CCI

Statistical Analysis Plan

Sponsor Name: Medicago R&D Inc.

Protocol Number: CP-PRO-QVLP-014

Protocol Title: A Randomized, Observer-blind, Active Comparator-controlled, Multicenter, Phase 3 Study to Assess the Efficacy, Safety, and Immunogenicity of a Plant-derived Quadrivalent VLP Influenza Vaccine in Adults 65 Years of Age and Older

Protocol Version and Date: Final version 1.2, 24 July, 2018

CCI **Project Code:** 7000108

PPD

Notice of Confidential and Proprietary Information:

The information contained in this document is confidential belonging to Medicago. Acceptance of this document constitutes agreement by the recipient that no information contained herein will be published or disclosed without prior written authorization from an official of Medicago. However, this document may be disclosed to appropriate Institutional Review Board and Ethics Committees or duly authorized representatives of a national regulatory authority under the condition that they are requested to keep it confidential. In the event of an actual or suspected breach of this obligation, CCI hould be notified promptly.

Revision History

Version #	Date (DD-Mmm-YYYY)	Document Owner	Revision Summary
0.1	28-Aug-2018	PPD	Initial Release Version
0.2	01-Oct-2018		Updated based on Medicago comments for the first draft SAP.
1.0	10-Oct-2018		Updated based on Medicago comments for the second draft SAP.
2.0	15-Jul-2019		Heterologous strains for CMI data (exploratory) will not be analyzed. Seroconversion cut-off for MN assay will be 7.1 as specified in SAP instead of protocol.

I confirm that I have reviewed this document and agree with the content.

Approvals	
CCI [redacted] Approval	
PPD	15-Jul-2019 Date (DD-Mmm-YYYY)
PPD	15-JUL-2019 Date (DD-Mmm-YYYY)
Medicago Approval	
PPD	15-JUL-2019 Date (DD-Mmm-YYYY)

Table of Contents

LIST OF TABLE

LIST OF FIGURE

1. GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ARV_C	Attack Rate in Subjects Vaccinated with the Active Comparator
ARV_V	Attack Rate in Subjects Vaccinated with the Quadrivalent VLP
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CMI	Cell-Mediated Immune (response)
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GMA	Geometric Mean Area
GMT	Geometric Mean Titer
GMFR	Geometric Mean Folder Rise
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ILI	Influenza-like Illness
IM	Intramuscular
IPP	Immunogenicity Per Protocol
HI	Hemagglutination Inhibition
HIV	Human Immunodeficiency Virus
HR	Heart Rate
LL	Lower limit
Max	Maximum

MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MN	Microneutralization
NOCD	New Onset of Chronic Disease
NP	Nasopharyngeal
N/A	Not Applicable
OT	Oral Temperature
PBMC	Peripheral Blood Mononuclear Cell
PP	Per Protocol
PT	Preferred Term
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SAS®	Statistical Analysis System®
SC	Seroconversion
SD	Standard Deviation
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
SRH	Single Radial Hemolysis
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
VE	Vaccine Efficacy
VLP	Virus-like Particle
WHO	World Health Organization
UL	Upper limit

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures that will be produced and the statistical methodologies that will be used are complete and appropriate to allow valid conclusions regarding the study objectives described under Medicago Protocol CP-PRO-QVLP-014 titled "A Randomized, Observer-blind, Active Comparator-controlled, Multicenter, Phase 3 Study to Assess the Efficacy, Safety, and Immunogenicity of a Plant-derived Quadrivalent VLP Influenza Vaccine in Adults 65 Years of Age and Older" Final Protocol version 1.2 dated 24July2018.

2.1. Responsibilities

CCI will perform the statistical analyses and is responsible for the production and quality control of all tables, listings and figures (TLFs).

Medicago will perform review of all tables, figures and listings before the finalization.

2.2. Timings of Analyses

The primary analysis is planned after all subjects complete the final study visit or terminate early from the study, and database is cleaned and locked.

3. STUDY OBJECTIVES

3.1. Primary Objective

1. To evaluate the efficacy, relative to an active comparator, of a single 30 µg/strain dose of the Quadrivalent Virus-like Article (VLP) Influenza Vaccine, against protocol-defined influenza-like illness (ILI) caused by any influenza viral type/subtype (RT-PCR);

3.2. Secondary Objectives

Efficacy:

1. To evaluate the efficacy, relative to an active comparator, of a single 30 µg/strain dose of the Quadrivalent VLP Influenza Vaccine, against laboratory-confirmed protocol-defined influenza-like illness (ILI) caused by vaccine-matched strains (sequential RT-PCR & serotyping);
2. To evaluate the efficacy, relative to an active comparator, of a single 30 µg/strain dose of the Quadrivalent VLP Influenza Vaccine, against laboratory-confirmed protocol-defined respiratory illness caused by vaccine-matched strains (sequential RT-PCR & serotyping);
3. To evaluate the efficacy, relative to an active comparator, of a single 30 µg/strain dose of the Quadrivalent VLP Influenza Vaccine, against laboratory-confirmed protocol-defined respiratory illness caused by any influenza viral types/subtypes (matched, mismatched, and un-typed) (sequential RT-PCR);
4. To evaluate the efficacy, relative to an active comparator, of a single 30 µg/strain dose of the Quadrivalent VLP Influenza Vaccine, as measured by the incidence of subjects presenting with symptoms of protocol-defined ILI, regardless of laboratory results.
5. To evaluate the efficacy, relative to an active comparator, of a single 30 µg/strain dose of the Quadrivalent VLP Influenza Vaccine, against laboratory-confirmed protocol-defined influenza-like illness (ILI) caused by any influenza viral types/subtypes (matched, mismatched, and un-typed) (sequential RT-PCR) according to prior exposure to influenza vaccines;

Safety:

1. To assess the safety and tolerability, relative to an active comparator, of a single 30 µg/strain dose of the Quadrivalent VLP Influenza Vaccine.

Immunogenicity:

1. To assess, in a subset of 420 subjects (210 subjects per treatment group), the immunogenicity of a single 30 µg/strain dose of Quadrivalent VLP Influenza Vaccine and an active comparator, as measured by Hemagglutination Inhibition (HI) assay, Microneutralization (MN) assay, and Single Radial Hemolysis (SRH) assay against homologous and heterologous (HI only) influenza strains.

3.3. Exploratory Objectives

Efficacy:

1. To evaluate the efficacy, relative to an active comparator, of a single 30 µg/strain dose of the Quadrivalent VLP Influenza Vaccine, against protocol-defined respiratory illness due to mismatched influenza strains (sequential RT-PCR & serotyping);
2. To determine the efficacy, relative to an active comparator, of a single 30 µg/strain dose of the Quadrivalent VLP Influenza Vaccine, as measured by the incidence of subjects presenting with symptoms of protocol-defined respiratory illness, regardless of laboratory results.
3. To evaluate whether or not vaccine efficacy (VE) is maintained (no waning) through time after vaccination for the primary efficacy endpoint, that is, protocol-defined ILI caused by any influenza viral type/subtype.

Safety:

1. To evaluate respiratory illness outcome, occurrences of pneumonia, new onset or exacerbations of cardio-respiratory conditions, and health care utilization of subjects administered the Quadrivalent VLP Influenza Vaccine at a dose of 30 µg/strain relative to subjects administered an active comparator.

Immunogenicity:

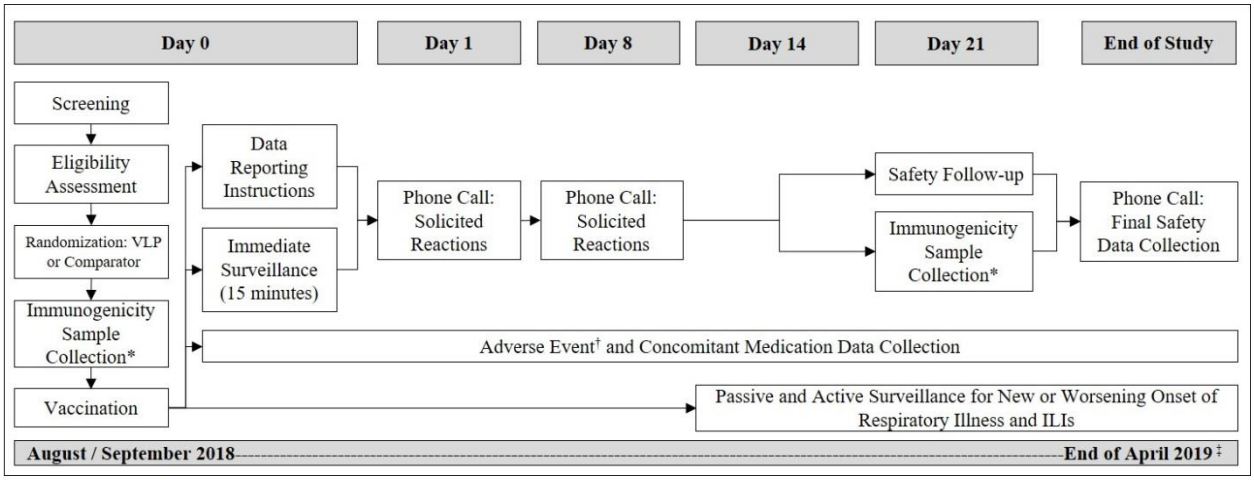
1. To assess the Cell-Mediated Immune (CMI) response against homologous strains of a single 30 µg/strain dose of Quadrivalent VLP Influenza Vaccine and an active comparator on Days 0 and 21 in a subset of 420 subjects (same subset as the immunogenicity subset; 210 subjects per treatment group).

3.4. Brief Description

This randomized, observer-blind, active comparator-controlled Phase 3 study will be conducted at multiple sites. The composition of the Quadrivalent VLP Influenza Vaccine to be used in this study includes a mix of recombinant H1, H3, and two B hemagglutinin proteins expressed as VLPs (see Investigational Product Management Manual) and will be based on the 2018-2019 recommended World Health Organization (WHO) strains for vaccination. The composition of the active comparator is also based on the 2018-2019 recommended WHO strains for vaccination.

Approximately 12,120 non-institutionalized male and female subjects 65 years of age and older with no acute or evolving medical problems will be randomized in a 1:1 ratio into one of two parallel treatment groups, such that approximately 6060 subjects will receive the Quadrivalent VLP Influenza Vaccine at a dose of 30 µg/strain and approximately 6060 subjects will receive an active comparator. Within the two treatment groups, subjects will be randomized by region into three strata (North America, Europe, and Asia) in a 8:4:1 ratio and by age into two strata (65 to 74 years of age and 75 years of age and older) in a 2:1 ratio for overall and within each region.

A basic outline of the study design is presented in Figure 1.



* Subset of 420 subjects for CMI and humoral assessments
† AEs will be collected up to Day 21; SAEs, AEs leading to withdrawal, and NOCDs will be collected through to the end of the study.
‡ The duration of the surveillance period may be adjusted, based on the observed epidemiology during the season.

