Clinical Protocol

A Randomized, Observer-blind, Placebo-controlled, Multicenter, Phase 3 Study to Assess the Efficacy, Safety, and Immunogenicity of a Plant-Derived Quadrivalent VLP Influenza Vaccine in Adults 18-64 Years of Age

CP-PRO-QVLP-012; Phase 3

Plant-Derived Quadrivalent VLP Influenza Vaccine

Name of Sponsor: Medicago R&D Inc.
1020 route de l'Église, bureau 600
Québec (Qc), Canada G1V 3V9

Status: Final version 3.1

Date: 13 September 2017

SIGNATURES

Study Title: A Randomized, Observer-blind, Placebo-controlled, Multicenter, Phase 3 Study to Assess the Efficacy, Safety, and Immunogenicity of a Plant-Derived Quadrivalent VLP Influenza Vaccine in Adults 18-64 Years of Age

Study Author(s): PPD

I confirm that Medicago R&D Inc. has approved the version 3.1 (dated 13 September, 2017) of the protocol CP-PRO-QVLP-012 and agree that it may be issued to the relevant authorized study personnel, Independent Ethics Committees and Regulatory Authorities.

PPD

2017-09-13
Date

Medicago

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SEP 13, 2017
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COORDINATING INVESTIGATOR SIGNATURE

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I have read the version 3.1 (dated 13 September, 2017) Protocol No. CP-PRO-QVLP-012 titled, "A Randomized, Observer-blind, Placebo-controlled, Multicenter, Phase 3 Study to Assess the Efficacy, Safety, and Immunogenicity of a Plant-Derived Quadrivalent VLP Influenza Vaccine in Adults 18-64 Years of Age".

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative and I agree to accept the responsibility to act as Coordinating Investigator for this study.

Coordinating Investigator:

Signature Date (YYYY-MM-DD)

INVESTIGATOR AGREEMENT

I have read the version 3.1 (dated 13 September, 2017) Protocol No. CP-PRO-QVLP-012 titled, "A Randomized, Observer-blind, Placebo-controlled, Multicenter, Phase 3 Study to Assess the Efficacy, Safety, and Immunogenicity of a Plant-Derived Quadrivalent VLP Influenza Vaccine in Adults 18-64 Years of Age".

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without prior written authorization from Medicago. It is, however, permissible to discuss information contained in this protocol with a subject in order to obtain consent once Institutional Review Board (IRB) approval is obtained.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation (ICH) guidelines, Good Clinical Practice (GCP), Investigational New Drug (IND) regulations, and other applicable regulatory requirements.

I understand that the Sponsor may decide to suspend or prematurely terminate this study at any time for whatever reason and that such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Principal Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

Telephone Number: _____

_____ _____

Signature Date (YYYY-MM-DD)

Note: If the address or the telephone number of the Investigator changes during the course of the study, written notification will be provided by the Investigator to the Sponsor, and a protocol amendment will not be required.

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SYNOPSIS

Sponsor:	Medicago R&D Inc.
Investigational Product:	Plant-Derived Quadrivalent VLP Influenza Vaccine (Quadrivalent VLP Influenza Vaccine)
Active Substance(s):	Mix of recombinant H1, H3, and two B hemagglutinin proteins expressed as virus-like particles (VLPs) for the 2017-2018 influenza virus strains
Control Product:	Placebo: phosphate buffered saline (PBS)
Protocol Title:	A Randomized, Observer-blind, Placebo-controlled, Multicenter, Phase 3 Study to Assess the Efficacy, Safety, and Immunogenicity of a Plant-Derived Quadrivalent VLP Influenza Vaccine in Adults 18-64 Years of Age
Protocol Number:	CP-PRO-QVLP-012
Development Phase:	Phase 3
Study Center(s):	The study will be conducted at multiples sites in several countries.
Study Rationale:	This Phase 3 study is intended to assess the efficacy of the Quadrivalent VLP Influenza Vaccine during the 2017-2018 influenza season in healthy adults 18 to 64 years of age. One dose of Quadrivalent VLP Influenza Vaccine (30 µg/strain) or of placebo will be administered to approximately 10,000 subjects.
Planned Study Period:	The Day 0 (screening/vaccination) visit will occur between August and September 2017 for North America and Europe and approximately the beginning of November 2017 for Asia. A follow up call will be performed at the end of the surveillance period, approximately April 30th, 2018 (the duration of surveillance period may be adjusted, based on the observed epidemiology during the season in participating countries). Throughout the influenza season, the number of laboratory confirmed influenza cases will be monitored and reviewed on a regular basis by the independent biostatistical team from the CRO. In the event that an insufficient number of cases are reported, the study will be either continued or extended into another season to enrol more subjects. A protocol amendment will be issued to address changes to the enrolment plan in case

