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

DMID Protocol Number: 14-0112

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BiondVax

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Version Number: 6.0

06 December 2018

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practices (GCP) as required by the following:

- United States Code of Federal Regulations (CFR) 45 CFR Part 46: Protection of Human Subjects
- Food and Drug Administration (FDA) Regulations, as applicable: 21 CFR Part 50 (Protection of Human Subjects), 21 CFR Part 54 (Financial Disclosure by Clinical Investigators), 21 CFR Part 56 (Institutional Review Boards), 21 CFR Part 11, and 21 CFR Part 312 (Investigational New Drug Application), 21 CFR 812 (Investigational Device Exemptions)
- International Council for Harmonisation: Good Clinical Practice (ICH E6); 62 Federal Register 25691 (1997); and future revisions
- Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
- National Institutes of Health (NIH) Office of Extramural Research, Research Involving Human Subjects, as applicable
- National Institute of Allergy and Infectious Diseases (NIAID) Clinical Terms of Award, as applicable
- Applicable Federal, State, and Local Regulations and Guidance

SIGNATURE PAGE

The signature below provides the necessary assurance that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH E6 Good Clinical Practice (GCP) guidelines.

I agree to conduct the study in compliance with GCP and applicable regulatory requirements.

I agree to conduct the study in accordance with the current protocol and will not make changes to the protocol without obtaining the sponsor's approval and IRB/IEC approval, except when necessary to protect the safety, rights, or welfare of subjects.

Site Investigator Signature:

Signed: _____ Date: _____

Principal Investigator

Name:

Title:

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AESIs	Adverse Events of Special Interest
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GBS	Guillain-Barre Syndrome
GCP	Good Clinical Practice
HAI/HI	Hemagglutinin Inhibition
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IEC	Independent or Institutional Ethics Committee
IIV	Inactivated influenza vaccine
IIV3	Trivalent inactivated influenza vaccine
IIV4	Quadrivalent inactivated influenza vaccine
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
JAMA	Journal of the American Medical Association
M-001	Multimeric-001
MedDRA ®	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to subjects)

NCI	National Cancer Institute, NIH, DHHS
NDA	New Drug Application
NEJM	New England Journal of Medicine
Neut	Neutralization (refers to Neutralizing antibodies)
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS
OHRP	Office for Human Research Protections
OHSR	Office for Human Subjects Research
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
PBS	Phosphate Buffered Saline
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PREP Act	Public Readiness and Emergency Preparedness Act
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SDCC	Statistical and Data Coordinating Center
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
sub-I	Sub-Investigator
US	United States
WHO	World Health Organization

PROTOCOL SUMMARY

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
Phase:	2
Population:	Up to 120 healthy males and non-pregnant females, aged 18 to 49 years (inclusive) will be enrolled.
Number of Sites:	Three sites: Baylor College of Medicine, the University of Iowa, and Cincinnati Children's Hospital Medical Center
Study Duration:	Approximately 24 months
Subject Participation Duration:	Approximately 7 months
Description of Agent or Intervention:	• M-001 manufactured by BiondVax • Licensed seasonal quadrivalent inactivated influenza vaccine (IIV4) • Normal saline placebo
Objectives:	Primary: <u>Safety</u> • 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 <u>Immunogenicity</u> • To assess the T cell responses to M-001 component peptides following two doses of M-001

Secondary:

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 adverse events (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 hemagglutination inhibition (HAI) and neutralizing (Neut) antibody responses to the 2018-2019 IIV4 vaccine viruses

Exploratory:

- 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 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

Study Outcome Measures

Primary:

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 AEs 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, interferon gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin 2 (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

Secondary:

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

Exploratory:

- 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

- 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, 21 and 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, 21 and 56 days following the second study vaccination and immediately prior to and approximately 14 and 28 days after IIV4

- Percentage of influenza-specific T cell memory subsets expressing discrete memory markers (CCR7, CD45RO,

and CD57) at baseline (Day 1) and on study days 15, 36, 43, 78, 172, 186 and 200

- 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+, CD1217+), and Tregs (CD25+, Foxp3+) at baseline (Day 1) and on study days 15, 36, 43, 78, 172, 186 and 200

Description of Study Design:

This is a Phase II randomized, double-blind, placebo-controlled trial in 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 will be assigned randomly to 1 of 2 treatment arms (60 subjects per treatment arm) to receive two doses of the M-001 vaccine or placebo (saline) followed by a single dose of IIV4 (2018-2019 formulation; see Table 1). Group A will receive two doses of M-001, each containing 1 mg of M-001, on Days 1 and 22, followed by a single dose of seasonal IIV4 on approximately Day 172 (window for this visit ranges from Day 142 to Day 202). Group B will receive saline placebo on Days 1 and 22, followed by a single dose of IIV4 on approximately Day 172.

Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions from the time of each study vaccination with M-001 (or placebo) through 7 days after the vaccination (inclusive of vaccination day). Unsolicited AEs will be collected from the time of each M-001 vaccination through approximately 21 days after each study vaccination. SAEs will be collected from the time of the first study vaccination through approximately 6 months after the second M-001 (or placebo) study vaccination. Clinical laboratory evaluations for safety will be performed on venous blood collected approximately 8 days after each M-001 (or placebo) vaccination (Days 9 and 30).

Immunogenicity testing will include performing HAI and Neut antibody assays on serum obtained immediately at baseline (Day 1) and on serum collected on Days 43, 172 and 200. ELISA antibody responses to the M-001 vaccine will be assessed on serum collected at baseline (Day 1) and on Days 22, 43, 78, 172 and 200. Cell-mediated immune responses to influenza antigens,

including epitopes represented in the M-001 vaccine, and seasonal and candidate pandemic influenza viruses, will be assessed at baseline (Day 1), 14 days after each vaccination (Days 15, 36, and 186), approximately 21 days (Day 43) and approximately 56 days (Day 78) following receipt of the second M-001 (or placebo) dose, and immediately prior to and approximately 28 days after the IIV4 dose (Days 172 and 200).

If visit 11 occurs before Study Day 200 (because Visit 9 occurred prior to Day 172), then an additional study visit (Visit 12, phone call) will occur on Day 200 to solicit SAE information.

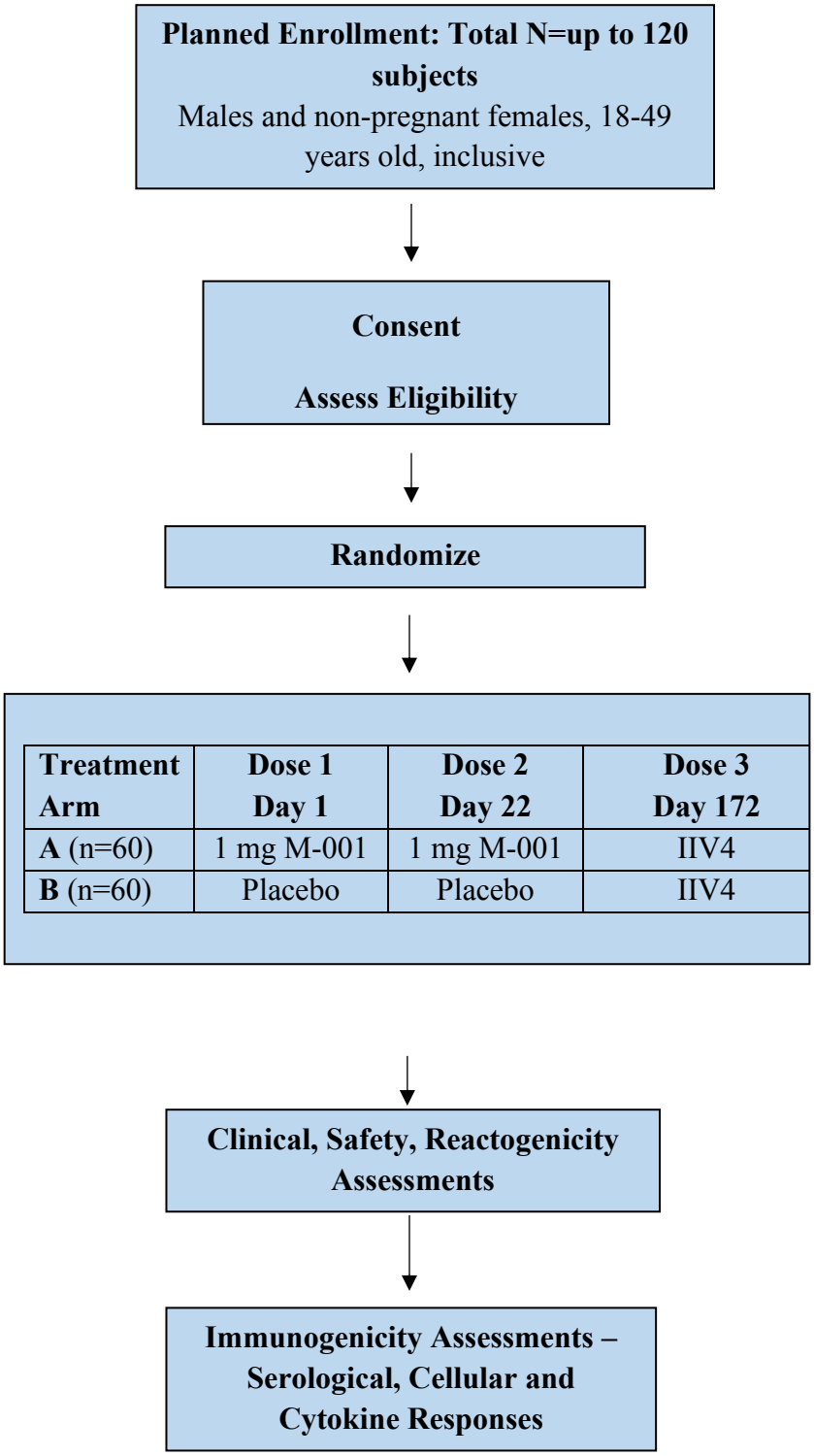
Estimated Time to Complete Enrollment: 2 to 3 months

Table 1: Treatment Arms

Treatment 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

Schematic of Study Design:

Figure 1: Schematic of Study Design



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2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. Background Information

2.1.1. Seasonal and pandemic influenza

Influenza is a common acute viral respiratory illness. Seasonal influenza occurs annually, and in the United States it causes an estimated 100 to 600 thousand hospitalization annually and up to 50,000 deaths a year (1-3). 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). Four pandemics occurred during the last century. It was estimated that during the 1918 influenza A/H1N1 pandemic as many as 40 million deaths occurred worldwide (10). Excess mortality, high morbidity, and social disruption were all noted during the 1957 influenza A/H2N2 and the 1968 influenza A/H3N2 pandemics (11). In April 2009, a novel influenza virus (2009 A/H1N1) originated in pigs and spread to humans around the world becoming the first pandemic of this century. In each of these influenza pandemics, human populations lacked significant levels of pre-existing immunity to a highly transmissible form of the virus enabling it to spread rapidly. Thus, each emergence of a new subtype of influenza virus in the human population has the potential to result in a global public health emergency.

Use of influenza vaccines is the primary means for preventing influenza. Current licensed inactivated vaccines (IIVs) are good for preventing influenza, but are less effective than desirable.

Serum IgG antibody to the influenza virus HA, the major component of inactivated subunit and split virus vaccines, has a major role in protective immunity to influenza virus infection (12). Resistance to infection with seasonal influenza virus strains correlates directly with both serum hemagglutination inhibition (HAI) and neutralizing (Neut) antibody levels, and measurements of serum HAI and Neut antibodies are used routinely to assess the immunogenicity of both seasonal and pandemic IIVs. Cellular immunity also can have a role in preventing influenza-associated illness (13).

Other strategies to improve immune responses to potential pandemic strains are needed. One such approach includes the use of a vaccine that enhances cellular immunity against all influenza viruses (a universal vaccine) and that might also prime for serological responses to inactivated influenza antigens.

2.1.2. Multimeric-001 (M-001)

The use of epitope-based vaccines is another approach that may be used to prime for immune responses to influenza antigens (14). The M-001 vaccine from BiondVax consists of [redacted]

[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 (14). Based upon these characteristics, the M-001 vaccine is hypothesized to provide priming immunity against both existing as well as future emergent seasonal and pandemic influenza virus strains.

The M-001 vaccine is produced as a [redacted]. In the current study, the vaccine is intended to be administered in a non-adjuvanted formulation at a 1 mg/dose level that has been found to be safe and immunogenic in previous clinical trials performed by BiondVax.