Figure 1 Flowchart of Study Procedures

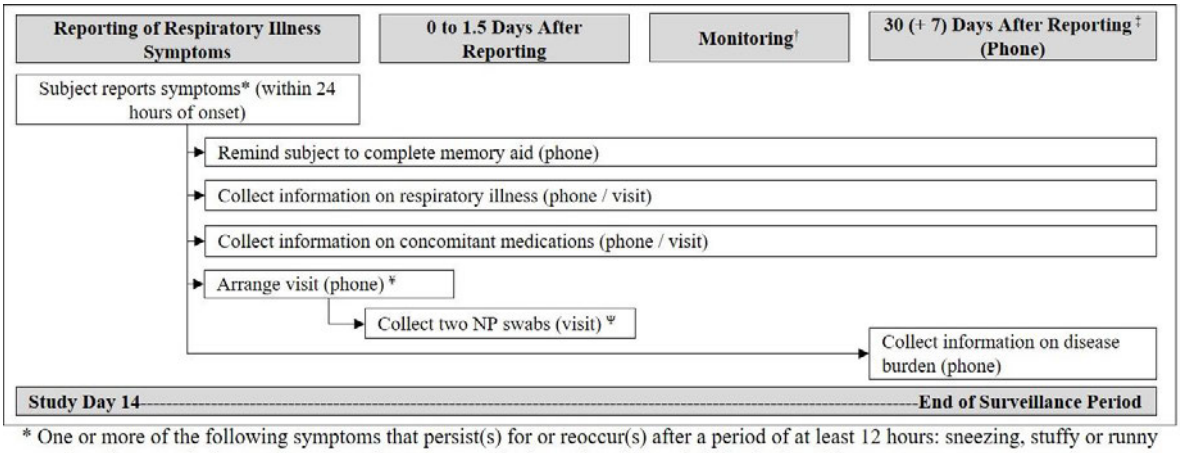
Subjects will participate in this study for approximately eight to ten months, during which a first visit will be scheduled on Day 0 for screening and vaccine administration; subjects will be instructed on how to record reactions, adverse events (AEs), concomitant medication use, and respiratory illness symptoms in their diary and memory aid, as applicable. A phone contact will be made on Days 1 and 8, specifically for review of the subject's safety and concomitant medication data. A visit to the investigator site will occur on Day 21 for a subset of 420 subjects from pre-defined sites in North America (210 subjects per treatment group) for serology sampling and immunogenicity assessments (HI, MN, SRH, and CMI). A final phone contact will be made for a safety assessment at approximately the end of April 2019 (the end of the surveillance period; however, the duration of the surveillance period may be adjusted, based on the observed epidemiology during the season in participating countries).

Active and passive surveillance will be conducted from Day 14 until approximately the end of April 2019 (end of the surveillance period). For passive surveillance, subjects will be instructed to report symptoms meeting the definition of a new or worsening respiratory illness and ILI. For active surveillance, subjects will be contacted at least once per week and asked about symptoms of a new or worsening respiratory illness and ILI. The frequency of active surveillance contacts will vary slightly with region:

- North America and Europe: Prior to the start of the influenza season (the start of influenza season will be determined by Medicago through local epidemiology and clinical experience), subjects will be contacted at least once per week, using the contact method most likely to be successful (e.g. subject's preferred method [phone, text, e-mail]). During the influenza season, subjects will be contacted a minimum of two times per week; at least one of these weekly contacts will be through a scripted telephone call, with the remaining contacts via the method most likely to be successful;
- Asia: Since there generally is no clearly defined influenza season, contacts will be made a minimum of two times per week, with at least one of these weekly contacts through a

scripted telephone call and the remaining contacts via the method most likely to be successful (e.g. subject's preferred method [phone, text, e-mail]).

Reports of respiratory illness will be followed up for the collection of information regarding symptoms, concomitant medication use, and disease burden and the collection of two nasopharyngeal (NP) swabs. For subjects in North America and Europe, swabs will only be collected for cases of respiratory illness that occur after the start of the influenza season (as determined by Medicago through local epidemiology and clinical experience); for subjects in Asia, swabs will be collected for any cases of respiratory illness reported during the surveillance period (Day 14 and onwards). Figure 2 outlines the process to be followed for reports of respiratory illness.



* One or more of the following symptoms that persist(s) for or reoccur(s) after a period of at least 12 hours: sneezing, stuffy or runny nose (nasal congestion), sore throat, cough, sputum production, wheezing, and difficulty breathing
† The planned active surveillance will continue and will include questions on the respiratory illness progression until the final 30 (+ 7) day follow-up for the illness.
‡ Data past Day 30 of onset of respiratory illness is not to be collected
¥ A visit for NP swab collection should be done for any subject who reports any respiratory illness as per regional specifications: after the start of the local influenza season (subjects in North America and Europe) or for any respiratory illness reported during the surveillance period (i.e. Day 14 onwards; subjects in Asia).
Ψ Swabs must be collected within preferably 24 hours after reporting of symptoms and prior to the use of influenza antiviral treatment medication. If swabs cannot be collected within 36 hours after reporting of the respiratory symptoms, this will be reported as a deviation; however NP swabs should still be collected if the subject still has at least one respiratory illness symptom.

Figure 2 Flowchart of Process of Respiratory Illness Report

Throughout the influenza season, the number of laboratory-confirmed influenza cases will be reviewed periodically by selected members of Medicago and the CRO who will be independent of study conduct and analysis. In the event of an insufficient attack rate of confirmed influenza (minimum of 198 cases), the study will be either continued or extended into another season to enroll more subjects and a protocol amendment will be issued to address changes to the enrolment plan.

3.5. Subject Selection

Non-institutionalized male and female subjects 65 years of age and older, with no acute or evolving medical problems and with no clinically significant disease at the time of vaccination, will be included in this study.

All subjects must give written informed consent to be enrolled into the study and must satisfy the study inclusion/exclusion criteria.

3.5.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study; no protocol waivers are allowed:

1. Subjects must have read, understood, and signed the informed consent form (ICF) prior to participating in the study; subjects must also complete study-related procedures and communicate with the study staff at visits and by phone during the study;
2. Subject must have a body mass index (BMI) ≤ 35 kg/m^2;
3. Subjects are considered by the Investigator to be reliable and likely to cooperate with the assessment procedures and be available for the duration of the study;
4. Male and female subjects must be 65 years of age and older at the Screening/Vaccination visit (Visit 1);
5. Subjects must be non-institutionalized (e.g. not living in rehabilitation centres or old-age homes; living in an elderly community is acceptable) and have no acute or evolving medical problems prior to study participation and no clinically relevant abnormalities that could jeopardize subject safety or interfere with study assessments, as assessed by the Principal Investigator or sub-Investigator (thereafter referred as Investigator) and determined by medical history, physical examination, and vital signs;

   Note: Subjects with a pre-existing chronic disease will be allowed to participate if the disease is stable and, according to the Investigator's judgment, the condition is unlikely to confound the results of the study or pose additional risk to the subject by participating in the study. Stable disease is generally defined as no new onset or exacerbation of pre-existing chronic disease three months prior to vaccination. Based on the Investigator's judgment, a subject with more recent stabilization of a disease could also be eligible.

3.5.2. Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participating in this study; no protocol waivers are allowed:

1. According to the Investigator's opinion, history of an ongoing acute or evolving medical or neuropsychiatric illness. 'Evolving' is defined as:
   - Requiring a new medical or surgical treatment during the three months prior to study vaccine administration unless the criteria outlined in inclusion criterion no. 5 can be met (i.e. the Investigator can justify inclusion based upon the innocuous nature of medical/surgical events and/or treatments);
   - Requiring any significant change in a chronic medication (i.e. drug, dose, frequency) during the three months prior to study vaccine administration due to uncontrolled symptoms or drug toxicity unless the innocuous nature of the medication change meets the criteria outlined in inclusion criterion no. 5 and is appropriately justified by the Investigator.
2. Any medical or neuropsychiatric condition or any history of excessive alcohol use or drug abuse that would render the subject unable to provide informed consent or unable to provide

valid safety observations and reporting, including methadone (methadone as treatment for opioid dependence may be acceptable if the subject has been otherwise opioid-free for at least three years);

3. Any autoimmune disease other than hypothyroidism on stable replacement therapy (including, but not limited to rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, type 1 diabetes, and inflammatory bowel disease) or any confirmed or suspected immunosuppressive condition or immunodeficiency including known or suspected human immunodeficiency virus (HIV), Hepatitis B or C infection, the presence of lymphoproliferative disease;
4. Any history of status asthmaticus or ongoing serious problems with asthma, hospitalization for asthma control, or recurrent asthma episodes requiring medical attention in the last three years (one or more episodes per year);
5. Administration or planned administration of any non-influenza vaccine within 30 days prior to randomization up to blood sampling on Day 21. Immunization on an emergency basis will be evaluated case-by-case by the Investigator;
6. Administration of any adjuvanted or investigational influenza vaccine within one year prior to randomization or planned administration prior to the completion of the study;
7. Administration of any 'standard', non-adjuvanted influenza vaccine (e.g. live attenuated trivalent/quadrivalent inactivated influenza vaccine or split trivalent/quadrivalent inactivated influenza vaccine administered by intranasal, intradermal, or intramuscular [IM] route) within six months prior to randomization and up to completion of the study;
8. Use of any investigational or non-registered product within 30 days or five half-lives, whichever is longer, prior to randomization or planned use during the study period. Subjects may not participate in any other investigational or marketed drug study while participating in this study until after the study;
9. Treatment with systemic glucocorticoids at a dose exceeding 10 mg of prednisone (or equivalent) per day for more than seven consecutive days or for ten or more days in total, within one month of study vaccine administration; any other cytotoxic or immunosuppressant drug, or any immunoglobulin preparation within three months of vaccination and until the completion of the study. Low doses of nasal or inhaled glucocorticoids are allowed. Topical steroids are permitted;
10. Any significant disorder of coagulation including, but not limited to, treatment with warfarin derivatives or heparin. Persons receiving prophylactic anti-platelet medications (e.g. low-dose aspirin [no more than 100 mg/day]), and without a clinically apparent bleeding tendency are eligible. Subjects treated with new generation drugs that do not increase the risk of IM bleeding (e.g. clopidogrel) are also eligible;
11. History of allergy to any of the constituents of the Quadrivalent VLP Influenza Vaccine, any components of the active comparator quadrivalent vaccine, or tobacco;
12. History of anaphylactic allergic reactions to plants or plants components (including fruits and nuts);
13. Use of antihistamines within 48 hours prior to study vaccination;

