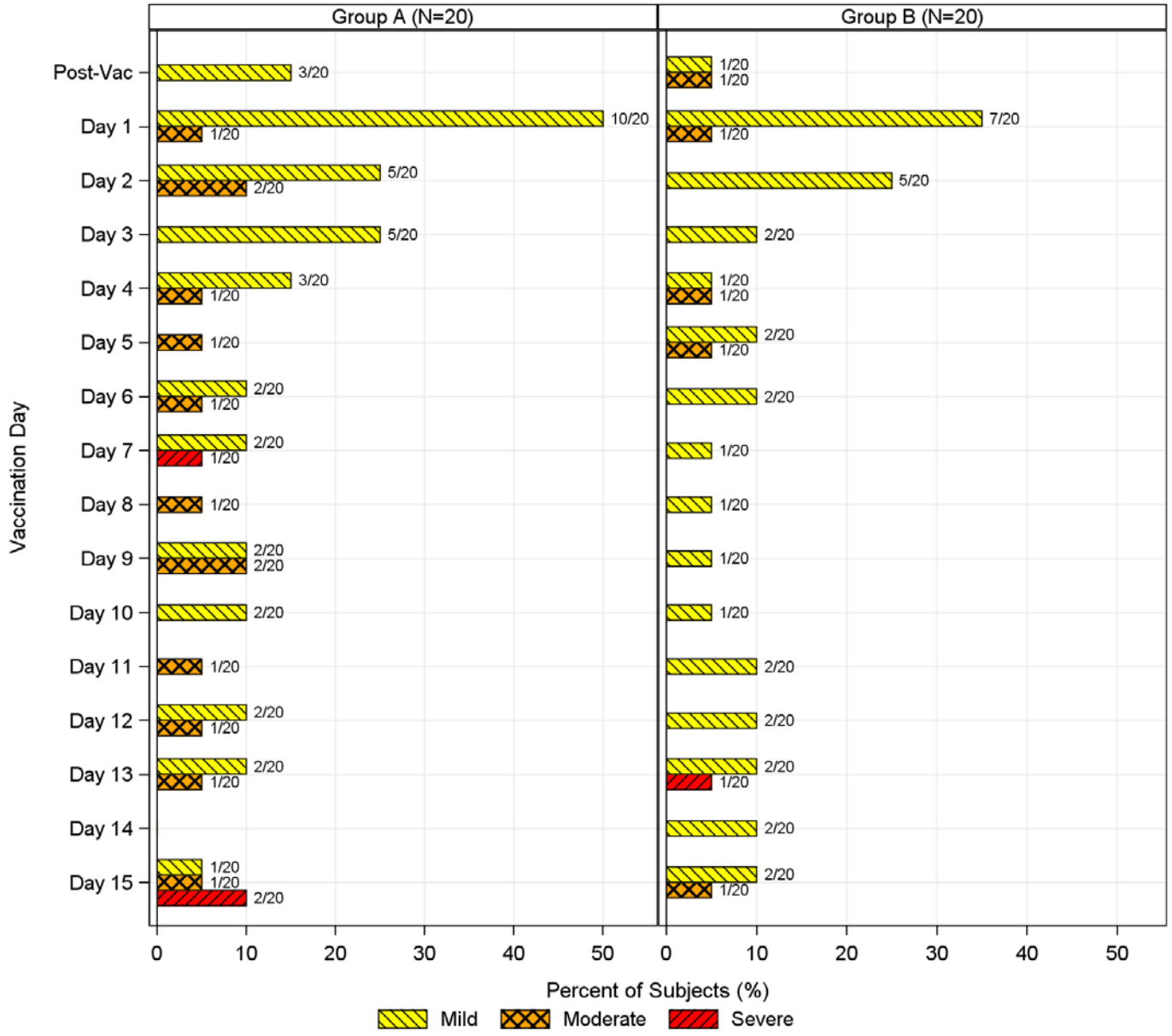


Figure 37: Maximum Severity of Solicited Local Symptoms per Subject by Day Post Vaccination

[Implementation Note: The figure can be shaded with the default coloring instead of the patterns.]