Preclinical studies using epitopes expressed in the vaccine in combination with adjuvant demonstrated both vaccine immunogenicity and protection from lethal challenge in a mouse model using highly pathogenic influenza A/H5N1 (15). The safety and efficacy results of M-001 in the preclinical studies led to its evaluation in people (16).

The initial study of M-001 in humans (BVX-002) was conducted in 63 healthy adults as a Phase 1 trial that evaluated the safety and immunogenicity of two doses of M-001 administered by the intramuscular (IM) route at 3 different dosage levels (125, 250 and 500 mcg) with or without Montanide ISA 51 VG adjuvant (17). No safety concerns were identified. Recipients of the adjuvanted 500 mcg dose of M-001 had 22-28% more frequent antibody-dependent, complement-mediated lysis of cells infected with influenza virus strains contained in seasonal vaccines compared to placebo recipients. This group also had significantly higher cellular (PBMC proliferation) responses after exposure to vaccine compared to unprimed groups.

The next study (BVX-003) performed in 60 older adults (55-75 years of age) evaluated the safety and ability of M-001 to [redacted] A greater proportion of recipients of [redacted]. Following this study and based upon the lack of safety concerns, [redacted]

BVX-004 evaluated the safety and immunogenicity of [redacted], when administered [redacted] when administered [redacted] was found [redacted]

The fourth study of M-001 (BVX-005) compared two priming doses of M-001 with one priming dose of alum-adjuvanted or non-adjuvanted M-001 administered 3 weeks prior to seasonal IIV3 in 120 elderly individuals (18). Seroconversion rates were significantly higher in the two-dose M-001 regimen for the seasonal A (H1N1) and B strains compared to placebo (IIV3 alone), and cellular immune responses (IFN-γ expressing CD4 and CD8 lymphocytes) were also significantly increased from pre-immunization levels after exposure to influenza antigens. No safety concerns were identified.

A fifth placebo-controlled study (BVX-006) examining two different dosage levels (0.5 mg and 1 mg) of M-001 as a three-dose prime for seasonal IIV3 immune responses has been conducted in 36 adults. No SAEs were observed and no safety concerns were identified (50). Elevated HAI responses were demonstrated in the experimental group receiving 1 mg M-001 before the IIV3 and hence, this dosage was selected for future trials.

2.1.3. Public Readiness and Emergency Preparedness Act

For this protocol the study product M-001 (manufactured by BiondVax Ltd.) is covered under the Public Readiness and Emergency Preparedness Act (PREP Act). Under the PREP Act, covered persons are immune from liability actions brought from the administration or use of a covered countermeasure that is the subject of a declaration. The PREP Act provides immunity for covered persons (such as manufacturers, distributers, program planners and other qualified persons who prescribe, administer or dispense the M-001 study vaccine) from tort liability, unless the injury was caused by willful misconduct.

The PREP Act also established the Countermeasures Injury Compensation Program (CICP) to provide compensation for serious injuries that occur as the result of the administration or use of certain countermeasures. Any requests for compensation must be filed within one year of administration or use of the countermeasure. Requests would go to the Health Resources and Services Administration (HRSA) Preparedness Countermeasures Injury Compensation Program (http://www.hrsa.gov/cicp/). Compensation may then be available for medical benefits, lost wages and death benefits to eligible individuals for specified injuries in accordance with regulations published by the Secretary of HRSA. Eligibility for compensation and the injuries for which compensation may be available are further defined by regulation.

An individual who suffers a serious physical injury or death from administration and use of the M-001 study vaccine may request benefits from CICP. A serious physical injury means an injury that is life threatening, results in, or requires medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to body structure. The CICP is the payer of last resort. This means that it only covers expenses or provides benefits that other third-party payers, such as health insurance, the Department of Veterans Affairs, or Workers' Compensation programs don't have an obligation to pay.

If no funds have been appropriated to the compensation program, the Secretary of HRSA does not make a final determination on the individual's request within 240 days, or if the individual decides not to accept the compensation, the injured individual or his representative may pursue a tort claim in the United States District Court for the District of Columbia, but only if the claim involves willful misconduct, is pled with particularity required under the PREP Act, verified, and accompanied by an affidavit by a physician who did not treat the individual and certified medical records. Any award is reduced by any public or private insurance or worker's compensation available to the injured individual. Awards for non-economic damages, such as pain, suffering, physical impairment, mental anguish, and loss of consortium are also limited. If the individual accepts compensation, or if there is no willful misconduct, then the individual does not have a tort claim that can be filed in a United States Federal or a State court.

2.2. Rationale

Seasonal and pandemic influenza pose perpetual threats to human populations. The rapid and constant evolution of influenza viruses likewise poses challenges to the development of vaccines for the prevention and control of influenza. Recent vaccine development efforts have focused on the development of "universal" influenza vaccines; that is, vaccines which could offer protection against multiple influenza subtypes. BiondVax has developed a novel vaccine, M-001, that has been shown in preclinical and clinical trials to stimulate both the humoral and cellular arms of the immune system. When used as a primer ahead of a strain-specific boost, M-001 enhances immunity to strains contained within the boost and to drifted strains. The goals of the study are to determine the safety of a M-001 prime followed by an IIV4 boost vaccine strategy, and to assess the effects of M-001 immunization on cellular and humoral immunity to seasonal influenza virus strains.

2.3. Potential Risks and Benefits

2.3.1. Potential Risks

The potential risks of this study are those associated with having blood drawn, IM injection of the M-001 and IIV4 vaccines, possible reactions to the M-001 and quadrivalent seasonal influenza vaccines, and breach of confidentiality.

Drawing blood may cause transient discomfort and fainting. Fainting is usually transient and managed by having the subject lie down. Bruising at the blood draw site may occur, but can be prevented or lessened by applying pressure to the draw site for several minutes. IM injection also may cause transient discomfort and fainting. Drawing blood and IM injection may also cause infection. The use of sterile technique will make infection at the site where blood will be drawn or where the study vaccination is given extremely unlikely.

Occasionally, adult recipients of seasonal non-adjuvanted, licensed IIVs may develop influenza-like reactions such as fever, feverishness, fatigue, malaise, myalgia, arthralgia, headache, and/or

nausea. Some subjects may develop reactions at the injection site, including pruritus, ecchymosis, erythema, induration /swelling, pain, and/or tenderness. With non-adjuvanted licensed, IIVs most of these reactions peak in intensity in the first 24 hours after vaccination and usually disappear without treatment within 1 or 2 days. Analgesics (e.g., acetaminophen, or ibuprofen or similar non-steroidal anti-inflammatory drugs (NSAIDs)) and rest may generally relieve or lessen these reactions. Bruising can sometimes occur due to the vaccination procedure.

In addition, post-marketing surveillance indicates the following autoimmune, auto-inflammatory and immune-mediated diseases as potential risks for the seasonal IIVs: neuritis, convulsions, severe allergic reactions, syncope, encephalitis, thrombocytopenia, vasculitis, and Guillain-Barré syndrome. Reports of these reactions were rare; therefore, exact incidence rates cannot be precisely calculated.

[redacted] have been completed to date (16). AEs described following receipt of [redacted] but have included [redacted]

Acute and potentially life-threatening allergic reactions are also possible. Very rarely, occurring in about 1 in 4 million people given a licensed IIV, there can be a serious allergic reaction to a vaccine. These reactions can manifest as skin rash (hives), swelling around the mouth, throat or eyes, difficulty breathing, a fast pulse, or loss of blood pressure. If these reactions occur, they can usually be stopped by the administration of emergency medications by the study personnel. As with any vaccine or medication, there is a very small chance of a fatal reaction, although researchers do not expect this to occur.

During the swine influenza (H1N1) vaccine campaign of 1976, some recipients developed a paralytic illness called Guillain-Barré syndrome (GBS). GBS is an acute inflammatory neuropathy characterized by weakness, hyporeflexia or areflexia, and elevated protein concentrations in cerebrospinal fluid. The rate of GBS was significantly increased in individuals receiving the 1976 swine influenza (H1N1) vaccine at about 1 per 100,000 vaccine recipients. This syndrome has not been seen consistently with other influenza vaccines. Most persons who develop GBS recover completely, although the recovery period may be as little as a few weeks or as long as a few years. About 30% of those with GBS still have residual weakness after 3 years and about 3% may suffer a relapse of muscle weakness and tingling sensations many years after the initial attack. Intensive surveillance of GBS after administration of IIVs since 1976 has shown a slight increase in risk over background cases (more than one additional case of GBS per million persons) following vaccination, typically with onset within 6 weeks after vaccination (19). Interestingly, although vaccination rates have increased in the last 10 years the numbers of reported cases of vaccine-associated GBS have declined (20). A recent study in Canada showed that the 2009 H1N1 vaccine was associated with a small but significant risk of GBS in persons

50 years and older (21). An active, population-based surveillance study conducted during the 2009-2010 influenza season found less than 1 excess GBS case per million doses of 2009 H1N1 vaccine administered – a rate similar to that associated with some previously administered annual influenza vaccines (22-25). Another study using the Medicare system showed an elevated risk of GBS with 2009 monovalent H1N1 vaccination (incidence rate ratio = 2.41, 95% confidence interval: 1.14, 5.11; attributable risk = 2.84 per million doses administered, 95% confidence interval: 0.21, 5.48) (26). An international collaboration study also supported a conclusion of an association between 2009 H1N1 vaccination and GBS (27).

It is unknown if the M-001 vaccine poses any risks to an unborn child. Female subjects of childbearing potential who are not surgically sterile via tubal sterilization, bilateral oophorectomy, hysterectomy, or successful Essure® placement with documented radiological confirmation at least 90 days after the procedure, or who are not postmenopausal for ≥ 1 year, must agree to practice highly effective contraception that may include, but is not limited to, abstinence from intercourse with a male partner, monogamous relationship with a vasectomized partner, male condoms with the use of applied spermicide, intrauterine devices, and licensed hormonal methods, for a minimum of 30 days prior to study product through 2 months (defined as 60 days) after the last dose of M-001 or placebo. A highly effective method of contraception is defined as one which results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. In addition to contraceptive use, all female subjects of childbearing potential will be required to have a negative serum or urine pregnancy test within 24 hours prior to receiving each dose of study vaccine. If a female subject becomes pregnant while participating in this study, we will ask her permission to follow-up with her about her health and the health of her baby through pregnancy outcome.

Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subjects' PHI. All records will be kept in a locked file cabinet or maintained in a locked room at the participating VTEU sites. Electronic files will be password protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects by name. Organizations that may inspect and/or copy research records maintained at the participating VTEU sites for quality assurance and data analysis include groups such as NIAID and FDA.

There may be other unknown risks, discomforts, or side effects.

2.3.2. Known Potential Benefits

There are no known benefits attributable to the receipt of the M-001 vaccine, but there is the prospect of benefit. It is possible that vaccination with M-001 will prime the participant for

improved responses to future seasonal or pandemic influenza vaccines. Vaccination with IIV4 likely will lead to protection against seasonal influenza viruses.

There may be pandemic preparedness benefits to society in the future if the M-001 is shown to have a significant priming effect that leads to improved cellular immune responses to influenza and proves to be sufficiently safe so that it can be employed if a need for widespread vaccination against pandemic influenza virus strains occurs.

3. OBJECTIVES

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

- 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. Study Outcome Measures

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 GMTs vs. IIV4 vaccine viruses on Days 1, 43, 172 and 200

3.2.3. Exploratory Outcome Measures

- 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, 21 and 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, 21 and 56 days following the second study vaccination and immediately prior to and approximately 14 and 28 days after IIV4

- Percentage of influenza-specific T cell memory subsets expressing discrete memory markers (CCR7, CD45RO, and CD57) at baseline (Day 1) and on study days 15, 36, 43, 78, 172, 186 and 200

- 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+, CD1217+), and Tregs (CD25+, Foxp3+) at baseline (Day 1) and on study days 15, 36, 43, 78, 172, 186 and 200

4. STUDY DESIGN

This is a Phase II randomized, double-blind, placebo-controlled trial in 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 will be assigned randomly to 1 of 2 treatment arms (60 subjects per treatment arm) to receive two doses of the M-001 vaccine or placebo (saline) followed by a single dose of IIV4 (see Table 1). Group A will receive two doses of M-001, each containing 1 mg of M-001, on Days 1 and 22 followed by a single dose of IIV4 on approximately Day 172 (window for this visit ranges from Day 142 to Day 202). Group B will receive saline placebo on both Days 1 and 22, followed by a single dose of IIV4 approximately on Day 172.

Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions from the time of each study vaccination with M-001 (or placebo) through 7 days after the vaccination (inclusive of vaccination day). Unsolicited AEs will be collected from the time of each M-001 (or placebo) vaccination through approximately 21 days after each study vaccination. SAEs will be collected from the time of the first study vaccination through approximately 6 months after the second M-001 (or placebo) study vaccination. Clinical laboratory evaluations for safety will be performed on venous blood collected approximately 8 days after each M-001 (or placebo) vaccination (Days 9 and 30).

Immunogenicity testing will include performing HAI and Neut antibody assays on serum obtained immediately at baseline (Day 1) and on serum collected on Days 43, 172 and 200. ELISA antibody responses to the M-001 vaccine will be assessed on serum collected at baseline (Day 1) and on Days 22, 43, 78, 172 and 200. Cell-mediated immune responses to influenza antigens, including epitopes represented in the M-001 vaccine, and seasonal and candidate pandemic influenza viruses, will be assessed at baseline (Day 1), 14 days after each vaccination (Days 15, 36, and 186), approximately 21 days (Day 43) and approximately 56 days (Day 78) following receipt of the second M-001 (or placebo) dose, and immediately prior to and approximately 28 days after the IIV4 dose (Days 172 and 200).

The duration of this trial for each subject will be approximately 7 months. If visit 11 occurs before Study Day 200 (because Visit 9 occurred prior to Day 172 and moved visits 10 and 11 to earlier times after study start), then an additional study visit (Visit 12, phone call) will occur on Day 200 to solicit SAE information.

For additional details on study procedures and evaluations and study schedule by study visits/days, see Sections 7 and 8 and Appendix A: Schedule of Study Procedures and Evaluations.

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. Subject Inclusion Criteria

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

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

   [*]*As determined by medical history and targeted physical examination to evaluate acute or currently ongoing chronic medical diagnoses or conditions, defined as those that have been present for at least 90 days, which would affect the assessment of the safety of subjects or the immunogenicity of study vaccinations. Chronic medical diagnoses or conditions should be stable for the last 60 days prior to investigational vaccine study product administration. This includes no change in chronic prescription medication, dose, or frequency as a result of deterioration of the chronic medical diagnosis or condition in the 60 days prior to enrollment and investigational vaccine study product administration . Any prescription change that is due to change of health care provider, insurance company, etc., or that is done for financial reasons, as long as in the same class of medication, will not be considered a deviation of this inclusion criterion. Any change in prescription medication due to* ***improvement*** *of a disease outcome, as determined by the site principal investigator or appropriate sub-investigator, will not be considered a deviation of this inclusion criterion. Subjects may be on chronic or as needed (prn) medications if, in the opinion of the site principal investigator or appropriate sub-investigator, they pose no additional risk to subject safety or assessment of reactogenicity and immunogenicity and do not indicate a worsening of medical diagnosis or condition. Similarly, medication changes subsequent to enrollment and investigational study product vaccination are acceptable provided there was no deterioration in the subject's chronic medical condition that necessitated a medication change. All chronic medical condtions should pose no additional risk to the subject or interference with the evaluation of responses to study vaccination. Note: Topical, nasal, and inhaled medications (with the exception of inhaled corticosteroids as outlined in the Subject Exclusion Criteria (see Section 5.2), herbals, vitamins, and supplements are permitted.*
5. Oral temperature is less than 100.0°F.
6. Pulse[†] is 50 to 100 bpm, inclusive.

   [†]*Acceptable pulse range prior to IIV4 dose is 45 to 115 bpm, inclusive and no symptoms.*
7. Systolic blood pressure[¶] is 85 to 150 mm Hg, inclusive.

   [¶]*Acceptable systolic blood pressure range prior to IIV4 dose is 80 to 155 mm Hg, inclusive and no symptoms.*
8. Diastolic blood pressure[**] is 55 to 95 mmHg, inclusive.

   [**]*Acceptable diastolic blood pressure range prior to IIV4 dose is 50 to 100 mm Hg, inclusive and no symptoms.*
9. Women of childbearing potential[‡] must use an acceptable method of contraception[§] from 30 days prior to vaccination until 60 days after the second of dose of M-001 or placebo.
10. 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.

    [‡]*Not sterilized via tubal ligation, bilateral oophorectomy, hysterectomy, or successful Essure® placement (permanent, non-surgical, non-hormonal sterilization with history of documented radiological confirmation test achieved or with*

use of another approved birth control method if confirmation test not confirmed) and still menstruating or < 1 year of the last menses if menopausal).

[§]Includes, but is not limited to, non-male sexual relationships, abstinence from sexual intercourse with a male partner, monogamous relationship with a vasectomized partner, male condoms with the use of applied spermicide, intrauterine devices, NuvaRing®, and licensed hormonal methods such as implants, injectables, contraceptive patches or oral contraceptives ("the pill"). Method of contraception will be captured on the appropriate data collection form.

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

5.2. Subject Exclusion Criteria

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

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

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

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

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

3. Have immunosuppression as a result of an underlying illness or treatment, or use of anticancer chemotherapy or radiation therapy (cytotoxic) within 3 years prior to study vaccination.
4. Have known active neoplastic disease or a history of any hematologic malignancy. Non-melanoma skin cancers that are not active are permitted.
5. Have known HIV, hepatitis B, or hepatitis C infection.
6. Have known hypersensitivity or allergy to eggs, egg or chicken protein, or other components of the study vaccine.
7. Have a history of severe reactions following previous immunization with licensed or unlicensed influenza vaccines.
8. Have a history of Guillain-Barré Syndrome.
9. Have a history of alcohol or drug abuse within 5 years prior to study vaccination.
10. Have any diagnosis, current or past, of schizophrenia, bipolar disease, or other psychiatric diagnosis that may interfere with subject compliance or safety evaluations.
11. 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.

12. Have taken oral or parenteral (including intraarticular) corticosteroids of any dose within 30 days prior to study vaccination.
13. Have taken high-dose[3] dose inhaled corticosteroids within 30 days prior to study vaccination[4].

    [3]High-dose defined as per age as using inhaled high dose per reference chart https://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/quick-reference-html#estimated-comparative-daily-doses.

    [4]Topical and nasal steroids are permissible.
14. Received any licensed live vaccine or plan to receive a licensed live vaccine within 30 days prior or 21 days after each M-001 study vaccination.
15. Received a licensed inactivated vaccine within 14 days prior to or 21 days after each M-001 study vaccination.
16. Plans to or received the current 2018-2019 influenza vaccine (inactivated or live prior to orduring the study (the 2018-2019 influenza vaccine will be given during the trial.)
17. Received immunoglobulin or other blood products (with exception of Rho D immunoglobulin) within 90 days prior to study vaccination.
18. Received an experimental agent[5] within 30 days prior to the first study vaccination, or expects to receive an experimental agent[6] during the 7-month trial-reporting period.

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

    [6]Other than from participation in this study.
19. Are participating or plan to participate in another clinical trial with an interventional agent[7] that will be received during the 7-month trial-reporting period.

    [7]Including agent (licensed or unlicensed vaccine, drug, biologic, device, blood product, or medication) during the 9-month study period.
20. 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[8].

    [8]Study vaccination refers to investigiational study product vaccination
21. Female subjects who are breastfeeding or plan to breastfeed at any given time from the first study vaccination until 30 days after the last study vaccination.
22. 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.
23. Have signs or symptoms that could confound or confuse assessment of study vaccine reactogenicity[9].

[9]*The study vaccination should be postponed/deferred until signs or symptoms have resolved and if within the acceptable protocol-specified window for that visit.*

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

5.3. Eligibility Criteria for Doses 2- 3

Subjects must meet all inclusion and none of the exclusion criteria as outlined in sections 5.1 and 5.2 for all subsequent vaccination visits (note that inclusion criteria for IIV4 administration are different than those for investigational study product administration). Subjects must not have received the 2018-2019 influenza vaccine prior to Dose #3. In addition, the presence of any unresolved or continuing solicited or unsolicited Grade 2 or 3 AE (Doses #2 to #3) or the presence of any Grade 2 or 3 clinical laboratory value (prior to Doses #2 or #3 administered on Days 22 and 172, respectively), will be exclusions to subsequent doses of vaccine. An unresolved or continuing Grade 1 AE is permissible unless, in the opinion of the site PI or sub-investigator (sub-I), it would render study vaccination unsafe or interfere with the evaluation of responses.

5.4. Treatment Assignment Procedures

5.4.1. Randomization Procedures

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

Once consented and upon entry of demographic data and confirmation of eligibility for this trial, the subject will be enrolled. One hundred twenty subjects will be randomly assigned to one of 2 treatment arms, as shown in Table 1. Randomization will be stratified based upon prior receipt of the 2017-2018 influenza vaccine. The list of randomized treatment assignments will be prepared by statisticians at the SDCC and included in the enrollment module for this trial. AdvantageEDC will assign each volunteer a treatment code from the list after demographic and eligibility data have been entered into the system. A designated individual at each site will be provided with a treatment key, which links the treatment code to the actual treatment assignment, which will be kept in a secure place.

Instructions for use of the enrollment module are included in the AdvantageEDC User's Guide. Manual back-up randomization procedures are provided in the MOP for use in the event that the site temporarily loses access to the Internet or the online enrollment system is unavailable.

The randomization scheme for this study is presented in Table 1Table 1.

5.4.2. Masking Procedures

This is a double-blind study.

Subjects, investigators, and study personnel performing any study-related assessments following study injection will be blinded to treatment assignment to the two M-001 dosing regimen or placebo. Laboratory personnel performing immunology assays will be blinded to treatment assignment.

The randomization scheme will be generated by the SDCC and provided to unblinded study personnel (i.e., pharmacists performing study product preparations and unblinded study product administrators).

The unblinded study product administrator is a study personnel licensed, registered, or certified to administer medications/vaccines, but will not be involved in study-related assessments or have subject contact for data collection following study injection. Following administration of the first two doses of either M-001 or placebo, the licensed seasonal influenza vaccine will be given to all subjects at Visit 09, but does not require administration by an unblinded study product administrator. The site PI may instead elect to assign administration of the licensed seasonal influenza vaccine at Visit 09 to the study personnel licensed, registered, or certified to administer medications/vaccines who may be otherwise blinded.

The Data and Safety Monitoring Board (DSMB) may receive data in aggregate and by treatment arm, or may be unblinded to individual subject treatment assignments, as needed, to adequately assess safety issues.

Refer to the MOP for unblinding procedures.

5.4.3. Reasons for Withdrawal

Subjects may voluntarily withdraw their consent for study participation at any time and for any reason, without penalty.

A subject may withdraw or be withdrawn from the study for any of the following reasons:

- Medical disease or condition, or any new clinical findings for which continued participation, in the opinion of the site PI or appropriate sub-I, would compromise the safety of the subject, or would interfere with the subject's successful completion of the study, or would interfere with the evaluation of responses.
- Subject no longer meets eligibility criteria.

- As deemed necessary by the site PI or appropriate sub-investigator for noncompliance or other reasons.
- Subject withdrawal of consent.
- Subject lost to follow-up.
- Termination of the study.
- New information becomes available that makes further participation unsafe.

Subsequent study vaccinations will not be administered to a subject if any of the following criteria are met:

- Medical condition for which continued participation, in the opinion of the site PI or appropriate sub-investigator, would pose a risk to the subject or would be likely to confound interpretation of the results.
- Presence of signs or symptoms that could confound or confuse assessment of study vaccine reactogenicity. For subjects with injection site or systemic signs or symptoms, or with an acute illness, including an oral temperature greater than or equal to 100.0°F, the subsequent study vaccinations should be postponed/deferred until signs, symptoms, or acute illness have resolved and if within the acceptable protocol-specified window for that visit. No exceptions to the protocol-specified window will be made.
- Any unresolved or continuing solicited or unsolicited Grade 2 or 3 AE. An unresolved or continuing Grade 1 AE is permissible unless, in the opinion of the site PI or sub-I, it would render study vaccination unsafe or interfere with the evaluation of responses.
- Subject no longer meets eligibility criteria.
- As deemed necessary by the site PI or appropriate sub-I for noncompliance or other reasons.
- Subject refusal of further study vaccination.
- Subject withdrawal of consent.
- Subject lost to follow-up.
- Termination of the study.
- New information becomes available that makes further participation unsafe.

Subsequent investigational study vaccinations will not be administered to a subject if any of the following criteria are met:

- Grade 2 or 3 clinical safety laboratory value (according to the toxicity table, Section 9.2.3) that does not decrease to Grade 1 or less prior to any subsequent study vaccination. Any clinical safety laboratory parameter may be re-evaluated for eligibility only once at the central (clinical) laboratory prior to any subsequent study vaccination. If the clinical safety laboratory value decreases to Grade 1 or less, the subject may receive the subsequent study vaccination. Subsequent study vaccinations should be scheduled to occur within the acceptable protocol-specified window for that visit.