14. Daily use of large doses of medication for pain control or inflammation (e.g. opioids, nonsteroidal anti-inflammatory drugs [NSAIDs]). Use of a singular regular dose either in the morning or at bedtime would not be exclusionary;
15. Use of prophylactic medications (e.g. acetaminophen/paracetamol, aspirin, naproxen, or ibuprofen) within 24 hours of randomization to prevent or pre-empt symptoms due to vaccination;
16. Planned use of influenza antiviral treatment medication before the collection of NP swabs (e.g. oseltamivir, zanamivir, rapivab);
17. Have a rash, dermatological condition, tattoos, muscle mass, or any other abnormalities at the injection site that may interfere with injection site reaction rating;
18. Subjects who have received a blood transfusion within 90 days prior to study vaccination;
19. Subjects with abnormal vital signs (systolic blood pressure [BP] ≥ 150 mmHg and/or diastolic BP ≥ 95 mmHg for individuals taking antihypertensive medication and ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg for individuals not taking antihypertensive medication; heart rate [HR] ≤ 45 beats/min and ≥ 100 beats/min) evaluated by an Investigator to be clinically significant. A subject with abnormal vital signs results may be included in the study based on Investigator's judgment (e.g. a resting HR ≤ 45 in highly trained athletes);
20. Presence of any febrile illness (including an oral temperature [OT] ≥ 38.0 ˚C within 24 hours prior to vaccination;
21. Cancer or treatment for cancer within three years prior to study vaccine administration. Persons with a history of cancer who are disease-free without treatment for three years or more are eligible. However, individuals with conditions such as treated and uncomplicated basal cell carcinoma of the skin or non-treated, non-disseminated local prostate cancer may be eligible;
22. Subjects identified as an Investigator or employee of the Investigator or clinical site with direct involvement in the proposed study, or identified as an immediate family member (i.e. parent, spouse) of the Investigator or any employee of Medicago (or their family members);
23. Subjects with a history of Guillain-Barré Syndrome.

3.6. Determination of Sample Size

The sample size of approximately 12,120 subjects (6060 subjects per treatment group) was selected to have 80 % power to determine non-inferiority, based on the assumption of 20 % VE, a 2 % or greater attack rate in the active comparator (ARV_C) for protocol-defined ILI caused by any influenza viral types/subtypes, and a 10 % dropout rate. Non-inferiority will be concluded if the lower bound of the two-sided 95 % CI is greater than -20 %.

In the event of an insufficient attack rate of confirmed influenza (minimum of 198 cases), the study will be either continued or extended into another season to enrol more subjects and a protocol amendment will be issued to address changes to the enrolment plan.

3.7. Randomization & Blinding

3.7.1. Randomization

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (e.g. demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Potential study subjects will be screened and assigned a subject number. Once all screening procedures, including Day 0 pre-randomization procedures, have been completed and the study eligibility is confirmed by the Investigator, the randomization numbers will be allocated to subjects within the appropriate treatment group by the randomization system.

Subjects will be randomized to one of two treatment groups, based on a computer-generated randomization schedule prepared by or under the supervision of Medicago before the study. Prior to randomization into the two treatment groups, subjects will be stratified by region into three strata (North America, Europe, and Asia) in a 8:4:1 ratio and by age into two groups (65 to 74 years of age and 75 years of age and older) in a 2:1 ratio for overall and within each region.

Once a randomization number has been assigned, it will not be re-used for any reason. No subjects will be randomized into the study more than once. If a randomization number is allocated incorrectly, no attempt will be made to remedy the error once the study vaccine has been dispensed: the subject will continue on the study with the assigned randomization number and associated treatment. The study staff will notify the Sponsor Contact as soon as the error is discovered without disclosing the study vaccine administered. Admission of subsequent eligible subjects will continue using the next unallocated number in the sequence.

The randomization number and treatment will be recorded along with the six-digit subject number for each subject in the investigational product accountability log. The Investigator will not be provided with randomization codes, but it will be possible to unblind the treatment in an emergency situation.

3.7.2. Blinding

Observer-blinded treatment will be used to reduce potential bias during data collection and evaluation of the clinical endpoints.

This is an observer-blind study: the subjects, the Investigators, and those responsible for study endpoint evaluations or review or analysis of the study data will not have access to the randomization codes. Any code break will be documented and reported to Medicago (or its designee) in a timely manner. In a medical emergency, the Investigator may unblind the treatment for that subject without prior consultation with the Sponsor. In such an event, the Investigator will need to contact the responsible Medical Officer as soon as possible after the unblinding to discuss the case.

Since there will be differences in the VLP vaccine and the active comparator preparations (e.g. possibly physical appearance), the site staff involved in the preparation and administration of the treatments will not be involved in any activity that could introduce a bias, such as the evaluations

of respiratory symptoms, ILI, AEs, or local or systemic reactions developed by the subjects following vaccination.

This study is blinded through to the end of the surveillance period of the last subject. The randomization code, will not be available during the course of the study to any investigator or any person directly involved in the clinical conduct of the study (including data cleaning and data analysis) except the independent team from the contract research organization (CRO) and selected individuals from Medicago. The selected individuals will be independent of study conduct and analysis and will review the number of influenza cases to allow for discussion of the clinical data and critical business decisions (e.g. extension of recruitment for another season) prior to study completion. It is anticipated that approximately five people from Medicago and the CRO will have access to the number of cases in an unblinded manner. Also, the central laboratories and the staff at the clinical site (except the staff involved in the preparation/administration of the study vaccine, the quality assurance auditor, and the quality control reviewers) will remain blinded throughout the entire study duration.

Blinding measures will be applied to maintain the observer-blindness of the blinded staff and to allow identification of the study treatment only by staff involved in the preparation/administration of the study vaccine/active comparator.

3.8. Administration of Study Medication

On Day 0, subjects will receive one IM injection, into the deltoid region of the non-dominant arm (if possible), of their assigned treatment (30 µg/strain of Quadrivalent VLP Influenza Vaccine or comparator Fluarix® Tetra/Quadrivalent [15 µg/strain]). The volume of injection will be 0.5 mL for both the VLP vaccine and comparators.

3.9. Study Procedures and Flowchart

The Time and Events Schedule: General Information (see Table 1) summarizes the frequency and timing of scheduled assessments applicable to this study.

The Time and Events Schedule: Respiratory Illness Onset (see Table 2) summarizes the frequency and timing of scheduled assessments associated with the onset of a respiratory illness.

Most subjects will have no blood sampled; the subset of subjects included in the immunogenicity analyses and who complete to the Day 21 visit will have blood volumes drawn of approximately 120 mL over a period of 21 days (Table 3).

Table 1 Time and Events Schedule: General Information

Visit Type	**Screening/ Vaccination**	**Post-vaccination Visits/Contacts**			**End of Surveillance[1]**
Study Day	**Day 0**	**Day 1 (+ 1)**	**Day 8 (- 1/+ 1)**	**Day 21 (- 2/+ 3)**	**(± 3)**
Visit Number	**1**	**Phone**	**Phone**	**2 (Visit or Phone)**	**Phone**
Informed consent	X				
Demographics	X				
Medical history/prior medication	X				
Vaccination history[2]	X				
Inclusion/exclusion criteria	X				
Randomization	X				

Visit Type	**Screening/ Vaccination**	**Post-vaccination Visits/Contacts**			**End of Surveillance[1]**
Study Day	**Day 0**	**Day 1 (+ 1)**	**Day 8 (- 1/+ 1)**	**Day 21 (- 2/+ 3)**	**(± 3)**
Visit Number	**1**	**Phone**	**Phone**	**2 (Visit or Phone)**	**Phone**
Vaccine administration	X				
Immediate surveillance (15 minutes)	X				
Provide diary and memory aid instructions to subjects	X				
Serology for HI, MN, and SRH titers	X[3]			X[3]	
CMI (peripheral blood mononuclear cell [PBMC] assay)	X[3]			X[3]	
Vital Signs (blood pressure [BP], heart rate [HR], oral temperature [OT])	X				
Height, weight, and body mass index (BMI)	X				
History/symptom-directed physical examination	X				
Oral digital thermometer and instructions on reactions and respiratory illness symptoms[4]	X				
Collection of solicited local/ systemic reactions	X	X	X		
Concomitant medications	At any time during the study period[5]				
Collection of respiratory illness symptoms through passive and active surveillance	Passive Surveillance: Subjects will be instructed to contact the study site if they experience symptoms of respiratory illness from Day 14 until the end of the surveillance period[1]. Active Surveillance: Between Day 14 and the end of the surveillance period[1], the subjects will be contacted a minimum of once per week: • North America and Europe: Prior to the start of the influenza season, subjects will be contacted at least once per week, using the contact method most likely to be successful (e.g. subject's preferred method [phone, text, e-mail]). During the influenza season, subjects will be contacted a minimum of two times per week; at least one of these weekly contacts will be through a scripted telephone call, with the remaining contacts via the method most likely to be successful; • Asia: Subjects will be contacted a minimum of two times per week, with at least one of these weekly contacts through a scripted telephone call and the remaining contacts via the method most likely to be successful.				
Collection of NP swabs for laboratory confirmation of influenza[6]	Nasopharyngeal swabs will be collected from subjects who report a new or a worsening respiratory illness (as defined in the protocol): • North America and Europe: after the start of influenza season; • Asia: after the start of active and passive surveillance (Day 14 and onwards); Swabs will be collected within 36 hours (preferably within 24 hours) after reporting of the qualifying respiratory illness symptoms.				
Collection of disease burden and health care information[7]	For each case of respiratory illness (as defined in the protocol), a questionnaire on disease burden (Protocol Section 19.2) will be completed by telephone at the end of the 30-day follow up period for the illness, regardless of whether or not a swab is obtained. Subjects will be provided with a memory aid (Protocol Section 19.3) to facilitate accurate reporting.				
AEs, SAEs, and NOCDs[8]	At any time during the study period				
Termination record					X

[1] The end of the surveillance period is targeted as approximately the end of April 2019; however, the duration of surveillance period may be adjusted, based on the observed epidemiology during the season in participating countries.