14.3.1.2 Unsolicited Adverse Events

Figure 38: Incidence of Unsolicited Adverse Events by MedDRA® System Organ Class and Severity

[Implementation Note: The SOCs should be sorted in descending incidence. The figure can be shaded with the default coloring instead of the patterns.]

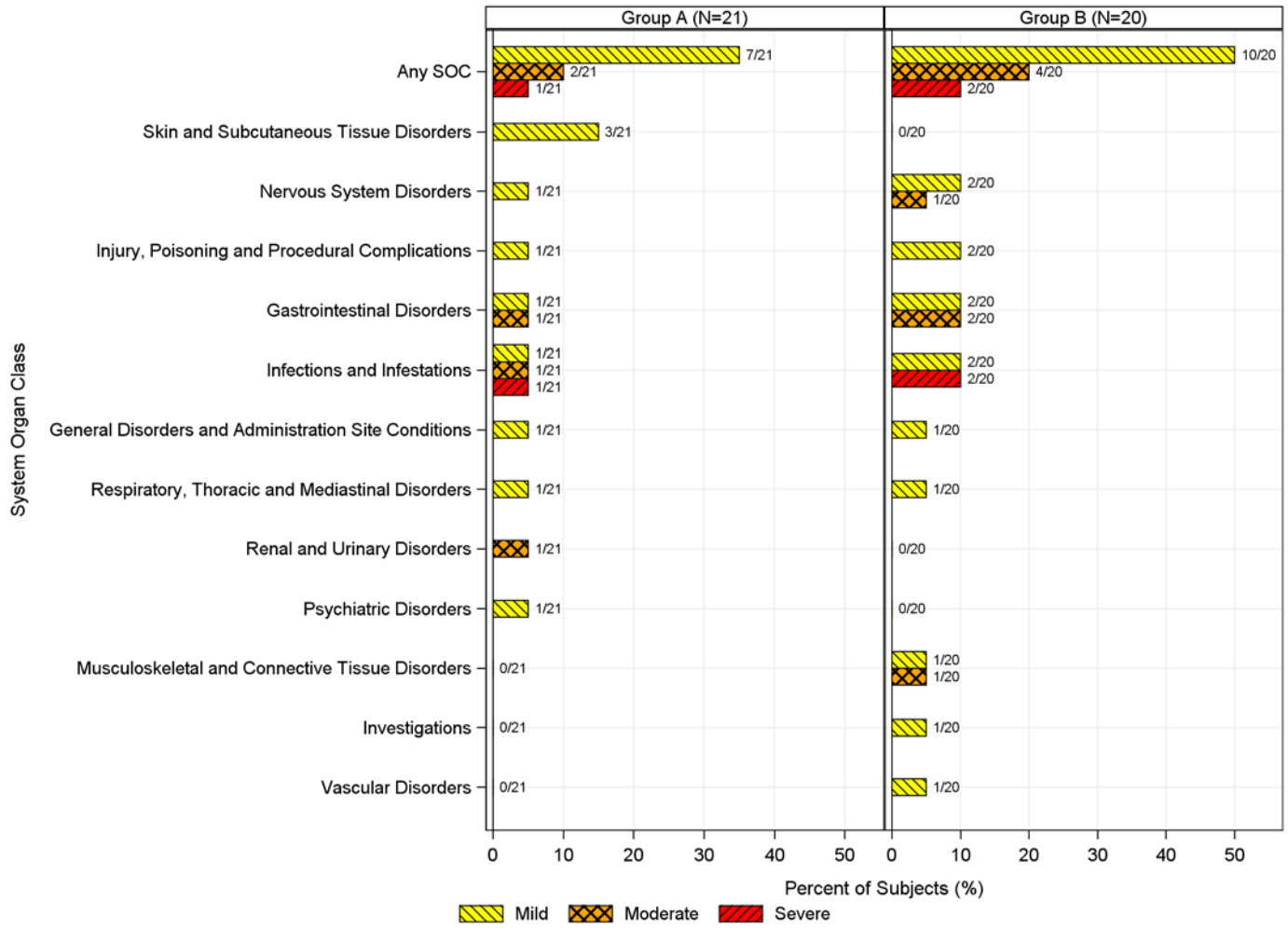


Figure 39: Frequency of Unsolicited Adverse Events by MedDRA System Organ Class and Relationship to Study Vaccination