- Grade 3 AE in the 8 days following a study vaccination that has no alternative etiology.

5.4.4. Handling of Withdrawals

The primary reason for withdrawal from the study will be recorded on the Study Status data collection form. Subjects will be encouraged to complete the Early Termination Visit. The Early Termination Visit procedures are listed in Section 7.4. Although subjects are free to withdraw at any time or may be withdrawn by the site PI or appropriate sub-I at any time, subjects who receive at least one dose of study vaccine will be encouraged to remain in the study for follow-up safety assessments and collection of venous blood samples for immunogenicity testing. Every attempt will be made to follow to resolution all AEs, including solicited injection site and systemic reactions, and/or SAEs that are ongoing at the time of early withdrawal.

In the case of subjects who fail to appear for a follow-up safety assessment, extensive effort (i.e., three documented contact attempts via phone calls, e-mails, etc., made on separate occasions and followed by a certified letter) will be made to locate or recall them, or at least to determine their health status. These efforts will be documented in the subjects' records. See the protocol-specific Manual of Procedures (MOP) for alternate follow-up requirements.

Subjects who withdraw, or are withdrawn or terminated from the study, or are lost to follow-up after signing the informed consent form, randomization, and receipt of study vaccine will not be replaced. If subjects who withdraw, or are withdrawn or terminated from the study, or are lost to follow-up after signing the informed consent form and randomization but before receipt of study vaccine, additional subjects may be enrolled and randomized for replacement.

5.4.5. Termination of Study

Although the study Sponsor has every intention of completing the study, it reserves the right to terminate the study at any time for clinical or administrative reasons. Reasons for termination include, but are not limited to, study closure due to DSMB review and recommendation and at the discretion of DMID.

6. STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1. Study Product Description

Seasonal Quadrivalent Inactivated Influenza Vaccine (IIV4)

Quadrivalent Inactivated Influenza Vaccine (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. IIV4 is manufactured using virus grown in eggs.

M-001

Multimeric-001 (M-001) vaccine developed by BiondVax is a [redacted] that are conservatively expressed among influenza A and B viruses.

It has been produced under aseptic conditions and according to the rules of current Good Manufacturing Practice and guidelines applicable to investigational medicinal products (IMPs). The vaccine lots used in this trial have been tested and released by the quality control department of the BiondVax.

Placebo (Normal Saline)

Sterile normal saline will be used as the placebo.

6.1.1. Acquisition

IIV4 will be purchased by DHHS.

M-001 will be provided by BiondVax under contract to DHHS.

Placebo (normal saline) will be provided by the DMID Clinical Agents Repository (CMS, Fisher BioServices).

IIV4, M-001 and normal saline will be provided through the DMID CMS to the participating VTEU site research pharmacies after all applicable regulatory and site approvals have been obtained. Should the site PI require additional study product during this trial, further instructions are provided in the protocol-specific MOP.

6.1.2. Formulation, Storage, Packaging, and Labeling

Seasonal Quadrivalent Inactivated Influenza Vaccine (IIV4)

The IIV4 is supplied as a sterile, clear, and colorless to slightly opalescent suspension in a single-dose, 0.5ml prefilled syringe. It is formulated to contain 60 mcg hemagglutinin (HA) per 0.5ml dose in the recommended ratio of 15 mcg HA for each of the four vaccine strains.
It contains no preservative (i.e., thimerosal-free).
The vaccine must be stored at 2°C to 8°C (36°F to 46°F). Do not freeze.

M-001

M-001 is supplied as a sterile, cloudy-white suspension in single-dose vials containing:

- 1 mg M-001 per 0.4 mL (dose for injection)

Each vial contains a fill volume of 0.6 mL at a concentration of 2.5mg/mL. It contains [redacted]

The vials containing study product must be stored at 2°C to 8°C (35.6°F to 46.4°F). Do not freeze.

Placebo (Normal Saline)

0.9% Sodium Chloride, USP or normal saline is a sterile, nonpyrogenic, isotonic solution; each mL contains sodium chloride 9 mg. It contains no bacteriostatic agent, antimicrobial agent, preservatives, or added buffer and is supplied only in single-dose containers. The solution may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (pH 5.3, range 4.5-7.0). The normal saline vials are to be stored at 20-25°C (68°F to 77ºF) [See USP Controlled Room Temperature; excursions between 15°C and 30°C (59°C and 86°F) are permitted].

Each study product will be labeled according to manufacturer specifications and include the statement "Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use."

Further details are included in the Investigator's Brochures for the M-001 vaccine and the IIV4 Package Insert, as well as in the protocol-specific MOP.

6.1.3. Product Storage and Stability Procedures

The temperature of the storage unit must be manually recorded daily (excluding non-business days and holidays as applicable), monitored during the duration of this trial per the participating VTEU sites' standard operating procedures, and documentation will be maintained. If the temperature fluctuates outside of the required range, the affected study product(s) must be quarantined at the correct storage temperature and labeled as 'Do Not Use' (until further notice). If any study product appears to have been damaged, contaminated or discolored, contains visible particulate matter (for normal saline and IIV4 vaccine), or if there are any concerns regarding its integrity, do NOT use the affected study product(s). The pharmacist must alert the site PI and study coordinator, if the temperature fluctuates outside of the required range. The site PI or responsible person should immediately contact the DMID Product Support Team at

DMIDProductSupportTeam@niaid.nih.gov for further instructions before any additional study vaccinations are administered. Based on the information collected, DMID and/or the manufacturer will determine whether the affected study product(s) can be used. If it cannot be used, the site will receive specific instructions on how to return the affected study product(s) to the DMID CMS or destroy it on site. Additional instructions for quarantine are provided in the protocol-specific MOP.

6.2. Dosage, Preparation and Administration of Study Intervention/ Investigational Product

See the protocol-specific MOP for detailed information on the preparation, labeling, storage, and administration of study vaccine. Study vaccine preparation will be performed by the participating VTEU site's research pharmacist on the same day of study vaccine administration.

M-001 investigational influenza vaccine product:

The [redacted] of M-001 dose will be administered as a single [redacted] intramuscular injection.

Visually inspect M-001 vaccine upon receipt and prior to use. After shaking well, the suspension will be cloudy white in appearance. If the M-001 vaccine precipitated, it should be re-suspended by tapping on the vial with the finger or mixing by vortex until the suspension looks homogeneous. If the M-001 vaccine appears to have been damaged, contaminated or discolored, or if there are any concerns regarding its integrity, do NOT use the affected study product(s).

Additional instructions for quarantine and DMID contact information are provided in the protocol-specific MOP.

Seasonal quadrivalent inactivated influenza vaccine product:

The IIV4 will be administered as an intramuscular injection using a single-dose [redacted] prefilled syringe.

Shake thoroughly and inspect visually before use. The vaccine product should be free of particulate matter and discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered. Administer the vaccine immediately after the thorough shaking and inspection.

Normal Saline (Placebo):

The saline placebo dose will be administered as a single 0.4 mL intramuscular injection.

Visually inspect the placebo (normal saline) upon receipt and prior to use. The solution will be clear to colorless in appearance. If the placebo appears to have been damaged, contaminated or discolored, contain visible particulate matter, or if there are any concerns regarding its integrity, do NOT use the affected study product(s). Additional instructions for quarantine and DMID contact information are provided in the protocol-specific MOP.

The first two doses of study vaccine administration will be performed by an unblinded study personnel member who is credentialed to administer medications/vaccines and may also participate in dose preparation. The licensed seasonal influenza vaccine to be given to all subjects at Visit 09 does not require administration by an unblinded study product administrator. The site PI may instead elect to assign administration of the licensed seasonal influenza vaccine at Visit 09 to the study personnel licensed, registered, or certified to administer medications/vaccines who may be otherwise blinded.

Each dose of study vaccine will be administered via a single IM injection given in the deltoid muscle of the subjects' preferred arm. The site of injection (right or left arm) will be recorded on the appropriate data collection form. Aseptic technique will be used for the withdrawal and administration of each dose of study vaccine using a disposable sterile needle appropriate in length for each subject and a disposable sterile 1-mL syringe. See the protocol-specific MOP for information on how to administer IM injections. Each dose of study vaccine must be administered within 30 minutes of drawing into the syringe, and the prepared syringe must be stored at room temperature until administered.

6.3. Modification of Study Intervention/Investigational Product for a Participant

Individuals must meet the appropriate inclusion and exclusion criteria prior to receiving the subsequently scheduled study injections. There will be no replacement of individuals who do not qualify to receive study doses 2 or 3. There will be no dose schedule modifications, other than within the protocol-specified windows. If a subject's study vaccination (study doses 2 or 3) is deferred, vaccination should be rescheduled to occur within the acceptable protocol-specified window for that visit. No exceptions to the protocol-specified window will be made.

Subjects who do not receive Dose 2 or Dose 3 will continue with follow-up safety assessments (may be conducted by phone call rather than in person) continuing through approximately 6 months after their last dose of M-001 or placebo. These subjects will also be asked to provide a venous blood sample for anti-viral antibody assays at approximately 21 days after their last dose of M-001. See Sections 5.4.3 and 5.4.4 for reasons for and handling of withdrawals and discontinuation of treatment. See the protocol-specific MOP for alternate follow-up requirements.

6.4. Accountability Procedures for the Study Intervention/ Investigational Product(s)

After receipt of the IIV4, M-001, and placebo vials, the site PI is responsible for study product distribution and disposition, and has ultimate responsibility for study product accountability. The Site PI may delegate to the site Research Pharmacist the responsibility for study product accountability. The site Research Pharmacist will be responsible for maintaining complete records and documentation of product receipt, accountability, dispensation, temperature and

storage conditions, and final disposition of study product. All study product, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log.

Used and unused vials of M-001 and placebo and IIV4 will be retained until monitored and released for disposition as applicable. Upon completion or termination of the study and after the final monitoring visit, final disposition of unused study products will be determined by DMID and communicated to the participating VTEU sites by the DMID Clinical Project Manager. For details regarding final disposition of study products see the Manual of Procedures (MOP).

6.5. Assessment of Subject Compliance with Study Intervention/ Investigational Product

The first two doses of study product will be administered to subjects by an unblinded vaccine administrator via IM injection according to subject treatment assignment and as described in Section 6.2. Thus, subject compliance is not anticipated to be an issue. Deviations from the dose schedule may only occur as described in Section 6.3. The licensed seasonal influenza vaccine to be given to all subjects at Visit 09 does not require administration by an unblinded study product administrator. The site PI may instead elect to assign administration of the licensed seasonal influenza vaccine at Visit 09 to the study personnel licensed, registered, or certified to administer medications/vaccines who may be otherwise blinded.

6.6. Concomitant Medications/Treatments

Administration of any medications, therapies, or vaccines will be recorded on the appropriate data collection form. Concomitant medications will include all current medications, vaccinations and medications taken in the 60 days prior to Day 1 through approximately Day 43. Subjects who do not receive both M-001 study vaccinations will have concomitant medications collected through approximately 21 days after the first study vaccination, or early termination, whichever occurs first. 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 study vaccination. Concomitant medications (vaccines only) will be recorded on the appropriate data collection form after Visit 7 through the end of the study. Prescription and over-the-counter drugs will be included as well as herbals, vitamins and supplements. In addition, receipt of any non-study vaccines will be solicited at each clinic visit or phone call, and reported in the eCRF.

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 should not be used unless absolutely necessary. Medications in this category include the prohibited

medications per the Subject Exclusion Criteria (see Section 5.2). In addition, the site PI or appropriate sub-I may identify other mediations that should not be used due to a risk to subject safety or assessment of reactogenicity and immunogenicity.