[2] Information on past influenza vaccinations for 24 months prior to study entry

Visit Type	**Screening/ Vaccination**	**Post-vaccination Visits/Contacts**			**End of Surveillance[1]**
Study Day	**Day 0**	**Day 1 (+ 1)**	**Day 8 (- 1/+ 1)**	**Day 21 (- 2/+ 3)**	**(± 3)**
Visit Number	**1**	**Phone**	**Phone**	**2 (Visit or Phone)**	**Phone**

[3] Only a subset of 420 subjects will have a blood draw for CMI and humoral immunogenicity testing. This subset will be comprised of the first subjects enrolled in pre-defined sites in North America; a representative age distribution will be targeted.
[4] After vaccination, subjects will be instructed on the diary and memory aid provided for their use for recording reactions, AEs, concomitant medication use, and respiratory illness symptoms. They will be reminded of the reportable respiratory illness symptoms that will trigger the need for NP swabbing, as well as of the overall active and passive surveillance process.
[5] After the Day 21 visit, concomitant medication collection will be limited to those used to treat a NOCD, SAE, AE leading to withdrawal, an AE that occurred before Day 21, or a protocol-defined respiratory illness or ILI; any vaccine not foreseen in the study protocol; and prohibited medications.
[6] Swabs are to be collected from any subject with a respiratory illness from Day 14 to the end of the surveillance period of the study, as per the region specifications (North America and Europe: only after the start of influenza season; Asia: Day 14 and onwards). If the respiratory illness starts prior to Day 14, swabs are not to be collected, even if symptoms persist beyond Day 14.
[7] A questionnaire for the collection of disease burden is available in Protocol Section 19.2 and includes occurrences of any of the following in association with any respiratory illness with onset from Day 14 to the end of the surveillance period: pneumonia (clinical diagnosis), new onset or exacerbations of pre-existing cardio-respiratory conditions, hospitalizations, emergency room visits, and non-routine medical office visits, as well as any additional diagnoses associated with the illness.
[8] AEs will be collected up to Day 21; SAEs, AEs leading to withdrawal, and NOCDs will be collected through to the end of the study. Specific contacts for the collection of information regarding all of these events will occur on Day 21 (in the surveillance telephone call on or shortly after Day 21 or during the Day 21 visit [for the subset of subjects participating CMI and humoral immunogenicity testing]) and during the end of surveillance telephone contact for SAEs, AEs leading to withdrawal, and NOCDs.

Table 2 Time and Events Schedule: Respiratory Illness Onset

Days after Reporting of Respiratory Illness[1]	**0-1.5 Days**	**0-1.5 Days[2]**	**Monitoring[3]**	**30 (+ 7) Days[4]**
Contact Type	**Phone**	**Visit**	**Phone / Text Messaging**	**Phone**
Verify information on respiratory illnesses and schedule appointment (at clinic or home) for two NP swabs within 36 hours (preferably within 24 hours) of the reporting of a respiratory illness	X			
Remind subject to continue to record data and in a timely manner	X			
Collection of the two NP swabs[1,2]		X		
Collection of reportable concomitant medications	X	X	X	X
Collection of information on respiratory illness symptoms[5]	X	X	X	X
Collection of disease burden and health care information				X

[1] Nasopharyngeal (NP) swabs are to be collected for any subject who reports any respiratory illness as per regional specifications: after the start of the local influenza season (subjects in North America and Europe) or for any respiratory illness reported during the surveillance period (i.e. Day 14 onwards; subjects in Asia).
[2] Swabs are to be collected within 36 hours after reporting of the respiratory illness (preferably within 24 hours) and prior to the use of influenza antiviral treatment medication (e.g. oseltamivir, zanamivir, rapivab). If swabs cannot be collected within 36 hours after reporting of the respiratory symptoms, NP swabs should still be collected if the subject still has at least one respiratory illness symptom.
[3] After NP swab collection and until the final 30 (+ 7) day follow-up, the planned active surveillance (phone and text messaging) will continue and will include questions on the respiratory illness progression.

Days after Reporting of Respiratory Illness[1]	**0-1.5 Days**	**0-1.5 Days[2]**	**Monitoring[3]**	**30 (+ 7) Days[4]**
Contact Type	**Phone**	**Visit**	**Phone / Text Messaging**	**Phone**

[4] The seven-day window allows provision to complete the telephone call. Information from more than 30 days from respiratory illness onset does not need to be collected.
[5] During collection of information on respiratory illness symptoms, the presence or absence of concurrent systemic symptoms (i.e. fever, feverishness [feeling of warmth], chills [shivering], tiredness [fatigue], headache, myalgia [muscle aches], nausea, vomiting, or diarrhea) will also be collected.

Table 3 Estimated Blood Volume Drawn

Type of Sample	**Volume per Sample (mL)**	**Number of Samples per Subject**	**Total Volume of Blood per Subject (mL)**
CMI response	50	2*	100*
HI, MN, and SRH titers	10	2*	20*

* Day 0 and Day 21 samples to be collected for a pre-defined subset of 420 subjects.

4. ENDPOINTS

4.1. Efficacy Endpoint

4.1.1. Primary Endpoint

Vaccine efficacy (VE) will be defined as per the applicable regulatory region-specific case definition, as follows:

1. Occurrences of protocol-defined ILI due to laboratory-confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral type/subtype (RT-PCR).

4.1.2. Secondary Endpoints

1. Occurrences of laboratory-confirmed influenza illnesses (according to protocol defined ILI; ≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are matched (and/or antigenically similar) to the strains covered in the vaccine formulation (sequential RT-PCR & serotyping);
2. Occurrences of laboratory-confirmed influenza illnesses (according to protocol defined respiratory illness; ≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are matched (and/or antigenically similar) to the strains covered in the vaccine formulation (sequential RT-PCR & serotyping);
3. Occurrences of laboratory-confirmed influenza illnesses (according to protocol defined respiratory illness; ≥ 14 days post-vaccination) caused by any influenza viral types/subtypes (matched, mismatched, and un-typed) (sequential RT-PCR);
4. Occurrences of protocol-defined ILI ≥ 14 days post-vaccination (confirmed or not by laboratory testing).
5. Occurrences of laboratory-confirmed influenza illnesses (according to protocol defined ILI; ≥ 14 days post-vaccination) caused by any influenza viral types/subtypes (matched, mismatched, and un-typed) according to prior exposure to influenza vaccines.

4.1.3. Exploratory Endpoints

1. Occurrences of laboratory-confirmed influenza illnesses (according to protocol defined respiratory illness; ≥ 14 days post-vaccination) caused by mismatched influenza viral strains (sequential RT-PCR & serotyping);
2. Occurrences of respiratory illnesses ≥ 14 days post-vaccination (confirmed or not by laboratory testing).
3. The slope estimate of the weighted Schoenfeld residuals against event time based on the Cox proportional hazard model for the primary endpoint, that is, protocol-defined ILI caused by any influenza viral type/subtype.

4.2. Safety Endpoints

4.2.1. Secondary Endpoints

1. Percentage, intensity, and relationship to vaccination of immediate complaints (15 minutes post-vaccination);
2. Percentage, intensity, and relationship to vaccination of solicited local and systemic signs and symptoms (for seven days following study vaccine administration);
3. Percentage, intensity, and relationship of TEAEs for 21 days following study vaccine administration;
4. Occurrences of deaths, SAEs, AEs leading to withdrawal, and NOCDs up to the end of the surveillance period.

4.2.2. Exploratory Endpoint

1. Information on respiratory illness outcome, occurrences of pneumonia, new onset or exacerbations of cardio-respiratory conditions, and health care utilization during the entire trial follow up period.

4.3. Immunogenicity Endpoints

4.3.1. Secondary Endpoints

HI antibody response induced against the homologous and heterologous influenza strains on Days 0 and 21 in a subset of 420 subjects (210 from each of the two treatment groups). HI antibody titers will be analyzed as follows:

1. Geometric mean titer (GMT) of HI antibody on Days 0 and 21;
2. Seroconversion (SC) rate: the proportion of subjects in a given treatment group with either a ≥ 4-fold increase in reciprocal HI titers between Day 0 and Day 21 or a rise of undetectable HI titer (i.e. < 10) pre-vaccination (Day 0) to an HI titer of ≥ 40 on Day 21;
3. Seroprotection (SP) rate: the proportion of subjects in a given treatment group attaining a reciprocal HI titer of ≥ 40 on Day 21 (the percentage of vaccine recipients with a serum HI titer of at least 1:40 following vaccination);
4. Geometric mean fold rise (GMFR): the geometric mean of the ratio of GMTs (Day 21/Day 0).

MN antibody response induced by the Quadrivalent VLP Influenza Vaccine against the homologous influenza strains on Days 0 and 21, in the subset of subjects, will be analyzed as follows:

1. GMT of MN antibody on Days 0 and 21;
2. SC rate on Day 21: the proportion of subjects in a given treatment group with either a ≥ 4-fold increase in reciprocal MN titers between Day 0 and Day 21 or a rise of

undetectable MN titer (i.e. 7.1) pre-vaccination (Day 0) to an MN titer of ≥ 28.3 at Day 21 post-vaccination

3. GMFR: the geometric mean of the ratio of GMT (Day 21/Day 0).

SRH antibody response induced by the Quadrivalent VLP Influenza Vaccine against the homologous strains on Days 0 and 21 in a subset of subjects, will be analyzed as follows:

1. Geometric mean area (GMA) of SRH antibody on Days 0 and 21;
2. SC rate: proportion of subjects in a given treatment group showing at least 50 % increase in GMA between Days 0 and 21;
3. SP rate: the proportion of subjects in a given treatment group attaining an area ≥ 25 mm^2 following vaccination (Day 21);
4. GMFR: the geometric mean of the ratio of GMA (Day 21/Day 0).

4.3.2. Exploratory Endpoint

CMI response induced by the Quadrivalent VLP Influenza Vaccine against homologous strains on Day 21 (subset of 420 subjects), as measured by the number of CD4+ T cells expressing each of three functional markers: interferon gamma (IFN-γ), interleukin-2 (IL-2), and tumor necrosis factor alpha (TNF-α), as well the number of cells producing at least one of these cytokines and the number of cells producing two or more of these cytokines.

5. ANALYSIS SETS

5.1. Safety Analysis Set

The safety analysis set (SAS) is defined as all subjects who received either the Quadrivalent VLP Influenza Vaccine or the active comparators. All safety analysis will be performed using the SAS, according to the treatment the subjects actually received.

5.2. Full Analysis Set

The full analysis set (FAS) will consist of the subset of subjects in the SAS who were successfully contacted at least once during the surveillance period. Subjects who received the wrong treatment will be analyzed as randomized.

5.3. Per Protocol Set

The per protocol (PP) set will consist of the subjects who participated in the study until at least the end of the peak period (approximately the end of February for Europe and North America) or for at least five months or until the end of the surveillance period (other countries); had no major protocol deviations related to subject eligibility, the ability to develop a valid immune response, prohibited medication use, or the efficacy analyses; and who received the VLP vaccine or the active comparator. Major protocol deviations will be identified and documented during a blinded data review prior to database lock and confirmed at the time of database lock. The PP set will be the primary analysis population for the efficacy and immunogenicity endpoints. Subjects who received the wrong treatment, but for whom the treatment received can be unequivocally confirmed, will be analyzed as treated, provided they have no other deviations that compromise their data.

The analyses of all efficacy endpoints will be performed using the efficacy PP population and the FAS population.

Note: Protocol deviations and the definition of the peak influenza period will be reviewed and documented during a blinded data review prior to database lock and confirmed at the time of database lock. Since peak influenza period in each region can vary from year to year, the exact period for individual regions will be defined at the end of the season, based on reported positive influenza tests (regional surveillance reporting). The handling of missing data and whether the potential impact of any protocol deviations require the exclusion of a subject from analyses will also be considered during the blinded data review.