[Implementation Note: A Generic figure is shown below. The bar chart should be presented in a single figure with separate panels for each for each treatment arm (total 2 panels: 2 rows x 1 column). Axes should be labeled as shown. The treatment arms should be indicated in the panel headers as follows: Group 1: 1 mg M-001 (N=X), Group 2: Placebo (N=X), where N = the number of subjects in the in the Safety Population. This figure includes serious and non-serious unsolicited adverse events.]

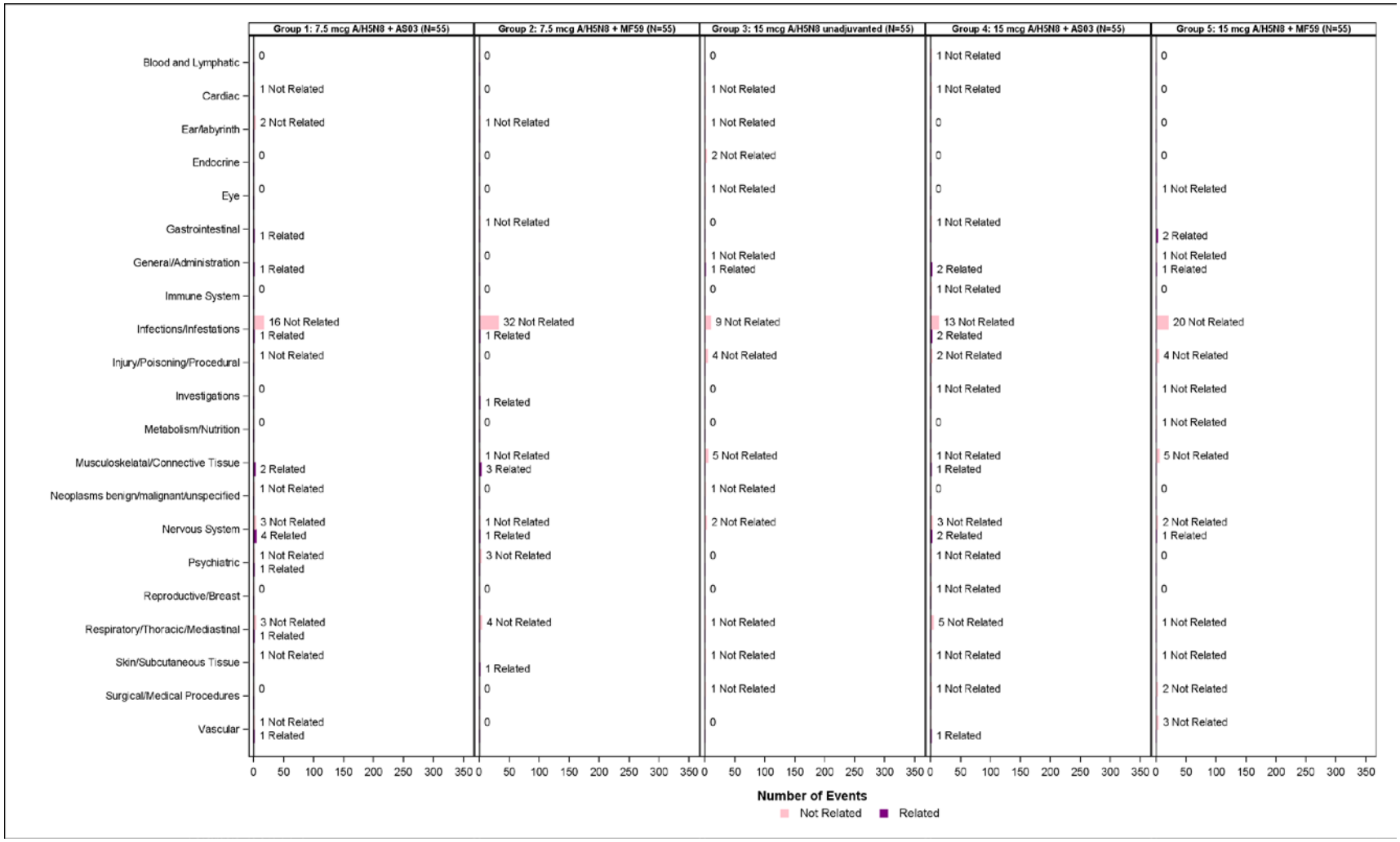
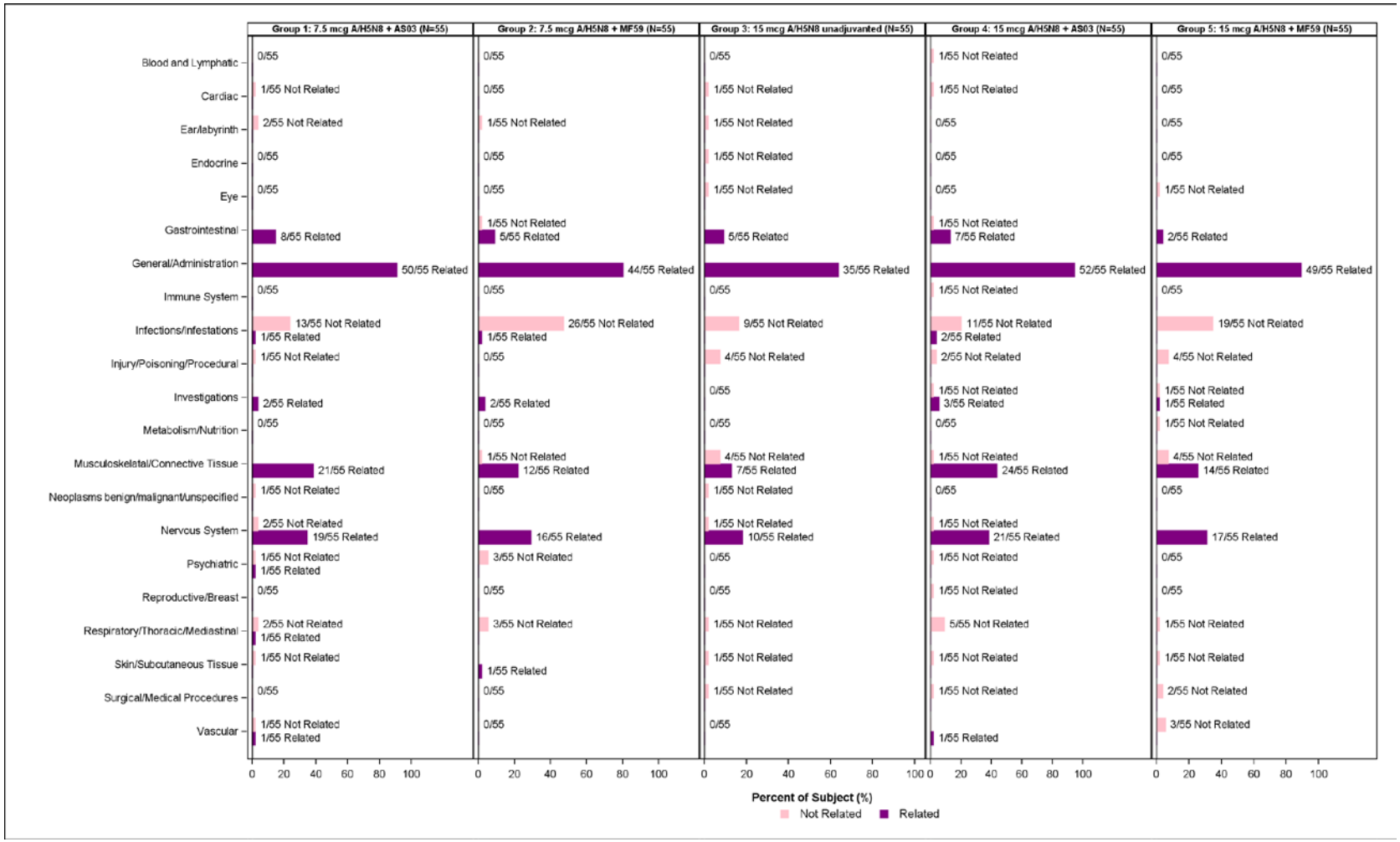