7. STUDY SCHEDULE

7.1. Enrollment/Baseline (Visit 01, Day 1, Dose 1, Clinic Visit)

- Subjects will be provided with a description of the study (purpose and study procedures) and asked to read and sign the informed consent form (ICF). The ICF will be signed prior to performing any study procedures, including administration of the first study vaccination.
- Eligibility criteria will be reviewed with subjects prior to the first study vaccination. Subject receipt of licensed 2016-2017 and 2017-2018 seasonal influenza vaccine, what type (LAIV or inactivated), and approximate date of vaccination will be recorded on the appropriate data collection form, if known.
- Complete medical history will be obtained by interview of subjects prior to the first study vaccination to assure eligibility.
- Demographic information will be obtained by interview of subjects.
- 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 and those taken within 30 days prior to signing the ICF will be recorded on the eCRF.
- Vital signs, including oral temperature, pulse, and blood pressure, will be obtained prior to the first study vaccination. Vital signs assessed on Day 1 (Visit 01) prior to the first study vaccination will be considered as baseline. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
- Height and weight will be collected on Day 1 prior to the first study vaccination for the calculation of Body Mass Index (BMI).
- A targeted physical examination may be performed prior to the first study vaccination by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-I, if indicated based on review of complete medical history.
- Counsel women of childbearing potential on contraception and avoidance of pregnancy.
- A urine or serum pregnancy test will be performed within 24 hours prior to the first study vaccination on all female subjects of childbearing potential. Results must be negative and known prior to randomization and first study vaccination.
- Approximately 10 mL of venous blood will be collected prior to the first study vaccination for safety labs.
- Approximately 10 mL of venous blood will be collected prior to the first study vaccination for baseline antibody assays.

- Approximately 60 mL of venous blood will be collected prior to the first study vaccination for isolation of PBMCs.
- Subjects will be enrolled in AdvantageEDC and randomly assigned to a treatment arm prior to the first study vaccination.
- Pre-administration reactogenicity assessments will be performed prior to the first study vaccination to establish baseline. Subjects will then receive a single dose of study vaccine via IM injection in the deltoid muscle of the preferred arm. The site of injection (right or left arm) and time of administration will be recorded on the appropriate data collection form. Subjects will be observed in the clinic for at least 20 minutes after the first study vaccination. The study vaccination site will be examined, and any AE/SAEs will be assessed and recorded on the appropriate data collection form prior to discharge from the clinic.
- Subjects will be provided with a Memory Aid and other study-related materials to record daily oral temperature, solicited injection site and systemic reactions, any unsolicited AEs, and concomitant medications/vaccinations. Subjects will be encouraged to take their temperature around the same time each day for 8 days post vaccination. Subjects will be instructed on how to use the Memory Aid and how to measure and record AEs prior to discharge from the clinic. Subjects will be instructed to notify the study center if they develop any severe reactions after the first study vaccination. If the site PI or appropriate sub-I deems the reaction severe enough, s/he will give further instructions on the proper course of action, including a return to the clinic for immediate evaluation if appropriate.

7.2. Follow-up

7.2.1. Visit 2, Day 9, Clinic Visit (8 days [+2 days] post first study vaccination)

- Study personnel will review the Memory Aid information with subjects and assess and record all AE/SAEs and concomitant medications on the appropriate data collection form.
- Counsel women of childbearing potential on contraception and avoidance of pregnancy.
- If indicated by review of Memory Aid, obtain vital signs.
- A targeted physical examination may be performed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-I, if indicated based on review of interim medical history.
- Examine the vaccination site for Dose 1.
- Approximately 10 mL of venous blood will be collected for safety labs.

7.2.2. Visit 3, Day 15, Clinic Visit (14 days [+2 days] post first study vaccination)

- Study personnel will review interim medical history with subjects and assess and record all AE/SAEs and concomitant medications on the appropriate data collection form.
- Counsel women of childbearing potential on contraception and avoidance of pregnancy.
- If indicated, obtain vital signs.
- A targeted physical examination may be performed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-I, if indicated based on review of interim medical history.
- Approximately 40 mL of venous blood will be collected for isolation of PBMCs.

7.2.3. Visit 4, Day 22, Dose 2, Clinic Visit (21 days [+2 days] post first study vaccination)

- Eligibility criteria will be reviewed with subjects prior to the second study vaccination to assure continued eligibility.
- Obtain interim medical history by interview of subjects prior to the second study vaccination and note any changes since the previous visit.
- All concomitant medications will be recorded on the appropriate data collection form prior to the second study vaccination.
- All AE/SAEs will be assessed and recorded on the appropriate data collection form prior to the second study vaccination.
- Vital signs, including oral temperature, pulse, and blood pressure, will be obtained prior to the second study vaccination. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
- A targeted physical examination may be performed prior to the second study vaccination by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-I, if indicated based on review of interim medical history.
- Counsel women of childbearing potential on contraception and avoidance of pregnancy.
- A urine or serum pregnancy test will be performed within 24 hours prior to the second study vaccination on all female subjects of childbearing potential. Results must be negative and known prior to the second study vaccination.

- Approximately 10 mL of venous blood will be collected prior to the study vaccination for antibody assays.
- Pre-administration reactogenicity assessments will be performed prior to the second study vaccination to establish baseline. Subjects will then receive a single dose of study vaccine via IM injection into the deltoid muscle of the same arm that received Dose 1 as long as there is no interference with the reactogenicity assessment. The site of injection (right or left arm) and time of administration will be recorded on the appropriate data collection form. Subjects will be observed in the clinic for at least 20 minutes after the second study vaccination. The study vaccination site for Dose 2 will be examined, and any AE/SAEs will be assessed and recorded on the appropriate data collection form prior to discharge from the clinic.
- Subjects will be provided with a Memory Aid and other study-related materials to record daily oral temperature, solicited injection site and systemic reactions, any unsolicited AEs, and concomitant medications. Subjects will be encouraged to take their temperature around the same time each day. Subjects will be instructed on how to use the Memory Aid and how to measure and record AEs prior to discharge from the clinic. Subjects will be instructed to notify the study center if they develop any severe reactions after the second study vaccination. If the site PI or appropriate sub-I deems the reaction severe enough, s/he will give further instructions on the proper course of action, including a return to the clinic for immediate evaluation if appropriate.

7.2.4. Visit 5, Day 30, Clinic Visit (8 days [+2 days] post second study vaccination)

- Study personnel will review the Memory Aid information with subjects and assess and record all AEs/SAEs and concomitant medications on the appropriate data collection form.
- Counsel women of childbearing potential on contraception and avoidance of pregnancy.
- If indicated, obtain vital signs.
- A targeted physical examination may be performed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-I, if indicated based on review of interim medical history.
- Examine the vaccination site for Dose 2.
- Approximately 10 mL of venous blood will be collected for safety labs.

7.2.5. Visit 6, Day 36, Clinic Visit (14 days [+2 days] post second study vaccination)

- Study personnel will review interim medical history with subjects and assess and record all AE/SAEs and concomitant medications on the appropriate data collection form.
- Counsel women of childbearing potential on contraception and avoidance of pregnancy.
- If indicated, obtain vital signs.
- A targeted physical examination may be performed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-I, if indicated based on review of interim medical history.
- Approximately 40 mL of venous blood will be collected for isolation of PBMCs.

7.2.6. Visit 7, Day 43, Clinic Visit (21 days [+7 days] post second study vaccination)

- Study personnel will review interim medical history with subjects and assess and record all AE/SAEs and concomitant medications on the appropriate data collection form.
- If indicated, obtain vital signs.
- A targeted physical examination may be performed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-I, if indicated based on review of interim medical history.
- Counsel women of childbearing potential on contraception and avoidance of pregnancy.
- Approximately 10 mL of venous blood will be collected for influenza antibody assays.
- Approximately 60 mL of venous blood will be collected for isolation of PBMCs.

7.2.7. Visit 8, Day 78, Clinic Visit (56 days [+7 days] post second study vaccination)

- Study personnel will review interim medical history with subjects and assess and record all SAEs on the appropriate data collection form.
- Concomitant medications (vaccines only) will be recorded on the appropriate data collection form.
- Counsel women of childbearing potential on contraception and avoidance of pregnancy through study day 82 (60 days after second vaccination).
- If indicated, obtain vital signs.

- A targeted physical examination may be performed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-I, if indicated based on review of interim medical history.
- Approximately 10 mL of venous blood will be collected for influenza antibody assays.
- Approximately 40 mL of venous blood will be collected for isolation of PBMCs.

7.2.8. Visit 9, Day 172, Dose 3 (150 days [±30 days] post second study vaccination)

- Eligibility criteria will be reviewed with subjects prior to the third study vaccination IIV4) to assure continued eligibility.
- Obtain interim medical history by interview of subjects.
- Concomitant medications (vaccines only) will be recorded on the appropriate data collection form.
- All SAEs will be assessed and recorded on the appropriate data collection form.
- Vital signs, including oral temperature, pulse, and blood pressure, will be obtained prior to the third study vaccination. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
- A targeted physical examination may be performed prior to the third study vaccination by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-I, if indicated based on review of interim medical history.
- Counsel women of childbearing potential on contraception and avoidance of pregnancy.
- A urine or serum pregnancy test will be performed within 24 hours prior to the third study vaccination on all female subjects of childbearing potential. Results must be negative and known prior to the third study vaccination.
- Approximately 20 mL of venous blood will be collected prior to the third study vaccination for influenza antibody assays.
- Approximately 40 mL of venous blood will be collected prior to the study vaccination for isolation of PBMCs.
- Subjects will then receive a single dose of IIV4 study vaccine via IM injection into the deltoid muscle of the same arm that received Dose 1. The site of injection (right or left arm) and time of administration will be recorded on the appropriate data collection form.

- Subjects will be instructed to notify the study center if they develop any worrisome adverse events or experienced an SAE.

7.2.9. Visit 10, Day 186, Clinic Visit (14 days [+3 days] post third study vaccination)

- Study personnel will review interim medical history and assess and record all SAEs.
- Concomitant medications (vaccines only) will be recorded on the appropriate data collection form.
- Counsel women of childbearing potential on contraception and avoidance of pregnancy.
- If indicated, obtain vital signs.
- A targeted physical examination may be performed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-I, if indicated based on review of interim medical history.
- Approximately 40 mL of venous blood will be collected for isolation of PBMCs.

7.3. Study Visit 11, Day 200 Clinic Visit (28 days +7 post third study vaccination)

7.3.1. Visit 11 activities

- Study personnel will review interim medical history with subjects and assess and record all SAEs on the appropriate data collection form.
- Concomitant medications (vaccines only) will be recorded on the appropriate data collection form.
- If indicated, obtain vital signs.
- A targeted physical examination may be performed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-I, if indicated based on review of interim medical history.
- Approximately 20 mL of venous blood will be collected for influenza antibody assays.
- Approximately 40 mL of venous blood will be collected for isolation of PBMCs.

7.3.2. Study Visit 12, Day 200 (+14 days), Safety Follow-up Phone Call (to be Performed Only If Visit 11 Occurs Before Study Day 200)

- Study personnel will review interim medical history with subjects and assess and record all SAEs on the appropriate data collection form.
- Concomitant medications (vaccines only) will be recorded on the appropriate data collection form.

7.4. Early Termination Visit

The following activities will be performed at the early termination visit for subjects who withdraw,
or are withdrawn or terminated from the study:

- Obtain interim medical history by interview of subjects and note any changes since the previous visit.
- Memory Aid information will be reviewed with subjects (if within 8 days after a M-001 study vaccination).
- If indicated by medical history, obtain vital signs. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
- Review and record all concomitant medications (if prior to 21 days after the last study vaccination).
- Information regarding AEs/SAEs will be recorded on the appropriate data collection form. AEs will be limited to SAEs if after 21 days following the second M-001 study vaccination.
- A targeted physical examinationmay be performed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-I, if indicated based on review of interim medical history.
- Examine study vaccination site, and perform post-administration reactogenicity assessment (if within 8 days after a M-001 study vaccination).
- Approximately 10 mL of venous blood will be collected for clinical labs, and performed by the central (clinical) laboratory (if within 7 (+2) days after a M-001 study vaccination), or if indicated based on review of interim medical history, or to follow-up on any grade 2 or higher laboratory abnormalities.
- Approximately 10 mL of venous blood will be collected for influenza antibody assays.
- Approximately 40 mL of venous blood will be collected for isolation of PBMCs.

7.5. Unscheduled Visit

Unscheduled visits may occur at any time during the study. Any of the following activities may be performed:

- Review Memory Aid (if within 8 days after the previous study vaccination, inclusive of vaccination day).
- Review and record all concomitant medications (if prior to 21 days after the last study vaccination).
- Counsel women of childbearing potential on contraception and avoidance of pregnancy.
- All AEs/SAEs will be recorded on the appropriate data collection form. AEs will be limited to SAEs if after 21 days after the last study vaccination.
- Obtain interim medical history by interview of subjects and note any changes since the previous visit (if indicated).
- If indicated, obtain vital signs. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
- A targeted physical examination may be performed by a study clinician licensed to make medical diagnoses and listed on the Form FDA 1572 as the site PI or sub-I, if indicated based on review of interim medical history.
- Examine study vaccination site and perform post- administration reactogenicity assessment (if within 8 days after the last study vaccination, inclusive of vaccination day).
- Approximately 10 mL of venous blood will be collected for clinical labs, and performed by the central (clinical) laboratory (if within 9 days after a M-001 study vaccination), or if indicated based on review of interim medical history, or to follow-up on any laboratory abnormalities determined to be AEs.