5.4. Immunogenicity Per Protocol Set

The immunogenicity PP (IPP) set will consist of the subset of subjects who participated in the immunogenicity portion of the study, who had a Day 21 immunogenicity sample collection; who had no major deviations related to subject eligibility, the ability to develop a valid immune response, prohibited medication use, or the immunogenicity analyses; and who received the vaccine or the active comparator. Subjects who received the wrong treatment, but for whom the treatment received can be unequivocally confirmed, will be analyzed as treated, provided they have no other deviations that compromise their data.

The analyses of all immunogenicity endpoints will be performed using the IPP set.

5.5. Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. Major and minor protocol deviations will be identified and documented during a blinded data review prior to database lock. Subjects will be excluded from analyses if the deviation is considered to impact the analyses.

Prematurely terminating study participation for reasons such as withdrawal of consent or occurrence of adverse events (including death) is not considered as a protocol deviation. The missing assessments that should have otherwise been collected for that subject later in the study are also not considered as a protocol deviation.

Protocol deviations will be reviewed by Medicago (or its designee) to identify any non-compliances likely to have a significant effect on the safety and rights of a subject or the reliability and robustness of the data generated. These deviations will be included in the clinical study report.

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1. General Methods

All statistical procedures will be completed using (SAS®) version 9.4 or higher.

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05. Two-sided 95% confidence intervals (CI) will be provided when relevant.

Continuous variables will be summarized using descriptive statistics, including number of subjects (n), mean, median, standard deviation (SD), minimum (Min) and maximum (Max).

For categorical variables, summaries will include counts of subjects and percentages. Percentages will be rounded to one decimal place.

All summaries will be presented by treatment group and age group, unless otherwise specified.

All subject data, including those derived, will be presented in individual subject data listings. All listings will be sorted by subject number, date/time and visit. The vaccine group (VLP and Comparator) as well as subject's age stratum will be stated on each listing.

A subject who is randomized but does not receive study drug will be included in the subject data listings. All pre- and post-vaccination results, including repeated and unscheduled assessments, will be included in the data listings. Data collected at unscheduled visits that occurred outside the time windows specified in the protocol will be included in the data listings but will not be included in the analyses.

6.2. Reporting Precision

The following decimal description will be used for the demography, efficacy, immunogenicity and safety analyses.

Category	Parameters	Number of Decimal Digits
Demographic characteristics	Mean, Median	1 (One more decimal place than the raw data)
	SD	2 (Two more decimal place than the raw data)
	Min, Max	0 (Same number of decimal places as the raw data)
	% of count	1
Efficacy	VE & 95% CI	1
Humoral and Cellular Immunogenicity evaluation	GMTs including LL & UL of 95% CI	1
	GMFR including LL & UL of 95% CI	2
	SC & SP rate including LL & UL of 95% CI	1
	CMI mean, median	1

Category	Parameters	Number of Decimal Digits
	CMI SD	2
	P-Value	3 (0.xxx format)
Safety	% of count	1

For some parameters (% of count, 95% CI and VE), careful consideration may be required in some instances (e.g. very low-incidence) and in such situations, details will be described in footnotes or programming notes.

6.3. Key Definitions and Derivations

6.3.1. Baseline Values

Unless otherwise specified, the last observed measurement prior to the dose of trial vaccine will be considered as the baseline measurement.

6.3.2. Study Day

Study Day is the number of days since the administration of the study vaccine, which is counted as Study Day 0. If the assessment date is after the date of the vaccination, the study day is calculated as date of assessment - date of the vaccination + 1. If the assessment date is prior to the date of the vaccination, the study day is calculated as date of assessment - date of the vaccination.

6.3.3. Onset day

Onset day is calculated as date of event – date of the vaccination +1.

6.3.4. Demographics

Age collected in CRF will be used on tables.

BMI (kg/m^2) is calculated using the following formula:

BMI=Weight (kg) / Height^2 (m^2)

6.3.5. Immunogenicity

Values below the HI antibody responses below the lower limit of quantification (Below limit of Quantification (BLQ)<10, recorded as "< 10") will be attributed a value of 5. All BLQ responses for the SRH antibody will be attributed a value of 2 mm^2.

<u>For HI assay:</u>

SC rate is defined as the proportion of subjects in a given treatment group with either a ≥ 4-fold increase in reciprocal HI titers between Day 0 and Day 21 or a rise of undetectable HI titer (i.e. < 10) pre-vaccination (Day 0) to an HI titer of ≥ 40 on Day 21.

SP rate is defined as the proportion of subjects in a given treatment group attaining a reciprocal HI titer of ≥ 40 on Day 21 (the percentage of vaccine recipients with a serum HI titer of at least 1:40 following vaccination).

For MN assay:

SC rate is defined as the proportion of subjects in a given treatment group with either a ≥ 4-fold increase in reciprocal MN titers between Day 0 and Day 21 or a rise of undetectable MN titer (i.e. 7.1) pre-vaccination (Day 0) to an MN titer of ≥ 28.3 at Day 21 post-vaccination.

For SRH assay:

SC rate is defined as the proportion of subjects in a given treatment group showing at least 50 % increase in GMA between Days 0 and 21.

SP rate is defined as the proportion of subjects in a given treatment group attaining an area ≥ 25 mm^2 following vaccination (Day 21).

GMT calculation:

The GMT calculations are performed by taking the anti-log of the mean of the log titer transformations. The back-transformation for mean GMT will be calculated with two-sided, 95% confidence limits, based on the Analysis of Variance (ANOVA) model.

GMFR calculation:

The GMFR will be derived by using Analysis of Covariance (ANCOVA) to model the difference in the log of the titer values between Day 21 and Day 0, with treatment group as main effect and baseline titer as covariate. The GMFR will be compared between the treatment groups. The comparisons between the treatment groups will be performed using two-sided, 95% confidence, based on the least-squares mean differences from the ANCOVA model.

6.4. Handling of Missing Data

For a given subject and a given efficacy/immunogenicity measurement, missing measurements will not be replaced. Therefore, an analysis will exclude subjects with missing values.

For the analysis of solicited symptoms, systemic reactions and respiratory illness symptoms, missing or non-evaluable measurements will not be replaced. Therefore the analysis of the solicited symptoms based on the Safety cohort will include only subjects/doses with documented safety data.

There is no imputation in cases where severity or relationship information is missing for AEs.

6.5. Handling of Missing or Incomplete Dates

6.5.1. Missing or Partial AE Start Date

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first vaccination dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date; otherwise, impute the AE start day as 1.
- Otherwise, impute the AE start day as 1.

Compare the imputed AE start date with the vaccination date to determine whether the AE is medical history or treatment emergent adverse event (TEAE).

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start Month and Day as the Month and Day of first dose date; otherwise, impute the AE start Month as January and the Day as 1.

Compare the imputed AE start date with the vaccination date to determine whether the AE is medical history or TEAE.

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing then query site with no imputation. Also compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date then the AE should be considered as a medical history. Otherwise, the AE will be considered as TEAE.

6.5.2. Missing or Partial Concomitant Medication Start/Stop Dates

Missing or partial concomitant medication start date:

- If only DAY is missing, use the first day of the month.
- If DAY and Month are both missing, use the first day of the year.

Missing or partial concomitant medication stop date:

- If only DAY is missing, use the last day of the month.
- If DAY and Month are both missing, use the last day of the year.
- If DAY, Month and year are all missing, assign 'continuing' status to stop date.

6.6. Visit Windows

The collected data will be summarized by scheduled visits based on the scheduled events indicated in Table 1. The visits indicated on the electronic Case Report Form (eCRF) will be used as the analysis visits.

6.7. Pooling of Centers

No center pooling will be employed.

6.8. Subgroups

The subgroup analysis by age stratum will be performed for all the endpoints as applicable.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1. Subject Disposition and Withdrawals

All subjects who provide informed consent will be accounted for in this study. Subject disposition information will be summarized by treatment group and overall. Screened subjects will be presented for the overall population. The frequencies and percentages of subjects who are vaccinated in each analysis set, completed through day 21, completed the study and early study withdrawals along with primary reasons for withdrawal will be presented. The same information will be repeated for the immunogenicity subset.

The number of subjects vaccinated will be used as the denominator for the percentage calculation.

Subject disposition will be listed.

In addition, a listing will be provided to include population sets, completion of the study and withdrawal information by subject and age stratum.

Screen failures will also be listed with reason for not being randomized.

7.2. Demographic and Baseline Characteristics

7.2.1. Demographics

Age, height, weight and BMI at baseline will be summarized descriptively. Age category (65-74 years and >75 years), sex, race, ethnicity, influenza immunization history, and coexisting conditions will be summarized using the SAS, PP and IPP.

The same information will be listed by subject and age stratum.

7.2.2. Baseline and Disease Characteristics

Continuous baseline variables such as OT (°C), systolic BP (mmHg), diastolic BP (mmHg), and HR (beats/min) will be summarized by descriptive statistics in the same way as continuous demographic variables for the SAS, PP and IPP subset.

7.2.3. Protocol Deviations

The protocol deviations by category will be summarized by treatment group and overall. Population membership details will be listed, including reason for exclusion from each population (on randomized patients).

A listing will include the protocol deviations identified based on data recorded on the eCRF and/or protocol deviation logs (on randomized patients) and presented along with the date the deviation occurred relative to study day, and deviation category.

7.2.4. Medical History

The frequencies and percentages of subjects with medical history findings will be presented by system organ class (SOC) using the Medical Dictionary for Regulatory Affairs (MedDRA®)

Version 21.0 or higher by treatment group and overall. Medical history data will be tabulated for the SAS following the order mentioned in Appendix A.

The details of medical history findings will be listed by subject and age stratum.

In addition, another listing will be added to include details of influenza immunization history by subject and age stratum

7.2.5. Prior and Concomitant Medication

Medications used in this study will be coded by using the World Health Organization Drug Dictionary Enhanced (WHO DDE) + Herbal, March 2018.

Prior medications are medications used only before the first study vaccination (medication end date < first study vaccination date).

Concomitant medications are defined as those medications with a start date on or after the vaccination dose of study drug or the medications started before the dose and continued on or after the vaccination.

Prior medications and concomitant medications will be summarized descriptively using frequency tables by Anatomical Therapeutic Chemical (ATC) class (ATC Level 1) and preferred term (PT) (or ATC Level 3) by treatment group. Details for imputing missing or partial start and/or stop dates of medication are described in Section 6.5.2.

In addition, prior medications and concomitant medications will be listed with ATC classification and preferred term (or ATC Level 3) by subject and age stratum.

7.2.6. Treatment Exposure

Since the subjects will receive only one dose of study vaccination, duration will not be calculated. An individual listing will be provided to include details of vaccine administration by subject and age stratum.

7.2.6.1. Treatment Duration

Since the subjects will receive only one dose of study vaccination, duration will not be calculated.