Figure 40: Incidence of Unsolicited Adverse Events by MedDRA System Organ Class and Relationship to Study Vaccination

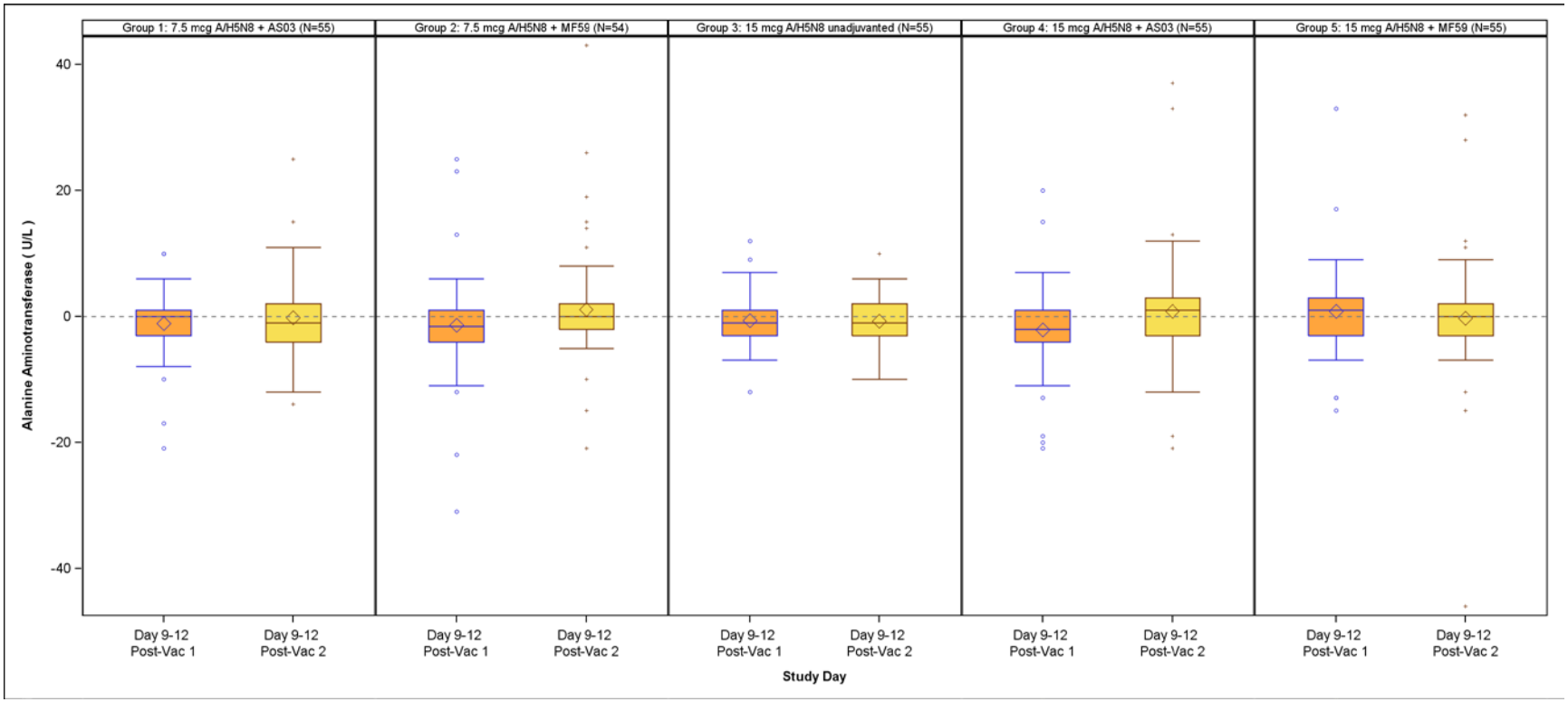
[Implementation Note: A Generic figure is shown below. The bar chart should be presented in a single figure with separate panels for each for each treatment arm (total 2 panels: 2 rows x 1 column). Axes should be labeled as follows: x-axis: Study Group, y-axis: Number of Events. The treatment arms should be indicated in the panel headers as follows: Group 1: 1 mg M-001 (N=X), Group 2: Placebo (N=X) where N = the number of subjects in the in the Safety Population. This figure includes serious and non-serious unsolicited adverse events.]