8. STUDY PROCEDURES/EVALUATIONS

8.1. Clinical Evaluations

Medical History: Will be obtained by interview of the subjects. Subjects will be queried regarding a history of significant medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, nervous system, blood, lymph glands, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, and substance abuse will be solicited. The collection of medical history information will include a review of vaccine history and plans for vaccinations.

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 also will include a review of prohibited medications (per the exclusion criteria).

Vitals signs: Blood pressure, oral temperature, and pulse will be collected at each of the study visits when a study vaccination is scheduled [Day 1 (Visit 01), Day 22 (Visit 04), Day 172 (Visit 09), and as needed at the other study visits.

Height, weight: These parameters will be measured at Day 1 (Visit 01).

Targeted Physical Examination: This may be conducted at any study visit based on indicated symptoms.

Reactogenicity Assessments: This will include an assessment of solicited AEs occurring from the time of each study vaccination [Day 1 (Visit 01), Day 22 (Visit 04), through 7 days after M-001study vaccinations (inclusive of vaccination day), which includes an assessment of erythema/redness, induration/swelling, pain, tenderness, ecchymosis and pruritus at the injection site; fever, chills, fatigue, malaise, body aches (exclusive of injection site), arthralgia (exclusive of injection site), headache, and nausea.

Memory Aids: All subjects will complete a subject Memory Aid from the time of each study vaccination [Day 1 (Visit 01) and Day 22 (Visit 04) through 7 days after the M-001 study vaccination. Subject Memory Aids will be reviewed with the subject for AEs at the clinic visit following each study injection. If a subject noted ongoing injection site or systemic

reactogenicity on the 7th day following the study injection, the Memory Aid will continue to be reviewed until resolved. The Memory Aids will be discarded after review.

8.2. Laboratory Evaluations

Schedules and volumes of clinical laboratory tests and immunogenicity assays are specified in Appendix A.

8.2.1. Clinical Laboratory Evaluations

Urine or serum pregnancy tests will be performed by the local or site laboratory within 24 hours prior to each study vaccination (Day 1 (Visit 01) and approximately Day 22 (Visit 04), and Day 172 (Visit 09)) on all female subjects of childbearing potential. Results must be negative and known prior to randomization on Day 1 (Visit 01) and administration of each study vaccination to be eligible for participation in the study and receipt of each dose of study vaccine, respectively.

Clinical safety laboratory parameters to be evaluated after receipt of the first two doses of study vaccine will include: WBC, hemoglobin, platelets, ALT, total bilirubin, and creatinine. These evaluations will be performed by the central (clinical) laboratory. Venous blood samples (approximately 10 mL) will be collected from each subject prior to vaccination at baseline (Visit 01) and approximately 8 days after Dose 1 and Dose 2 of study vaccination (Visits 02 and 05, respectively).

8.2.2. Special Assays or Procedures

HAI and Neut Antibody

Assays to determine serum levels of HAI and Neut antibodies will be performed at St Louis University. Subjects who withdraw early will have HAI and Neut antibody assays run on available sera.

M-001 Antibody

Assays to determine serum levels of antibodies to M-001 will be performed by BiondVax. Subjects who withdraw early will have M-001 antibody assays run on available sera.

Cellular Studies

Assays to measure T cell responses will be performed at Baylor College of Medicine.

8.2.3. Specimen Preparation, Handling, and Shipping

8.2.3.1. Instructions for Specimen Preparation, Handling, and Storage

Instructions for specimen preparation, handling, and storage are included in the protocol-specific MOP, as appropriate.

8.2.3.2. Specimen Shipment

Specimen shipment will occur at intervals during the course of this study following all applicable International Air Transport Association (IATA) requirements and according to the specifics for storage temperature and documentation as detailed in the central (clinical) laboratory manual and protocol-specific MOP as appropriate.

Sera and PBMCs will be shipped from the participating VTEU sites to the DMID CMS. Sera for HAI and neut assays will then be provided by the DMID CMS to St Louis University in a blinded manner once they become available to the DMID CMS. Serum samples for detection of antibody responses to M-001 will be provided to BiondVax by the DMID CMS in a blinded fashion once they become available. PBMC samples will be provided by the DMID CMS to Baylor College of Medicine for the planned cellular assays.

Further instructions for specimen shipment are included in the central clinical laboratory manual and the protocol-specific MOP, as appropriate.

9. ASSESSMENT OF SAFETY

9.1. Specification of Safety Parameters

Safety will be assessed by the frequency and severity of:

1. All SAEs occuring 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

9.2. Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.1. Adverse Events

Adverse Event (AE): International Conference on Harmonisation (ICH) E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

AEs, including solicited injection site and systemic (subjective and quantitative) reactions, not meeting the protocol-defined criteria for SAEs will be captured on the appropriate data collection form and electronic case report form (eCRF). Information to be collected for unsolicited AEs includes event description, date of onset, licensed study physician's assessment of severity and

relationship to study product and alternate etiology (if not related to study product) (assessed only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site PI or sub-I), date of resolution of the event, seriousness and outcome. AEs while on study will be documented appropriately regardless of relationship. AEs will be followed to resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it will be recorded as an AE.

AEs must be graded for severity and assessed for relationship to study product (see definitions below). AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF.

FDA defines an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Severity of Event: AEs will be assessed by a licensed study physician listed on the Form FDA 1572 as the site PI or appropriate sub-I using a protocol-defined grading system (see Section 9.2.2). For events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity:

- Mild (Grade 1): Events require minimal or no therapeutic measure(s) and do not interfere with the subject's usual daily activities.
- Moderate (Grade 2): Events result in a low level of inconvenience or concern with therapeutic measures. Moderate events cause some interference with functioning and usual daily activities.
- Severe (Grade 3): Events interrupt the subject's usual daily activities and therapeutic measure(s) indicated. Severe events are usually incapacitating.

Relationship to Study Product: The study physician's assessment of an AE's relationship to study product is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. The relationship to study product must be assessed for AEs using the terms: related or not related. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used:

- Related – There is a reasonable possibility that the study product caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the AE.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

9.2.2. Reactogenicity

Reactogenicity events are AEs that are common and known to occur following administration of this type of study vaccine. The following Toxicity Grading Scales will be used to grade solicited injection site and systemic (subjective and quantitative) reactions:

Table 2: 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.

Ecchymosis, erythema, and induration /edema as analyzed by measurement will be graded as follows:

Table 3: 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 4: 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.

Oral temperature[#] will be graded as follows:

Table 5: 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

[#] 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.

9.2.3. Additional Adverse Event Severity Grading

Pulse and blood pressure[#] will be graded as follows:

Table 6: 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

Physiologic Parameter	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Hypotension (diastolic) mm Hg	50 – 54	45 – 49	<45
Hypertension (systolic) mm Hg	151 – 155	156 – 160	>160
Hypertension (diastolic) mm Hg	96 – 100	101 – 105	>105

[#] Pulse and blood pressure assessed on Day 1 prior to the first study vaccination will be considered as baseline.

Clinical safety laboratory results[#] will be graded as follows:

Table 7: Clinical Safety Laboratory Adverse Event Grading (28)

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
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	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
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

[#] Clinical laboratory evaluations assessed at the enrollment visit (Visit 01) will be considered as baseline.

9.2.4. Serious Adverse Events

An AE or suspected AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening AE*,

- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.
- important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- all events described as Guillain-Barré syndrome will also be considered SAEs

* Life-threatening AE. An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

All SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 such as the site PI or sub-I.
- Recorded on the appropriate SAE CRF.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572.
- Reviewed and evaluated by an Independent Safety Monitor (ISM), the DSMB (periodic review unless related), DMID, and the IRB.

9.2.5. Procedures to be Followed in the Event of Abnormal Laboratory Test Values or Abnormal Clinical Findings

The site PI or appropriate sub-I is responsible for reporting all AE/SAEs that are observed or reported during the study, regardless of the relationship to study product. AE/SAEs, abnormal clinical laboratory test values, or abnormal clinical findings will be documented, reported, and followed appropriately.

9.3. Reporting Procedures

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.

Unsolicited AEs will be 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).

SAEs will be documented from the time of the first study vaccination (Day 1 (Visit 01)) through the end of the study.

9.3.1. Serious Adverse Events

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the DMID Pharmacovigilance Group at the following address:

DMID Pharmacovigilance Group
Clinical Research Operations and Management Support (CROMS)
6500 Rock Spring Dr. Suite 650
Bethesda, MD 20817, USA
SAE Hot Line: 1-800-537-9979 (US) or 1-301-897-1709 (outside US)
SAE FAX: 1-800-275-7619 (US) or 1-301-897-1710 (outside US)
SAE Email Address: PVG@dmidcroms.com

In addition to the SAE form, selected SAE data fields must also be entered into AdvantageEDC. Please see the protocol-specific MOP for details regarding this procedure.

Other supporting documentation of the event may be requested by the DMID Pharmacovigilance Group and should be provided as soon as possible.

The site will send a copy of the SAE report(s) to the ISM when they are provided to the DMID Pharmacovigilance Group. The DMID Medical Monitor and DMID Clinical Project Manager will be notified of the SAE by the DMID Pharmacovigilance Group. The DMID Medical Monitor will review and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct.

At any time after completion of the study, if the site PI or appropriate sub-I becomes aware of an SAE that is suspected to be related to study product, the site PI or appropriate sub-I will report the event to the DMID Pharmacovigilance Group.

9.3.2. Regulatory Reporting for Studies Conducted Under DMID-Sponsored IND

Following notification from the site PI or appropriate sub-I, DMID, the Investigational New Drug (IND) sponsor, will report any suspected adverse reaction that is both serious and unexpected. DMID will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the AE. DMID will notify FDA and all participating site PIs (i.e., all PIs to whom the sponsor is providing drug under its IND(s) or under any PI's IND(s)) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting as specified in 21 CFR Part 312.32. DMID will also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. Relevant follow up information to an IND safety report will be submitted as soon as the information is available. Upon request from FDA, DMID will submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

All serious events designated as "not related" to study product(s), will be reported to the FDA at least annually in a summary format.

9.3.3. Reporting of Pregnancy

Pregnancies occurring in study subjects will be reported via AdvantageEDC on the Pregnancy Case Report form. No further study vaccinations will be administered to pregnant subjects, but, with the subject's permission, all study mandated blood samples will be obtained and the subject will continue in follow-up for safety events. Efforts will be made to follow all pregnancies reported during the course of the study to pregnancy outcome pending the subject's permission.

9.4. Type and Duration of Follow-up of Subjects after Adverse Events

AEs will be followed 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)

SAEs will be followed from the time of the first study vaccination (Day 1 (Visit 01)) through resolution even if this extends beyond the study-reporting period (end of study)). Resolution of an AE/SAE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Follow-up procedures, evaluations, and outcomes will be recorded on the appropriate data collection form.

9.5. Halting Rules

Further enrollment and study vaccinations will be halted for DSMB review/recommendation if any of the following are reported:

- Any subject experiences ulceration, abscess, or necrosis at the injection site related to study product administration.
- Any subject experiences laryngospasm, bronchospasm, or anaphylaxis within 1 day after administration of study product that is considered related to study product.
- Two or more subjects experience generalized urticaria within 3 days after administration of study product that is considered related to study product.
- Any subject experiences a study vaccine-related SAE from the time of the first study vaccination through the subject's last study visit.
- Any subject experiences acute weakness of limbs and/or cranial nerve innervated muscles (description of potential signal of GBS) after administration of study product.

This study will also be halted for DSMB review/recommendation if, within 8 days after administration of either of the first 2 vaccine doses of M-001 or placebo, any of the following occurs:

- 5% or more of subjects (with a minimum of 3 subjects) who received at least one dose of study vaccine to date experience the same severe (Grade 3) study vaccine-related injection site reaction. Ecchymosis (bruising), erythema (redness), and induration (hardness)/edema(swelling) will also be measured in mm but size will not be used as halting criteria.
- 5% or more of subjects (with a minimum of 3 subjects) who received at least one dose of study vaccine to date experience the same severe (Grade 3) study vaccine-related subjective systemic reaction, for which the severity (grade) is corroborated by study personnel.
- 5% or more of subjects (with a minimum of 3 subjects) who received at least one dose of study vaccine to date experience the same severe (Grade 3) study vaccine-related quantitative systemic reaction.
- 5% or more of subjects (with a minimum of 3 subjects) who received at least one dose of study vaccine to date experience the same severe (Grade 3) study vaccine-related clinical safety laboratory AE.