7.2.6.2. Treatment Compliance

Treatment compliance is expected to be 100%, since the study treatments will be administered IM at each Investigator site by site staff. In addition, the Investigator or designated study center personnel will maintain a log of all study treatments dispensed and returned during the study.

Compliance information will not be summarized.

8. EFFICACY

8.1. Efficacy Evaluation

Following randomization and vaccination, subjects will be instructed to report respiratory symptoms and symptoms meeting the definition of ILI from Day 14 until the end of the surveillance period (passive surveillance). The subjects will be given a memory aid listing the symptoms of respiratory illness and ILI and contact information for the study site. During this same period, active surveillance will also be performed to solicit respiratory illness symptoms a minimum of once per week:

- North America and Europe: Prior to the start of the influenza season (the start of influenza season will be determined by Medicago through local epidemiology and clinical experience), subjects will be contacted at least once per week, using the contact method most likely to be successful (e.g. subject's preferred method [phone, text, e-mail]). During the influenza season, subjects will be contacted a minimum of two times per week; at least one of these weekly contacts will be through a scripted telephone call, with the remaining contacts via the method most likely to be successful;
- Asia: Since there generally is no clearly defined influenza season, contacts will be made a minimum of two times per week, with at least one of these weekly contacts through a scripted telephone call and the remaining contacts via the method most likely to be successful (e.g. subject's preferred method [phone, text, e-mail]).

A respiratory illness will be defined as the occurrence of a new onset of one or more of the following symptoms that persist(s) for or reoccur(s) after a period of at least 12 hours:

- Sneezing;
- Stuffy or runny nose (nasal congestion);
- Sore throat;
- Cough;
- Sputum production;
- Wheezing;
- Difficulty breathing.

An episode is considered to extend from the first day of the first symptom to the last day of the last symptom. In most instances a new episode can only begin after resolution of all symptoms of the previous episode, with a separation of a seven-day symptom-free interval between episodes.

Within 36 hours (preferably within 24 hours) after the reporting of a respiratory illness, the clinic site will collect NP swabs from the subject (two per subject per event) if the start of the respiratory illness falls in the indicated regional timeframe:

- North America and Europe: after the start of influenza season;
- Asia: after the start of active and passive surveillance (Day 14 and onwards).

The swabs must be collected prior to the use of any influenza antiviral treatment medication (e.g. oseltamivir, zanamivir, rapivab). If the respiratory illness starts prior to Day 14, swabs are not to be collected, even if symptoms persist beyond Day 14.

A swab will be submitted for analysis by multiplex RT-PCR. In the event of a positive RT-PCR result (positive for A or B strains), additional testing will be done to attempt to isolate the virus or for additional cell-culture testing (typing, subtyping, and strain identification and genetic sequencing using HI assay against a panel of known standard ferret reference antisera to different viral strains) to determine if the virus detected is matched or similar to any of the strains covered in the vaccine formulation for the respective season. A positive RT-PCR result will be considered a laboratory-confirmed case of influenza. The NP swabs will be analyzed in a central laboratory; information on processing and the central laboratories will be provided in the study-specific documentation.

Any respiratory illness must be followed up for 30 days following the start date; this follow up will be conducted via the planned active surveillance contacts (telephone and text messaging), using a script. At the end of the 30-day follow up, a questionnaire regarding disease burden due to the respiratory illness will be completed; subjects will be provided with a memory aid for use over the 30 days, to facilitate accurate reporting at the end of the follow-up period.

ILI will also be monitored during this study. A subject will be considered to have protocol-defined ILI if the following two conditions are both met between Day 14 and the end of the surveillance period:

- He/she has at least one of the following pre-defined respiratory symptoms:
    - Sore throat;
    - Cough;
    - Sputum production;
    - Wheezing; or
    - Difficulty breathing;

AND

- He/she has at least one of the following systemic symptoms:
    - Fever (defined as a temperature > 37.2 °C or > 99.0 °F);
    - Chills;
    - Tiredness;
    - Headache; or
    - Myalgia.

In addition, information on the following uncommon ILI symptoms will be collected for any subjects with a protocol-defined respiratory illness during the surveillance period: nausea, vomiting, and diarrhea.

8.2. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint defined in Section 4.1.1 will be analyzed using the PP set as outlined below:

For the primary endpoint, VE will be evaluated as the relative risk of subjects vaccinated with Quadrivalent VLP Influenza Vaccine (30 µg/strain) or an active comparator to develop protocol-defined ILI as a result of laboratory-confirmed infection with any influenza virus (RT-PCR) ≥14 days after vaccination.

VE will be calculated using the following formula:

$$VE=(1-RR)=(1-ARV_V/ARV_C)*100\ \%$$

Where:

RR = relative risk

ARV_V = attack rate in subjects vaccinated with the Quadrivalent VLP Influenza Vaccine; and

ARV_C = attack rate in subjects vaccinated with an active comparator.

Non-inferiority will be concluded if the lower limit of the two-sided 95 % CI for relative VE is > -20 % for the primary endpoint. If non-inferiority is demonstrated, VE of the VLP vaccine will be tested for superiority over the active comparator as an exploratory analysis (VE for superiority testing will use the same definitions as in the primary endpoint). Superiority will be concluded if the lower limit of the two-sided 95 % CI for relative VE is > 9 % for the primary endpoint.

The primary endpoint will be summarized descriptively with VE and its 95% CI.

The analyses of the primary efficacy endpoint will be repeated for the FAS.

8.2.1. Multiplicity

Multiplicity adjustment will not be done for the primary endpoint because there is only one.

8.2.2. Methodology for Computing CI

8.2.2.1. Wilson Score 95% CIs

The 95% CI around RR will be calculated based on score confidence limits.

SAS® Code [4, Orenstein 1985]:

```
Proc freq data= ADZ (with the appropriate analysis dataset);
table group*resp/relrisk (cl=SCORE) ;
run;
Note: 95% Lower Confidence Limit for VE = 1-95% Upper Score Confidence Limit.
```

8.3. Analysis of Secondary Efficacy Endpoints

The secondary efficacy endpoints which are defined in Section 4.1.2 will be analyzed in the following manner:

VE and 95% CI will be calculated for the secondary efficacy endpoints using the same formula indicated for the primary efficacy analysis.

For secondary efficacy endpoints, the sub-analyses (VE and its 95% CI) by each strain (homologous A/Michigan/45/2015 [H1N1], homologous A/Singapore/INFIMH-16-0019/2016 [H3N2], homologous B/Colorado/06/2017 and homologous B/Phuket/3073/2013), where applicable, and by age group (65-74 and >75) will be summarized.

Non-inferiority will be tested using the same criterion as with the primary endpoint; superiority testing will be conducted if non-inferiority is concluded (the same criterion as with the primary endpoint will be used for superiority testing).

All the secondary efficacy analyses will be based on the PP and will be repeated for the FAS as well.

8.3.1. Multiplicity

Multiplicity adjustment will not be done for the secondary efficacy endpoints. The inclusion of secondary endpoints is intended to yield supportive evidence related to the primary efficacy endpoint by providing additional clinical characterization of the treatment effect. Therefore, the use of statistical strategy to control the overall Type 1 error is not necessary.

8.3.2. Methodology for computing CI

8.3.2.1. Wilson Score 95% CIs

The 95% CIs will be calculated in the same way as for the primary analysis mentioned above (Section 8.2.2).

8.4. Analysis of Exploratory Endpoints

The exploratory efficacy endpoints 1 and 2 which are defined in Section 4.1.3 will be analyzed using the same formula indicated for the primary efficacy analysis. The sub-analyses (VE and its 95% CI) by age group will be summarized.

Non-inferiority will be tested using the same criterion as with the primary endpoint; superiority testing will be conducted if non-inferiority is concluded (the same criterion as with the primary endpoint will be used for superiority testing).

Summaries of study outcomes for those with ‘respiratory illness’ or systemic illness (ILI) will be presented for the overall population as well as by age and treatment group.

In addition, an individual listing will be included to present details of the results of RT-PCR and typing (laboratory-confirmed influenza vaccine matched, mismatched strains, or un-typed strains), respiratory illness symptoms, and ILI by subject and age stratum.

For the exploratory efficacy endpoint 3 defined in Section 4.1.3, the presence of VE waning can be tested by the linear trend (i.e., the proportional hazards) in the scaled Schoenfeld residuals from the Cox proportional hazard model [Petrie 2016, Durham 1998]. Specifically, it will be analyzed as below:

Step 1: Fit a regular Cox proportional hazard model with the treatment group as the main effect, and Fluarix will be coded as the reference group in the model.

Step 2: Find the scaled Schoenfeld residual from the Cox proportional hazard model in step 1. The scaled Schoenfeld residual has value at all event-time for the main effect (treatment group);

Sample SAS® Code:

```
Proc phreg data = ADZ (with the appropriate analysis dataset);
model AVAL*Censor(1) = TRTP / (ref = 'Fluarix');
output out=res wtressch = TRTP_r;
run;
Note: Censor indicates censoring status: 1 = Censored; 0 = protocol-defined
ILI due to laboratory-confirmed influenza.
```

Step 3: Fit a linear regression on the scaled Schoenfeld residuals against event time.

Sample SAS® Code:

```
Proc GLM data = res;
model TRTP_r = AVAL;
 ods output ParameterEstimates= prms;
run;
Note: AVAL in step 2 and 3 is the event time for the primary efficacy
endpoint, protocol-defined ILI caused by any influenza viral type/subtype.
```

Step 4: The slope and p-value will be output. VE(t)=1-exp(beta(t)), VE(t) waning (smaller with time) is corresponding to the increasing beta(t). Thus, a positive slope with significant p-value (<0.05) will indicate VE is waning though time.

All the exploratory efficacy analyses will be based on the PP and will be repeated for the FAS as well.

9. ANALYSIS OF IMMUNOGENICITY

9.1. Immunogenicity Evaluation

Immunogenicity will be evaluated by the humoral immune response (HI, MN, and SRH assays) and the CMI response induced in subjects on Days 0 and 21 in a subset of 420 subjects (210 from each treatment group) from selected sites. The North American sites selected for this subset of 420 subjects will be pre-defined prior to study start and will target providing a representative age distribution. The number of subjects in each age group (65 to 74 years of age and 75 years of age and older) included in the immunogenicity analyses will be similar in proportion to that of the overall study.

9.2. Analysis of Secondary Endpoints

The secondary immunogenicity endpoints are defined in Section 4.3.1.

HI antibody titers will be analyzed and evaluated as follows:

- GMTs of HI antibody: The point estimates and the corresponding two sided 95 % CI by treatment group and strain will be calculated as the antilog of the mean and 95 % CI of log transformed titer values on Days 0 and 21;
- SC rate: The point estimates and the corresponding two-sided 95 % CI for subjects achieving SC by treatment group and strain will be calculated and reported;
- SP rate: The point estimates and the corresponding two-sided 95 % CI for subjects achieving SP by treatment group and strain will be calculated and reported.
- GMFR: the geometric mean of the ratio of GMTs (Day 21/Day 0).