	of an insufficient number of cases.
Study Objectives **Primary Objective:**	• To evaluate the efficacy, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, against protocol-defined respiratory illness due to laboratory-confirmed influenza caused by vaccine-matched strains.
Secondary Objectives:	**Efficacy:** • To evaluate the efficacy, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, against protocol-defined respiratory illness due to any laboratory-confirmed influenza strain; • To evaluate the efficacy, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, against laboratory-confirmed protocol-defined influenza-like illness (ILI) caused by vaccine-matched strains. • To evaluate the efficacy, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, against laboratory-confirmed protocol-defined influenza-like illness (ILI) caused by any influenza viral types/subtypes (matched, mismatched, and un-typed). • To evaluate the efficacy, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, as measured by the incidence of subjects presenting with symptoms of protocol-defined ILI, regardless of laboratory results. **Safety:** • To assess the safety and tolerability, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain. **Immunogenicity:** • To assess, in a subset of 400 subjects, the immunogenicity of a single dose of Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, as measured by hemagglutination inhibition (HI) assay, microneutralization (MN) assay, and single radial hemolysis (SRH) assay against homologous and heterologous (HI only) influenza strains.
Exploratory Objectives:	**Efficacy:** • To evaluate per age stratum the efficacy, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, against laboratory-confirmed influenza illness caused by vaccine-matched strains;

	• To evaluate the efficacy, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain against mismatched influenza strains; • To determine the efficacy, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, as measured by the incidence of subjects presenting with symptoms of protocol-defined respiratory illness, regardless of laboratory results. **Immunogenicity:** • To assess the cell-mediated immune (CMI) response against homologous and heterologous strains on Days 0 and 21 in a subset of 400 subjects (same subset as the immunogenicity subset). **Safety:** • 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 given at a dose of 30 µg/strain relative to subjects administered the placebo.
Number of Planned Subjects:	Approximately 10,000 subjects are planned for randomization in a 1:1 ratio to receive the Quadrivalent VLP Influenza Vaccine at a dose of 30 µg/strain or the placebo. Within the two treatment groups, subjects will be stratified by site and two age groups (18 to 49 years of age and 50 to 64 years of age in a 1:1 ratio). Individuals will be randomly assigned to a treatment group by use of an interactive randomization system.
Sample Size Determination:	The sample size of approximately 10,000 subjects (5,000 subjects per treatment group) was selected based on the assumption that the Quadrivalent VLP Influenza Vaccine would have a vaccine efficacy (VE) of at least 70 % and that the influenza attack rate in unvaccinated subjects (ARU) would be 2 % or greater for laboratory-confirmed influenza caused by vaccine-matched strains. The sample size was chosen to have 90 % power to determine whether the lower bound of the two-sided 95 % confidence interval (CI) for the primary endpoint (VE) would be greater than 40 %, assuming a 10 % attrition rate. If the ARU is lower than 2 %, but greater than or equal to 1.5 %, this sample size will have an 80 % power to determine whether the lower bound of the two-sided 95 % CI for the primary endpoint (VE) would be greater than 40 %, assuming a 10 %

	attrition rate. In the event of an insufficient number of events, a protocol amendment will be issued.
Study Population:	Healthy male and female subjects 18 to 64 years of age and with no clinically significant disease at the time of vaccination will be included in this study.
Dosage and Administration:	On Day 0, subjects will receive one intramuscular (IM) injection into the deltoid region of the arm of 0.5 mL of 30 µg/strain of the Quadrivalent VLP Influenza Vaccine or placebo.
Study Design:	This is a randomized, observer-blind, placebo-controlled, multicenter, Phase 3 efficacy study. The influenza strain composition of the Quadrivalent VLP Influenza Vaccine will be based on the 2017-2018 recommended World Health Organization (WHO) strains for vaccination. 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. 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 at the investigator site will occur on Day 21 for immunogenicity assessments (CMI, HI, MN, and SRH) for a subset of 400 subjects from pre-defined sites in North America. From Day 14 until the end of the surveillance period, subjects will be instructed to report symptoms meeting the definition of a new or worsening respiratory illness and ILI (passive surveillance). In addition, active surveillance will be performed during this same period: symptoms of a new or worsening respiratory illness and ILI will be solicited a minimum of three times per week. At least one of these contacts each week will be through a scripted telephone call, with the remaining contacts via text messaging; a higher proportion of telephone contacts may be used if deemed appropriate by the clinic site (e.g. difficulty in obtaining responses via text messaging). A final phone contact will be made at the end of the follow up period for a safety assessment.
Efficacy Evaluations:	Following randomization and vaccination, subjects will be instructed to report respiratory symptoms from Day 14 until the end of the surveillance period (passive surveillance). During the period from Day 14 post-vaccination until the end of the surveillance period, the site will collect nasopharyngeal (NP) swabs (two per subject per event) for any subject who reports