Grading scales for solicited injection site and systemic (subjective and quantitative) reactions are included in Section 9.2.2.

If any of the halting rules are met following any subject receipt of any study vaccination, then this study will not continue with the remaining enrollments or study vaccinations without a review by and recommendation from the DSMB to proceed.

DMID retains the authority to suspend additional enrollment and study interventions/ administration of study product during the entire study, as applicable.

9.6. Safety Oversight (ISM plus DSMB)

9.6.1. Independent Safety Monitor (ISM)

The ISM is a physician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. The ISM will review SAEs and other AEs as needed and provide an independent assessment to DMID. Each participating study site will have an ISM with experience in infectious diseases or internal medicine, in close proximity to the participating VTEU site, and have the authority to readily access study participant records.

9.6.2. Data and Safety Monitoring Board (DSMB)

Safety oversight will be conducted by a DSMB that is an independent group of experts that monitors subject safety and advises DMID. The DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflict of interest related to this trial. The DSMB will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial.

The DSMB will review study progress and participant, clinical, safety, and reactogenicity data at the following time points. A review of immunogenicity data will be performed as specified below.

- Data review for safety at study-specific time frames; at least annually.
- After all 8-day post second study vaccination safety data are available for all study participants.
- Final review meeting: 6 to 8 months after clinical database lock to review the cumulative unblinded safety and immunogenicity data for this trial. The data will be provided in a standard summary format. The DSMB may be asked to provide recommendations in response to questions posed by DMID.
- Ad hoc when a halting rule is met, for immediate concerns regarding observations during this trial, or as needed.

The DSMB will operate under the rules of a DMID-approved charter that will be written at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. Procedures for DSMB reviews/meetings will be defined in the charter. The DSMB will review applicable data to include, but not limited to, study progress and participant, clinical, safety, and reactogenicity data. Reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited and unsolicited AE/SAEs. Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by DMID. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion, and may request the treatment arm be unblinded for an individual subject if required for safety assessment. The DSMB will review grouped and unblinded data in the closed session only. The DSMB will meet and review this data at scheduled time points or ad hoc as needed during this trial as defined in the DSMB charter. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study vaccinations (as applicable), and to continue, modify, or terminate this trial.

Additionally, SDCC web reports using data entered into AdvantageEDC will be monitored to determine if any of the halting rules described in Section 9.5 are met.

If any of the halting rules are met, the study will not proceed with the remaining enrollment or study injections without a review by and recommendation from the DSMB to proceed.

Upon completion of this review and receipt of the advice of the DSMB, DMID will determine if study entry or study dosing should be interrupted or if study entry and study dosing may continue according to the protocol.

10. CLINICAL MONITORING

10.1. Site Monitoring Plan

Site Monitoring will be conducted to ensure that human subject protection, study procedures, laboratory procedures, study intervention administration, and data collection processes are of high quality and meet sponsor, CGP/ICH, and regulatory guidelines, and that the study is conducted in accordance with the protocol and sponsor SOPs. DMID, the sponsoring agency, or its designee will conduct site monitoring visits as detailed in the monitoring plan or in the Manual of Procedures.

Site visits will be made at standard intervals as defined by DMID and may be made more frequently as directed by DMID. Monitoring visits will include, but are not limited to, review of regulatory files, accountability records, case report forms, informed consent forms, medical and laboratory reports, and protocol compliance. Study monitors will meet with investigators to discuss any problems and actions to be taken and document visit findings and discussions.

11. STATISTICAL CONSIDERATIONS

11.1. Study Hypotheses

The study is not designed to test a specific hypothesis for the primary safety objectives. Nevertheless, this trial represents an important opportunity to extend the M-001 safety base.

The primary immunogenicity objective is to determine whether priming with M-001 improves T cell responses. The hypothesis that will be tested is:

H_0: $GMP_M/GMP_c = 1 \rightarrow \log_{10}(GMP_M)-\log(GMP_c) = 0$
H_1: $GMP_M/GMP_c \neq 1 \rightarrow \log_{10}(GMP_M)-\log(GMP_c) \neq 0$

Where GMP_M and GMP_c are the geometric mean percentage (GMP) percentage of T cell subsets expressing perforin, CD107a, INFg, TNF-a, and IL-2 for the M-001 and control (placebo) treatment arms, respectively.

11.2. Study Outcome Measures

Please refer to Section 3.2.

11.3. Sample Size Considerations

11.3.1. Study Design

This is a Phase II, randomized, double-blind, controlled trial in 120 males and non-pregnant females, 18 to 49 years old, inclusive, who are in good health and meet all eligibility criteria. Subjects will be assigned randomly to 1 of 2 treatment arms (60 subjects per treatment arm) to receive two doses of M-001 or two placebo controls, followed by IIV4 (see Table 1). All doses will be administered IM approximately 21 days apart.

Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions from the time of each M-001 study vaccination through 8 days after each study vaccination (inclusive of vaccination day). Unsolicited non-serious AEs will be collected from the time of each M-001 study vaccination through approximately 21 days after each M-001 study vaccination. SAEs will be collected from the time of the first study vaccination through end of the study. Clinical laboratory evaluations for safety will be performed on venous blood collected approximately 8 days after each M-001 study vaccination (inclusive of vaccination day).

Immunogenicity testing will be performed as described in Section 8.2.2.

11.3.2. Study Population

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

11.3.3. Subject Enrollment and Follow-up

Based on the accrual rate for similar studies, it seems reasonable to expect that the participating VTEUs will be able to enroll this trial in a timely fashion. Prior experience suggests up to 5% of subjects may be excluded from the per protocol analysis for the primary immunogenicity outcome either because they were 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.

11.3.4. Sample Size

This study is planned to enroll 120 subjects (60 per treatment arm). The following illustrates the precision and power that is available for select estimates and comparisons of interest.

Table 8 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 treatment arm (N=60) and all enrolled subjects (N=120).

Table 8: Power (%) to Detect Safety Events

Event Frequency	Single Treatment Arm N=60	Two Treatment 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

Binomial confidence intervals (CI) are widest (have the least precision) when the response rate is 50%. Table 9 is presented to indicate the worst case scenario for precision of observed exact (Clopper-Pearson) binomial confidence intervals.

Table 9: Precision of Binomial Confidence Intervals:

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

With N = 60 subjects per arm and assuming the standard deviation of logGMP 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 10 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 am, and further includes the power under the conservative assumption of 10% drop out in each treatment arm. Power is calculated for a two-sided t-test with significance level (alpha) 0.05 using PROC POWER in SAS 9.4.

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.

Table 10: 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

11.4. Planned Interim Analyses

No interim analysis is planned.

11.4.1. Interim Safety Review

A DSMB will be convened by DMID to review study progress and participant, clinical, safety, reactogenicity, and immunogenicity data as described in section 9.6.2. Interim Immunogenicity Review

No interim analysis of immunogenicity data is planned.

11.5. Final Analysis Plan

Once the last subject completes the final visit, the clinical database will be cleaned, monitored and locked. Upon receipt 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, a set of topline tables will be generated. These tables will include summaries of clinical safety data and immunogenicity data (as described above) through the end of the study, with data presented aggregated by study arm. This topline report will represent a final analysis of safety data including reactogenicity, unsolicited non-serious AEs, and SAEs. The immunogenicity analyses will represent the final analyses of the included immunogenicity endpoints, and as such no p-value adjustment is required. The topline report will be made available to the study team for planning subsequent trials and may be used for publication. A formal Statistical Analysis Plan (SAP) that specifies all planned analyses will be finalized prior to generating the topline report.

The CSR will be completed when all cellular and humoral immunogenicity data through Day 200 are available.

11.5.1. Analysis Populations

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

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

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

- Data from all available visits for subjects found to be ineligible at baseline
- Data from all visits subsequent to major protocol deviations, such as:
    - Second 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

In the case of mis-randomization, subjects will be analyzed according to the study product actually received for all analysis populations.

11.5.2. Safety Data

Summaries and analysis of safety data will be presented for the Safety Analysis Population.

Solicited AEs will be summarized by severity for each day after each study vaccination (Days 1-8 post each study vaccination) and as the maximum severity over all 8 days. Additionally, solicited AEs will be analyzed by taking the most severe response over the follow-up period, dichotomizing into a binary variable (none versus mild, moderate, or severe) and using standard techniques, such as exact confidence intervals, to summarize the proportion of subjects reporting each symptom, any injection site symptom, and any systemic symptom. Summaries of solicited AEs will be presented separately for each study vaccination as well as overall study vaccinations by treatment arm. The proportion of subjects reporting symptoms may be compared between treatment arms using Chi-square or Fisher's exact test, as appropriate. The proportion of subjects reporting solicited symptoms between the different study vaccinations (e.g., dose 1 vs. dose 2 or dose 3 vs dose 4) will be compared using McNemar's test.

Unsolicited AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA®) for preferred term and system organ class (SOC). The numbers of SAEs are expected to be small in this trial and will be reported by detailed listings showing the event description, MedDRA® preferred term and SOC, relevant dates (study vaccinations and AEs), 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® preferred term and SOC, cross tabulated by severity and relationship to study product. Additionally, the proportion of subjects and exact 95% confidence intervals of AEs in aggregate and by MedDRA® categories will be computed.

Clinical laboratory data will be summarized by severity for each visit and as the maximum over all post-study vaccination visits. Graphical presentations such as box plots will be used to illustrate the change from baseline.

11.5.3. Humoral Immunogenicity Data

Summaries and analysis of immunogenicity data will be presented for the ITT and PP populations; the PP population will be considered the primary analysis.

Immune responses in terms of strain-specific (IIV4 strains) HAI and Neut antibody titers will be summarized by treatment arm at each time point. Analyses at all time points will include proportion of subjects with titers ≥40 and geometric mean titers (GMTs). Additionally the proportion of subjects achieving seroconversion from Day 172 to Day 200 (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) will be presented. All summaries will include the corresponding 95% confidence intervals.

The proportion of subjects with seroconversion from Day 172 to 200 will be compared to evaluate the effect of M-001 priming using a two-sided Likelihood Ratio Test.

M-001 antibody response will be summarized by GMTs 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.

The correlation between HAI, Neut, and M-001 antibody titers will be evaluated. Plots such as reverse cumulative distributions or longitudinal presentations of GMTs will be presented for each assay.

11.5.4. Cell Mediated Immunity Data

Cellular immunogenicity assays will also be performed to assess if M-001 induces a cellular immune response, or primes for a cellular immune response to IIV4. T cell response will be measured as the percentage of T cell subsets expressing perforin, CD107a, IFN-γ, TNF-α, and IL2, alone or in combination in CD4 or CD8 T cells. For each measure at all time points, the GMP and corresponding 95% confidence interval will be presented. For the primary endpoint of T cell response against M-001 peptides 14 days post dose 2, a t-test will be used to compare GMPs between treatment arms.

11.5.5. Missing Values and Outliers

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

impact of including or excluding the outliers. Any substantive differences in these analyses will be reported.

12. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating VTEU site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of subjects. Each participating VTEU site will permit authorized representatives of the DMID, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical study records for the purposes of quality assurance reviews, audits, monitoring and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

13. QUALITY CONTROL AND QUALITY ASSURANCE

Following a written DMID-accepted site quality management plan, the participating VTEU site is responsible for conducting routine quality assurance (QA) and quality control (QC) activities to internally monitor study progress and protocol compliance. The site PI will provide direct access to all trial-related sites, source data/data collection forms, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities. The site PI will ensure all study personnel are appropriately trained and applicable documentations are maintained on site.

The SDCC will implement quality control procedures beginning with the data entry system and generate data quality control checks that will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification and resolution.

14. ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1. Ethical Standard

The site PI will ensure that this trial is conducted in full conformity with principles of the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR 46, 21 CFR 50 and 56, and ICH E6; 62 Federal Regulations 25691 (1997), if applicable. The site PI's Institution will hold a current Federal Wide Assurance (FWA) issued by the Office of Human Research Protection (OHRP) for federally funded research.

14.2. Institutional Review Board

Prior to enrollment of subjects into this trial, the approved protocol and informed consent form will be reviewed and approved by the appropriate IRB listed on its FWA.

The responsible official for the IRB will sign the IRB letter of approval of the protocol prior to the start of this trial and a copy will be provided to DMID. The IRB Federal Wide Assurance number will be provided to DMID.

Should amendments to the protocol be required, the amendments will be written by the sponsor and provided to the site PI for submission to the IRB.