MN antibody response against the homologous influenza strains on Days 0 and 21will be analyzed as follows:

- GMTs of MN antibody on Days 0 and 21(as defined above for HI);
- SC rate: the proportion of subjects in a given treatment group with either a ≥ 4-fold increase in reciprocal MN titers between Day 0 and Day 21 or a rise of undetectable MN titer (i.e. 7.1) pre-vaccination (Day 0) to an MN titer of ≥ 28.3 at Day 21 post-vaccination.
- GMFR: the geometric mean of the ratio of GMTs (Day 21/Day 0).

SRH antibody response against the homologous influenza strains will be analyzed as follows:

- GMAs of SRH antibody on Days 0 and 21;
- SC rate: proportion of subjects in a given treatment group showing at least 50% increase in GMA between Days 0 and 21;
- SP rate: the proportion of subjects in a given treatment group attaining an area ≥ 25 mm^2 following vaccination (Day 21);
- GMFR: the geometric mean of the ratio of GMAs (Day 21/Day 0).

The GMFR will be derived by using ANCOVA to model the difference in the log of the titer values between Day 21 and Day 0, with treatment group as main effect and baseline titer as covariate.

The GMTs, GMFRs, SP and SC rates of the HI antibody assay, the GMTs, GMFRs and SC rates of and the MN antibody assay, and the GMAs, GMFRs, SC rates, and SP rates for the SRH antibody assay will be compared between the treatment groups using descriptive statistics and 95% CI.

For SC rate and SP rate, Fisher's exact tests will be used. GMT for HI, MN and GMA for SRH will be compared between treatment groups using the ANOVA model. GMFR for HI, MN and SRH will be compared using the ANCOVA model.

A sub-analyses stratified by age group for the secondary immunogenicity endpoints will performed.

The analyses of the secondary immunogenicity endpoints will be repeated for the FAS.

An individual listing will be provided to include all assay results (HI, MN and SRH) and whether a particular subject has seroconverted/seroprotected based on IPP set.

In addition, the below listed figures will be generated:

- Reverse Cumulative Distribution Curves (RCDC) for Homologous Strains Measured and Heterologous Strains Measured by HI based on IPP.
- RCDC for Homologous Strains Measured by HI based on FAS.
- RCDC for Homologous Strains Measured by MN based on IPP.
- RCDC for Homologous Strains Measured by SRH based on IPP.

9.2.1. Multiplicity

No multiplicity adjustment will be performed as only seroconversion and seroprotection rates, and the 95 % CI will be reported.

9.2.2. Methodology for computing CI

9.2.2.1. 95% CIs

The 95% CI for GMTs will be obtained within each group separately. The 95% CI for the mean of log-transformed titer/concentration will be first obtained assuming that log-transformed concentrations/titers are normally distributed with an unknown variance. The 95% CI for GMTs will be then obtained by exponential-transformation (anti-log with power 10) of the 95% CI for the mean of log-transformed titers.

SAS® Code for comparing GMTs:

```
PROC MIXED DATA=<Data>; * specify and sub-select data set as applicable;
      *BY Agegrp; * as applicable;
  CLASS trtpn; * other factors may be added, if applicable;
  MODEL AVAL = trtpn; * AVAL=logtiter
```

```
      * add factors and options (e.g. ALPHA=.. Solutions) as applicable;
   LSMEANS trtpn / CL ALPHA=0.05 STDERR; * modify/adapt as applicable
   Ods output LSMEANS =_outmix;
RUN;
QUIT;
Data _outmix;
Set _outmix;
    GMT= 10**(Estimate);
    GMT_LCL = 10**(Lower);
    GMT_UCL = 10**(Upper);
RUN;
```

SAS® Code for comparing GMFR:

```
PROC MIXED DATA=<Data> (analysis dataset);
      class trtpn;
      model diff= trtpn Base; * diff = log10Day21 – log10Day0. Base=log10Day0
      Lsmeans trtpn/cl alpha=0.05;
      Ods output LSMEANS =_outmix;
run;
Quit;
Data _outmix;
Set _outmix;
    GMFR = 10**(Estimate);
    GMFR_LCL = 10**(Lower);
    GMFR_UCL = 10**(Upper);
Run;
```

9.2.2.2. Exact 95% CIs

The exact 95% CIs (Clopper-Pearson method) will be used for proportion of SC and SP subjects within a group.

SAS® Code for SC and SP (Exact 95% CIs):

```
PROC FREQ data=<Data>;
      BY ANTIGEN trtpn;
      TABLE SC/out=CNT binomial; *SC or SP
      EXACT binomial;
      ODS OUTPUT binomialprop=bin (where=(name1 in ('XL_BIN', 'XU_BIN')));
run;
```

9.3. Analysis of Exploratory Endpoint

The exploratory immunogenicity endpoint is defined in Section 4.3.2.

The CMI response induced by the Quadrivalent VLP Influenza Vaccine against homologous strains on Day 21 (in the subset of 420 subjects) will be compared between the treatment groups using non-parametric (Wilcoxon) models for each strain and parameter by age group and overall.

For CMI response CD4+ cells results will be presented along with available subjects (n), in terms of mean, median, SD, min and max. For the p-value calculation between the treatment groups for individual parameters, Wilcoxon rank-sum test will be used for Day 21, whereas the p-value will be calculated using Wilcoxon signed rank test for the difference between Day 0 and Day 21 values.

In addition, an individual listing will be provided to include CMI CD4+ cells response for each parameter with % response CD4+cells by subject and age stratum. The responses of each parameter will be illustrated using plots such as box plots by treatment group with parameters as X-axis and percentage of CD4+ T cells (%) as Y-axis.

10. SAFETY

10.1. Evaluations

Safety and tolerability will be evaluated by solicited local and systemic reactions (immediate complaints within 15 minutes post-vaccination and solicited reactions up to seven days post-vaccination), unsolicited AEs up to 21 days post-vaccination, and serious adverse events (SAEs) and new onset of chronic diseases (NOCDs), and AEs leading to withdrawal up to the end of the surveillance period. In addition, events will be monitored for a possible hypersensitivity component, from all reported events during the study (collected AEs, SAEs, NOCDs, and AEs leading to withdrawal).

Subjects will be monitored for both solicited local reactions (erythema, swelling, and pain at the injection site) and solicited systemic reactions (fever, headache, fatigue, muscle aches, joint aches, chills, a feeling of general discomfort, swelling in the axilla, and swelling in the neck) from the time of vaccination through Day 7. While the subjects remain in the clinic following vaccine administration, staff will monitor them for local and systemic reactions; after release from the clinic facility, from the evening of Day 0 to the evening of Day 7, subjects will measure and record their local and systemic reactions in their diary.

The intensity of the solicited local and systemic reactions will be graded as: mild (1), moderate (2), severe (3), or potentially life threatening (4) (please refer to Table 4). Their causal relationship with the study vaccine will be assessed by the Investigator (definitely not related, probably not related, possibly related, probably related or definitely related).

Table 4 Severity Grades for Solicited Local and Systemic Reactions

Symptoms	**Severity**				
	None	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Potentially life-threatening)**
Injection Site Reactions (Local Reactions)					
Erythema (redness)	< 25 mm	25 - 50 mm	51 - 100 mm	> 100 mm	Necrosis or exfoliative dermatitis
Swelling	< 25 mm	25 - 50 mm and does not interfere with activity	51 – 100 mm or interferes with activity	> 100 mm or prevents daily activity	Necrosis
Pain	None	Does not interfere with activity	Repeated use of non-narcotic pain reliever for more than 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Results in a visit to emergency room (ER) or hospitalization
Solicited Systemic Reactions					
Fever (ºC or ºF)	< 38.0 ºC < 100.4 ºF	38.0 - 38.4 ºC 100.4 - 101.1 ºF	38.5 - 38.9 ºC 101.2 - 102.0 ºF	39.0 - 40.0 ºC 102.1 - 104.0 ºF	> 40.0 ºC > 104.0 ºF

Symptoms	**Severity**				
	None	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Potentially life-threatening)**
Headache	None	No interference with activity	Repeated use of non-narcotic pain reliever for more than 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Results in a visit to emergency room (ER) or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Results in a visit to emergency room (ER) or hospitalization
Muscle aches	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Results in a visit to emergency room (ER) or hospitalization
Joint aches, chills, feeling of general discomfort or uneasiness (malaise), swelling in the axilla, swelling in the neck	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Results in a visit to emergency room (ER) or hospitalization

10.2. Adverse Events

All Adverse events (AEs) will be classified by Primary SOC and PT according to the Medical Dictionary for Regulatory Activities (MedDRA®) Version 21.0 or higher. An AE is considered treatment-emergent if it began on or after the date and time of Study Day 0 vaccination.

All spontaneous AEs occurring within 21 days after vaccination will be reported in the "Adverse Event" screen in the subject's eCRF, irrespective of intensity or whether or not they are considered to be vaccination-related. Thereafter, from Day 22 to the end of the surveillance period, SAEs, AEs leading to withdrawal, and NOCDs will be monitored and reported in the eCRF.

The intensity of AEs will be graded as: mild (1), moderate (2), severe (3) or potentially life threatening (4), according to the Food and Drug Administration (FDA) Guidance for Industry (FDA, 2007). Their causal relationship with the study vaccine will be assessed by the Investigator (definitely not related, probably not related, possibly related, probably related or definitely related); see Section 13.1.9 in protocol for a definition of these causal relationships.

10.3. Analysis of Secondary Endpoints

The secondary endpoints of safety that are mentioned in Section 4.2.1 will be analyzed as follows: All safety analyses will be based on the SAS.

Safety and tolerability endpoints (immediate complaints, solicited local and systemic reactions, and TEAEs, deaths, SAEs, AEs leading to subject withdrawal, and NOCDs) will be summarized by treatment and by age group using descriptive statistics.

The original terms used in the eCRFs by Investigators to identify AEs will be coded using the MedDRA® dictionary. All eCRF reported AEs with onset post-vaccination will be included in the safety analyses.

Special attention will be given to those subjects who die, who discontinue from the study due to an AE, who experience an SAE (e.g. summaries, listings, and narrative preparation may be provided, as appropriate), or who experience an allergic or allergic-like reaction (hypersensitivity cases).

Overall summaries of subjects with solicited reactions and Unsolicited Treatment Emergent Adverse Events (TEAE) will be prepared as follows:

- Any solicited local and systemic reactions occurring 15 minutes after vaccination (immediate complains)
- Solicited reactions including immediate complains
- Severe and potentially life-threatening solicited reactions
- Severe and potentially life-threatening related solicited reactions
- Solicited local reactions
- Solicited systemic reactions
- Unsolicited TEAEs (Day 0 to Day 21)
- Related unsolicited TEAEs
- Severe and potentially life-threatening unsolicited TEAEs
- Severe and potentially life-threatening related unsolicited TEAEs
- Serious TEAEs (Day 0 to Day 21)
- Serious TEAES (Day 0 to End of study)

The percentage of subjects with at least one immediate complaint (local or systemic reactions) and the percent of subjects with at least one immediate complaint of each of the individual local and systemic reactions will be summarized by treatment group and by age group.