14.3.5 Displays of Laboratory Results

Figure 41: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Study Day and Study Arm – Chemistry Parameters

[Implementation note: Plot should be generated with all study groups in a single image file with panels for each study group (3 rows – one for each parameter: Alanine Aminotransferase, Total Bilirubin, Creatinine for chemistry parameters, White Blood Cells, Hemoglobin, Platelets for hematology parameters – by 2 columns – one for each group – similar in style to below). Box-plots should be plotted for each post-vaccination visit (Visit 02 & Visit 05). Y-axis should be labeled "[Parameter] Change from baseline ([units])"]



Figures with similar format:

Figure 42: Laboratory Results by Scheduled Visits: Mean Changes from Baseline by Study Day and Study Arm – Hematology Parameters

APPENDIX 3. LISTINGS MOCK-UPS

LISTING OF LISTINGS

16.1.6 Listing of Subjects Receiving Investigational Product

Listing 1: 16.1.6 Listing of Subjects Receiving Investigational Product

Randomized Treatment Group	Actual Treatment Group	Subject ID	Enrollment Date

16.2 Database Listings by Subject

16.2.1 Discontinued Subjects

Listing 2: 16.2.1 Early Terminations or Discontinued Subjects

[Implementation Note: In the "Reason" column, concatenate any "specify" fields, including AE number and DV number. In the CSR, Subject ID should be USUBJID (not PATID). Listings should be sorted by Study Arm, then by Subject ID, and here then alphabetically by Category.]

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

16.2.2 Protocol Deviations

Listing 3: 16.2.2.1 Subject-Specific Protocol Deviations

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

Listing 4: 16.2.2.2 Non-Subject-Specific Protocol Deviations

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

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing 5: 16.2.3 Subjects Excluded from Analysis Populations

Study Arm	Subject ID	Analyses in which Subject is Included	Analyses from which Subject is Excluded	Results Available?	Reason Subject Excluded
		[e.g., Safety, mITT, PP]	[e.g., Safety, mITT, PP, Day x]		

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

16.2.4 Demographic Data

Listing 6: 16.2.4.1 Demographic Data

Study Arm	Subject ID	Sex	Age at Enrollment (years)	Ethnicity	Race	Prior Seasonal Influenza Vaccination

Listing 7: 16.2.4.2 Pre-Existing and Concurrent Medical Conditions

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

16.2.6 Individual Immunogenicity Response Data

Listing 8: 16.2.6.1 Individual Immunogenicity Response Data – Hemagglutination Inhibition against A/H1N1

Study Arm	Subject ID	Planned Study Day	Actual Study Day	Titer

Listings with similar format:

Listing 9: 16.2.6.2 Individual Immunogenicity Response Data – Hemagglutination Inhibition against A/H3N2

Listing 10: 16.2.6.3 Individual Immunogenicity Response Data – Hemagglutination Inhibition against B/Colorado/6/2017

Listing 11: 16.2.6.4 Individual Immunogenicity Response Data – Hemagglutination Inhibition against B/Phuket/3073/2013

Listing 12: 16.2.6.5 Individual Immunogenicity Response Data – Neutralizing Antibody against A/H1N1