14.3. Informed Consent Process

The site PI will choose subjects in accordance with the eligibility criteria detailed in Section 5. Before any study procedures are performed, subjects must sign an informed consent form that complies with the requirements of 21 CFR Part 50 and 45 CFR 46 and the local IRB.

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continuing throughout the individual's trial participation. Before any study procedures are performed, subjects will receive a comprehensive explanation of the proposed study procedures and study interventions/products, including the nature and risks of the trial, alternate therapies, any known AEs, the investigational status of the components, and the other elements that are part of obtaining proper informed consent. Subjects will also receive a detailed explanation of the proposed use and disclosure of their protected health information, including specifically their serum samples. Subjects will be allowed sufficient time to consider participation in the trial, after having the nature and risks of the trial explained to them, and have the opportunity to discuss the trial with their family, friends or legally authorized representative or think about it prior to agreeing to participate.

Informed consent forms describing in detail the study interventions/products, study procedures, risks and possible benefits are given to subjects. The informed consent form must not include any exculpatory statements. Informed consent forms will be IRB-approved and subjects will be asked to read and review the appropriate document. Upon reviewing the appropriate document, the site PI (or designee) will explain the research study to subjects and answer any questions that may arise. Subjects must sign the informed consent form, and written documentation of the informed consent process is required prior to starting any study procedures/interventions being done specifically for the trial, including administering study product.

DMID will provide the site PI, in writing, any new information that significantly impacts the subjects' risk of receiving the investigational product. This new information will be communicated by the site PI to subjects who consent to participate in the trial in accordance with IRB requirements. The informed consent document will be updated and subjects will be re-consented per IRB requirements, if necessary.

Study personnel may employ IRB-approved recruitment efforts prior to obtaining the subjects consent; however, before any study procedures are performed to determine protocol eligibility an informed consent form must be signed. Subjects will be given a copy of all informed consent forms that they sign.

By signing the informed consent form, subjects agree to complete all evaluations required by the trial, unless the subject withdraws voluntarily, or is withdrawn or terminated from the trial for any reason.

The rights and welfare of subjects will be protected by emphasizing to subjects that the quality of their medical care will not be adversely affected if they decline to participate in or withdraw from this trial.

14.4. Exclusion of Women, Minorities, and Children (Special Populations)

This trial will be inclusive of all adults who meet the Subject Inclusion/Exclusion Criteria, regardless of religion, sex, or ethnic background. Should the outcome of this trial be deemed acceptable, additional trials may be initiated in other populations.

It is unknown if the M-001 vaccine poses any risks to an unborn child. Female subjects of childbearing potential who are not surgically sterile via tubal sterilization, bilateral oophorectomy, or hysterectomy or who are not postmenopausal for ≥ 1 year must agree to practice highly effective contraception that may include, but is not limited to, abstinence from intercourse with a male partner, monogamous relationship with a vasectomized partner, male condoms with the use of applied spermicide, intrauterine devices, and licensed hormonal methods, with use of a highly effective method of contraception for a minimum of 30 days prior to study product exposure and agree to practice highly effective contraception for the duration of

study product exposure, including 2 months (defined as 60 days) after the last study vaccination. A highly effective method of contraception is defined as one which results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. In addition to contraceptive use, all female subjects of childbearing potential will be required to have a negative serum or urine pregnancy test within 24 hours prior to receiving each dose of study vaccine. If a female subject becomes pregnant while participating in this study, we will ask her permission to follow-up with her about her health and the health of her baby through pregnancy outcome.

Children will not be included in this trial as presently there are no safety or efficacy data on this regimen in adults. Should the outcome of this trial be deemed acceptable, additional trials may be initiated in other populations.

14.5. Subject Confidentiality

Subjects will have code numbers and will not be identified by name. Subject confidentiality is strictly held in trust by the participating site PIs, their study personnel, the sponsor(s), and their agents. This confidentiality is extended to cover testing of biological samples, in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the trial or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All information provided by the Sponsor and all data and information generated by the participating VTEU site as part of the trial (other than a subject's medical records) will be kept confidential by the site PI and other study personnel to the extent permitted by law. This information and data will not be used by the site PI or other study personnel for any purpose other than conducting the trial. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the site PI or other study personnel; (2) information which is necessary to disclose in confidence to an IRB solely for the evaluation of the trial (3) information which is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in Section 16. If a written contract for the conduct of the trial which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

The study monitor, applicable regulatory authorities, such as the FDA, or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the site PI. This includes, but is not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this trial. The participating VTEU sites will permit access to such records.

To protect privacy, we have received a Certificate of Confidentiality. With this Certificate, the researchers cannot be forced to release information that may identify the research subject, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify the subject, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects, like this study, or for information that must be released in order to meet the requirements of the Federal Food and Drug Administration (FDA).

A Certificate of Confidentiality does not prevent the subject from voluntarily releasing information about themselves or their involvement in this research. If any person or agency obtains a written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

The Certificate of Confidentiality does not prevent the researchers from reporting without the subject's consent, information that would identify the subject as a participant in the research project regarding matters that must be legally reported including: child and elder abuse, sexual abuse, or wanting to harm themselves or others.

14.6. Study Discontinuation

If the trial is discontinued, subjects who sign the informed consent form, and are randomized and vaccinated will continue to be followed for safety assessments. No further study vaccinations will be administered.

14.7. Costs, Subject Compensation, and Research Related Injuries

There is no cost to subjects for taking part in this trial.

Subjects may be compensated for their participation in this trial. Compensation will be in accordance with the local IRB's policies and procedures, and subject to IRB approval.

If it is determined by the participating VTEU site and the site PI that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject. Study personnel will try to reduce, control, and treat any complications from this trial. Immediate medical treatment may be provided by the participating VTEU site, such as giving emergency medications to stop immediate allergic reactions to the study vaccine. No financial compensation will be provided to the subject by the participating VTEU site for any injury suffered due to participation in this trial beyond that provided by clinical trial insurance and the PREP act.

14.8. Future Use of Stored Specimens

Residual samples/specimens are those that are left over after the study has been completed. Subjects will be asked for permission to keep any remaining (residual) samples (serum) derived from venous blood samples for possible use in future research studies, such as examining additional immunological assessments or testing for antibodies against other viruses or bacteria. Samples will be stored at a central clinical storage facility for future use and may be shared with investigators at the participating VTEU sites and with other investigators at other institutions once the clinical study report has been finalized. The samples will not be sold or used directly for production of any commercial product. No human genetic tests will be performed on samples. Each sample will be encoded (labeled) only with a barcode and a unique tracking number to protect subject's confidentiality.

There are no benefits to subjects in the collection, storage and subsequent research use of specimens. Reports about future research done with subject's samples will NOT be kept in their health records.

Subjects may be given the option to decide if they want their samples to be used for future research or have their samples destroyed at the end of this trial. The subject's decision can be changed at any time by notifying the study doctors or nurses in writing. However, if the subject originally consents to future use and subsequently changes his/her decision, any data from a previously collected sample may still be used for this research.

14.9. Disclosure of Individual Research Information

In this protocol, we intend to provide each participant with a lay summary of overall study results. In addition, participants may choose to receive their treatment assignment and will be informed about any risks and benefits of disclosure. Offering participants the option to decline and explaining the clinical significance of individual treatments is intended to minimize the negligible risks associated with disclosure. Interested subjects will be asked to provide contact information for receipt of the information. Results will be provided in an IRB-approved written document after the Clinical Study Report has been finalized.

15. DATA HANDLING AND RECORD KEEPING

The site PI is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported.

Data collection forms will be derived from the eCRF and provided by the SDCC to record and maintain data for each subject enrolled in the study. All data collection forms should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making a change or correction, cross out the original entry with a single line and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the eCRF derived from the data collection forms should be consistent with the data collection forms or the discrepancies should be explained.

The sponsor and/or its designee will provide guidance to site PIs and other study personnel on making corrections to the data collection forms and eCRF.

15.1. Data Management Responsibilities

All data collection forms and laboratory reports must be reviewed by the clinical team and data entry personnel, who will ensure that they are accurate and complete. AEs must be recorded on the appropriate data collection form, assessed for severity and relationship, and reviewed by the site PI or appropriate sub-I.

Data collection is the responsibility of the study personnel at the participating VTEU sites under the supervision of the respective site PI. During the study, the site PI must maintain complete and accurate documentation for the study.

The SDCC for this study will be responsible for data management, quality review, analysis, and reporting of the study data.

15.2. Data Capture Methods

Clinical (including, but not limited to, AE/SAEs, concomitant medications, medical history, physical assessments, and clinical laboratory values), reactogenicity, and immunogenicity data will be entered into a 21 CFR 11-compliant Internet Data Entry System provided by the SDCC.

The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the data collection forms completed by the study personnel.

15.3. Types of Data

Data for this study will include clinical, safety, and outcome measures (e.g., clinical laboratory values, reactogenicity, and immunogenicity data).

15.4. Timing/Reports

The clinical study report (CSR) will include clinical, safety, reactogenicity, and humoral and cellular immunogenicity data through the final visit. Once the last subject completes the final visit, the clinical database will be cleaned, monitored and locked.

Upon receipt 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, a set of topline tables will be generated. These tables will include summaries of clinical safety data and immunogenicity data (as described above) through the end of the study, with data presented aggregated by study arm. This topline report will represent a final analysis of safety data including reactogenicity, unsolicited non-serious AEs, and SAEs. The immunogenicity analyses will represent the final analyses of the included immunogenicity endpoints, and as such no p-value adjustment is required. The topline report will be made available to the study team for planning subsequent trials and may be used for publication.

Unblinded analyses of safety, reactogenicity, and immunogenicity, including all primary and secondary endpoint data will be performed by the SDCC after the clinical database is locked.The CSR will be completed when all cellular and humoral immunogenicity data through day 28 following receipt of IIV4 are available.

After full analysis and final reporting is complete, and upon request and DMID approval, the SDCC will provide the participating VTEU sites with a summary of results by treatment arm and/or subject treatment assignments. In this regard, the participating VTEU sites requesting such information to share with study subjects must do so in compliance with their respective IRB guidelines.

15.5. Study Records Retention

Study records and reports, including, but not limited to, eCRFs, source documents, informed consent forms, and study drug disposition records, shall be maintained for 2 years after a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for the drug, until 2 years after the investigation is discontinued and FDA has been so notified. Informed consent forms for future use will be maintained as long as the sample exists.

The participating VTEU site must contact DMID for authorization prior to the destruction of any study records.

15.6. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedures requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3

5.1 Quality Assurance and Quality Control, section 5.1.1

5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site principal investigator and other study personnel to use continuous vigilance to identify and report deviations within five working days of identification of the protocol deviation, or within five working days of the scheduled protocol-required activity. All deviations must be promptly reported to DMID, via the SDCC's AdvantageEDC^{SM}.

All protocol deviations, as defined above, must be addressed in study subject DCFs. A completed copy of the DMID Protocol Deviation Form must be maintained in the Regulatory File as well as in the subject's chart. Protocol deviations must be sent to the local IRB per its guidelines. The site principal investigator and other study personnel are responsible for knowing and adhering to their IRB requirements.

16. PUBLICATION POLICY

All investigators funded by the NIH must submit or have submitted for them to the National Library of Medicine's PubMed Central (http://www.ncbi.nlm.nih.gov/pmc/) an electronic version of their final, peer-reviewed manuscripts upon acceptance for publication, to be made publicly available no later than 12 months after the official date of publication. The NIH Public Access Policy ensures the public has access to the published results of NIH funded research. It requires investigators to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. Further, the policy stipulates that these papers must be accessible to the public on PubMed Central no later than 12 months after publication.

Refer to:

- NIH Public Access Policy, http://publicaccess.nih.gov/
- NIH Office of Extramural Research (OER) Grants and Funding, http://grants.nih.gov/grants/oer.htm

As of January 2018, all clinical trials supported by the NIH must be registered on ClinicalTrials.gov, no later than 21 days after the enrollment of the first subject. Results of all clinical trials supported by the NIH, generally, need to be submitted no later than 12 months following the primary completion date. A delay of up to 2 years is available for trials that meet certain criteria and have applied for certification of delayed posting.

As part of the result posting a copy of this protocol (and its amendments) and a copy of the Statistical Analysis Plan will be posted on ClincialTrials.gov.

For this trial the responsible party is DMID which will register the trial and post results.

The responsible party does not plan to request certification of delayed posting.

Refer to:

- Public Law 110-85, Section 801, Clinical Trial Databases
- 42CFR11
- NIH NOT-OD-16-149

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SUPPLEMENTS/APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

Table 11: 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"

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.