In addition, the same summary will be tabulated by maximum severity grading and by causality for each treatment group overall and by age group.

The maximum event severity will be considered to be the greatest severity associated with each reaction according to the following order: mild < moderate < severe <potentially life-threatening. Causality will be presented as “Unrelated” (definitely not related and probably not related) and “Related” (possibly related, probably related and definitely related).

Similar summaries will be presented for solicited local and systemic reactions collected from Day 0 to Day 7 and unsolicited TEAEs collected up to Day 21. In addition, summaries of severe and potentially life-threatening solicited local and systemic reactions and unsolicited TEAEs will also be provided.

The analysis of unsolicited adverse events comprises the following categories:

- Occurrence of any unsolicited TEAE by system organ class (SOC) and PT from the administration of the vaccine dose up to day 21 (day 0 to day 21)
- Unsolicited TEAEs by SOC, PT and Maximum severity (Day 0 to 21)
- Unsolicited TEAEs by SOC, PT and relationship status (Day 0 to 21)
- Grade 3 and Grade 4 related unsolicited TEAEs by SOC and PT (Day 0 to Day 21)

AE summary tables will be presented for the below categories as well:

- AEs leading to death (Day 0 to End of study)
- Serious TEAEs (Day 0 to Day 21) by SOC and PT
- Serious TEAEs (Day 0 to End of study) by SOC and PT
- AEs leading to withdrawal (Day 0 to End of study)
- Occurrence of New Onset of a Chronic Disease (NOCD)s (Day 0 to Day 21) by SOC and PT
- Occurrence of NOCDs (Day 0 to End of study) by SOC and PT
- Occurrence of Hypersensitivity Cases (Day 0 to Day 21) by SOC and PT

Events that are considered to be a new onset of chronic disease (NOCD), as defined in the study protocol, will be collected until the end of surveillance. A summary of the occurrence of NOCDs, by SOC and PT, will be provided for Day 0 to Day 21 and from Day 0 to the end of surveillance.

Hypersensitivity cases will be identified using a standardized MedDRA® query (SMQ) for hypersensitivity. A summary of the occurrence of hypersensitivity events, by SOC and PT, will be provided for Day 0 to Day 21.

In summaries by SOC and PT, events will be sorted by internationally order (please refer to Appendix A).

Where the same reaction or same adverse event, based on preferred terminology, is reported multiple times for the same subject in a treatment period, the subject will only be counted once in the preferred terminology level in summary frequency tables.

Individual listings will be provided for the categories below:

- Solicited local and systemic reactions Day 0 to Day 7
- Unsolicited AEs (Day 0 to Day 21)
- Serious TEAEs (Day 0 to End of Surveillance)
- NOCD (Day 0 to End of Surveillance)
- Hypersensitivity Cases (Day 0 to Day 21)

10.4. Analysis of Exploratory Endpoints

The exploratory safety endpoints defined in Section 4.2.2 will be analyzed as follows:

The occurrences of medical visits, hospitalizations, and workdays missed (if applicable) will be summarized by treatment using descriptive statistics. These analyses will be done separately and not be included in the CSR.

10.5. Vital Signs

Vital signs measurements (resting BP, HR, and OT) will be performed as part of screening procedures (during eligibility assessment on Day 0) and after the 15-minute post-vaccination surveillance period.

Vital signs data (actual values and Change from baseline) will be summarized by treatment group and assessment timepoint using standard summary statistics.

An individual listing will be provided for vital signs measurements by subject and age stratum.

10.6. Electrocardiograms

Electrocardiograms are not planned for this study.

10.7. Physical Examination

A history- or symptom-directed physical examination will be performed by the Investigator as part of screening procedures (during the eligibility assessment on Day 0).

An individual listing will be provided for Physical Examination results by subject and age stratum.

10.8. Other Safety

No other safety assessments are planned for this study.

11. INTERIM ANALYSES

No interim analysis is scheduled.

12. CHANGES FROM ANALYSIS PLANNED IN PROTOCOL

1). According to the scientific advices of European Medicines Agency (EMA), a new secondary efficacy endpoint is added:

- Occurrences of laboratory-confirmed influenza illnesses (according to protocol defined ILI; ≥ 14 days post-vaccination) caused by any influenza viral types/subtypes (matched, mismatched, and un-typed) according to prior exposure to influenza vaccines.

The occurrence and vaccine efficacy (95% CI) for subjects with and without influenza vaccination history will be summarized.

2). A new exploratory efficacy endpoint is added:

- To evaluate whether or not vaccine efficacy (VE) is maintained (no waning) through time after vaccination for the primary efficacy endpoint, that is, protocol-defined ILI caused by any influenza viral type/subtype.

The relevant analysis is described in Section 8.4.

3). Heterologous strains for the exploratory CMI data will not be analyzed due to the reason below:

As it was already demonstrated in previous clinical trials that the Quadrivalent VLP Influenza Vaccine elicited cross-reactive CD4 T cell response, it was decided to wait so see if the 2018-2019 season would be a match or a mismatch season. In case of a mismatch season, Medicago will therefore has the possibility to test the CMI response generated by the Quadrivalent VLP Influenza Vaccine against the strain(s) that were actually circulating during the season.

4). There is a discrepancy between the protocol and the SAP regarding the seroconversion calculations for MN titers. The definition used in the SAP (cut-off at 7.1) is the one prevailing over the protocol definition (in which it is said that the same approach as for HI titers will be used).

13. REFERENCE LIST

1. ICH Topic E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95- adopted December 1995).
2. ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 – adopted March 1998).
3. FDA. (2007). Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials.
4. SAS® Institute Inc. SAS 9.4 Help and Documentation
5. Orenstein WA, Bernier RH, Dondero TJ, Hinman AR, Marks JS, Bart KJ, Sirotkin B. Field evaluation of vaccine efficacy. Bulletin of the World Health Organization 1985;63 (6): 1055-1068.
6. Petrie JG, Ohmit SE, Truscon R, Johnson E, Braun TM, Levine MZ, Eichelberger MC, Monto AS. Modest Waning of Influenza Vaccine Efficacy and Antibody Titers During the 2007–2008 Influenza Season. The Journal of Infectious Diseases 2016;214:1142–9.
7. Durham LK, Longini IM Jr, Halloran ME, Clemens JD, Nizam A, Rao M. Estimation of vaccine efficacy in the presence of waning: application to cholera vaccines. Am J Epidemiol 1998;147:948-59.

14. PROGRAMMING CONSIDERATIONS

14.1. General Considerations

- A separate SAS® program will be created for each output.
- Each output will be stored in a separate file.
- Output files will be delivered in Word format.
- Numbering of TLFs will follow International Conference of Harmonization (ICH) E3 guidance.

14.2. Table, Listing and Figure Format

14.2.1. General

- All TLFs will be produced in landscape format, unless otherwise specified.
- All TLFs will be produced using the Times New Roman font, size 10. A smaller font size can be used if the width of the table or listing would not fit well across a single page.
- The data displays for all TLFs will have a 1.5-inch binding margin on top of a landscape oriented page and a minimum 1-inch margin on the other 3 sides.
- Headers and footers for figures will be in the Times New Roman font, size 10. For headers, a smaller font size can be used if necessary.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TLFs will be in black and white (no color), unless otherwise specified
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

14.3. Headers

- All output should have the following header at the top left of each page:

  Medicago R&D Inc.

  Protocol CP-PRO-QVLP-014

- All output should have Page n of N at the top right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).
- The date (date output was generated) should appear along with program name as the last footer on each page.

14.3.1. Display Titles

- Each TLF should be identified by the designation and a numeral (i.e., Table 14.1.1). ICH E3 numbering will be followed. A decimal system (x.y and x.y.z) should be used to identify TLFs with related contents. The title is centered. The analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

Table x.y.z
First Line of Title
Second Line of Title if Needed
Safety Population

14.3.2. Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). For numeric variables, include "unit" in column or row heading when appropriate.
- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.

14.3.3. Body of the Data Display

14.3.3.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

- alphanumeric values are left-justified;
- numbers containing fractional portions are decimal aligned.

14.3.3.2. Table Conventions

- Units will be included where available.
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that

parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
mild	3
moderate	8
severe	0

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.
- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and SDs should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	xx
Mean (SD)	xx.x (xx.xx)
Median	xx.x
Min, Max	xx, xx

- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant treatment group (or overall) for the analysis set presented. However, careful consideration is required in many instances due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Describe details of this in footnotes or programming notes.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject should be included in the summary statistics for all relevant categories or just 1 category and the criteria for selecting the criteria.
- Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

14.3.3.3. Listing Conventions

- Listings will be sorted for presentation in order of subject number, visit/collection day, and visit/collection time.

- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.
- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

14.3.3.4. Figure Conventions

- Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from Baseline) values will be displayed on the Y-axis.

14.3.3.5. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or 1, 2, 3, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Footnotes will be present on the page where they are first referenced and thereafter on each page of the table, unless the footnote is specific only to certain pages. Subject specific footnotes should be avoided.
- Footnotes will be used sparingly and must add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.
- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display, date the program was run, and the listing source (i.e., 'Program : myprogram.sas Listing source: 16.x.y.z').

15. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in CCI Standard Operating Procedure (SOP) Developing Statistical Programs CCI CCI SOPs Developing Statistical Programs CCI and Quality Deliveries (SDTM, ADaM, TLF) CCI describes the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

16. APPENDICES

Appendix A: Order of SOC (Medical History, Unsolicited Treatment-Emergent AE)

SOC *Infections and infestations*
SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*
SOC *Blood and lymphatic system disorders*
SOC *Immune system disorders*
SOC *Endocrine disorders*
SOC *Metabolism and nutrition disorders*
SOC Psychiatric disorders
SOC *Nervous system disorders*
SOC *Eye disorders*
SOC *Ear and labyrinth disorders*
SOC *Cardiac disorders*
SOC *Vascular disorders*
SOC *Respiratory, thoracic and mediastinal disorders*
SOC *Gastrointestinal disorders*
SOC *Hepatobiliary disorders*
SOC *Skin and subcutaneous tissue disorders*
SOC *Musculoskeletal and connective tissue disorders*
SOC *Renal and urinary disorders*
SOC *Pregnancy, puerperium and perinatal conditions*
SOC *Reproductive system and breast disorders*
SOC *Congenital, familial and genetic disorders*
SOC *General disorders and administration site conditions*
SOC *Investigations*
SOC *Injury, poisoning and procedural complications*
SOC *Surgical and medical procedures*
SOC *Social circumstances*
SOC *Product issues*

Table 3-2. The MedDRA Terminology SOC List – Internationally Agreed Order