Listing 13: 16.2.6.6 Individual Immunogenicity Response Data – Neutralizing Antibody against A/H3N2

Listing 14: 16.2.6.7 Individual Immunogenicity Response Data – Neutralizing Antibody against B/Colorado/6/2017

Listing 15: 16.2.6.8 Individual Immunogenicity Response Data – Neutralizing Antibody against B/Phuket/3073/2013

Listing 16: 16.2.6.9 Individual Immunogenicity Response Data – ELISA Antibody against M-001

Listing 17: 16.2.6.10 Individual Immunogenicity Response Data – Flow Cytometry Results

Study Arm	Subject ID	Planned Study Day	Actual Study Day	% Influenza-Specific T Cell Memory Subsets Expressing Discrete Memory Markers	% CD4 T Cells Expressing IL-4 or IL-17	% CD4 T Cells Expressing Tfh Cells	% CD 4 T Cells Expressing Tfr Cells	% CD4 T Cells Expressing Tregs

Listing 18: 16.2.6.11 Individual Immunogenicity Response Data – Cell Mediated Immunity

Study Arm	Subject ID	Planned Study Day	Actual Study Day	Stimulus (M-001 Peptides or Influenza A Antigens)	Cell Type (CD4 or CD8)	Cytokine Combination	Percentage T Cells Expressing Combination
Notes: Cytokines are perforin, CD107a, IFN-γ, TNF-α, and IL2. Do not include rows where the percentage expressed is 0.							

16.2.7 Adverse Events

Listing 19: 16.2.7.1 Solicited Events – Systemic Symptoms

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

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

Listing 20: 16.2.7.2 Solicited Events – Local Symptoms

Study Arm	Subject ID	Dose Number	Post Dose Day	Assessment[a]	Symptom	Severity
				MA		
				Clinic		

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

Listing 21: 16.2.7.3 Unsolicited Adverse Events

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

16.2.8 Individual Laboratory Measurements

Listing 22: 16.2.8.1 Clinical Laboratory Results – Chemistry

Study Arm	Subject ID	Planned Study Day	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High

Listing 23: 16.2.8.2 Clinical Laboratory Results – Hematology

Study Arm	Subject ID	Planned Study Day	Actual Study Day	Sex	Age (years)	Laboratory Parameter (Units)	Result (Severity Grade)	Reference Range Low	Reference Range High

16.2.9 Vital Signs and Physical Exam Findings

Listing 24: 16.2.9.1 Vital Signs

Study Arm	Subject ID	Planned Study Day	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 25: 16.2.9.2 Physical Exam Findings

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

16.2.10 Concomitant Medications

Listing 26: 16.2.10 Concomitant Medications

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

16.2.11 Pregnancy Reports

Listing 27: 16.2.11.1 Pregnancy Reports – Maternal Information

Study Arm	Subject ID	Pregnancy Number	Study Day Corresponding to Estimated Date of Conception	Source of Maternal Information	Pregnancy Status	Mother's Pre-Pregnancy BMI	Mother's Weight Gain During Pregnancy	Tobacco, Alcohol, or Drug Use During Pregnancy?	Medications During Pregnancy?	Maternal Complications During Pregnancy?	Maternal Complications During Labor, Delivery, or Post-Partum?

Notes: Maternal Complications are included in the Adverse Event listing.
Medications taken during pregnancy are included in the Concomitant Medications Listing.

Listing 28: 16.2.11.2 Pregnancy Reports – Gravida and Para

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

Notes: Gravida includes the current pregnancy, para events do not.
[a] Preterm Birth
[b] Term Birth

Listing 29: 16.2.11.3 Pregnancy Reports – Live Birth Outcomes

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 30: 16.2.11.4 Pregnancy Reports – Still Birth Outcomes

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 31: 16.2.11.5 Pregnancy Reports – Spontaneous, Elective, or Therapeutic Abortion Outcomes

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

APPENDIX 4. NCA TEMPLATE

See separate document, if applicable.