	any respiratory illness. 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.
	The swabs will be collected within 36 hours (preferably within 24 hours) of the reporting of a respiratory illness.
	One swab will be submitted for analysis by multiplex reverse transcription polymerase chain reaction (RT-PCR). The second swab will be used for influenza virus culture, serosubtyping, detailed antigenic characterization, and vaccine match analysis of the isolates only in the event of a positive RT-PCR result.
	A positive RT-PCR result will be considered a laboratory-confirmed case of influenza. Any respiratory illness must be followed up for 30 days following the start date (through the planned active surveillance contacts), using a phone script. At the end of the 30-day follow-up, subjects will complete a disease burden questionnaire (Section 19.2); subjects will be provided with a memory aid (Section 19.3) that they can use during the 30 days to facilitate accurate reporting at the end of the follow-up period.
	Some degree of site investigator discretion will be permitted in defining new episodes (e.g. a non-productive cough and fatigue persisting for ten days from one episode, with a new onset of myalgia, headache, and sore throat would constitute the onset of a valid new episode).
	ILI will also be monitored during the study, but the presence of a respiratory illness symptom as described above will be the trigger for swab collection. A subject will be considered to have ILI if he/she meets the protocol-defined ILI (≥ 14 days post-vaccination) conditions:
	• At least one of the following respiratory symptoms:
	  • Sore throat;
	  • Cough;
	  • Sputum production;

	• Wheezing; • Difficulty breathing; **AND** • At least one of the following systemic symptoms: • Fever (defined as temperature > 99.0 °F or > 37.2 °C); • Chills; • Tiredness; • Headache; • Myalgia. The subjects will also be given a reminder aid listing the symptoms of respiratory illness and systemic symptoms and contact information for the study site. Active surveillance will also be performed, during which respiratory and systemic symptoms will be solicited. Subjects will be contacted a minimum of three times per week (at least one of these contacts each week will be through a scripted telephone call, with the remaining contacts via text messaging).
Safety Evaluations:	Safety and tolerability endpoints will include immediate complaints (15 minutes post-vaccination), solicited local and systemic reactions (up to seven days post-vaccination), treatment-emergent adverse events (TEAEs) up to Day 21, and serious adverse events (SAEs), adverse events (AEs) leading to withdrawal, and new onset of chronic diseases (NOCDs) up to the end of the surveillance period. Subjects will be observed at the study site for 15 minutes following vaccination, during which they will be given an oral digital thermometer and instructions on how to measure and record their solicited local and systemic reactions for the first seven days after vaccination and to record AEs during the first 21 days after vaccination. During the surveillance period, subjects will be instructed to collect and report any SAEs, NOCDs, concomitant medication use, or change in their health status. A questionnaire will be completed for subjects with respiratory illness regarding disease burden and health care resource utilization. Surveillance will be performed during visits to the clinic and/or home visits, as applicable. The site will make a final telephone call to each subject at the end of the surveillance period. Final information about respiratory illness outcome, occurrences of pneumonia, and new

	onset or exacerbations of cardio-respiratory conditions, health care utilization, medication use, SAEs, and NOCDs will be collected and the termination record will be completed.
Immunogenicity Evaluations:	Immunogenicity will be evaluated by the immune response induced in a subset of 400 subjects (300 from the VLP vaccine group and 100 from the placebo group) as measured by the serum HI, MN, and SRH antibody titers on Day 0 and Day 21. A blood sample for exploratory CMI analyses will be collected on Days 0 and 21 for a subset of 400 subjects (the same subset as for HI, MN, and SRH analysis). The North American sites selected for immunogenicity sample collection for this subset of 400 subjects will be pre-defined prior to study start and will target providing a representative age distribution. The subjects identified for the immunogenicity analyses will be also be stratified by age group (1:1 ratio).
Primary Endpoint:	**Efficacy:** • Occurrences of protocol-defined respiratory illness due to laboratory-confirmed influenza (≥ 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.
Secondary Endpoints:	**Efficacy:** • Occurrences of protocol-defined respiratory illness due to laboratory-confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes (matched, mismatched, and un-typed); • Occurrences of laboratory-confirmed influenza (according to protocol defined ILI) illnesses (≥ 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; • Occurrences of laboratory-confirmed influenza (according to protocol defined ILI) illnesses (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes (matched, mismatched, and un-typed); • Occurrences of protocol-defined ILI ≥ 14 days post-vaccination (confirmed or not). **Safety:** • Percentage, intensity, and relationship to vaccination of immediate complaints (15 minutes post-vaccination);

	• Percentage, intensity, and relationship to vaccination of solicited local and systemic signs and symptoms (for seven days following study vaccine administration); • Percentage, intensity, and relationship of TEAEs for 21 days following study vaccine administration; • Occurrences of deaths, SAEs, AEs leading to withdrawal, and NOCDs up to the end of the surveillance period. **Immunogenicity (subset of subjects):** • HI antibody response induced by the Quadrivalent VLP Influenza Vaccine against the homologous and heterologous influenza strains on Days 0 and 21 will be assessed in a subset of 400 subjects (300 who received the VLP vaccine and 100 who received the placebo). HI antibody titers will be analyzed using the following parameters: geometric mean titers (GMT), seroconversion (SC) rate, seroprotection (SP) rate, and geometric mean fold rise (GMFR); • MN antibody response induced by the Quadrivalent VLP Influenza Vaccine against the homologous influenza strains on Days 0 and 21, in a subset of subjects, will be analyzed using the following parameters: GMT, SC rate, and GMFR; • SRH antibody response induced by the Quadrivalent VLP Influenza Vaccine against the homologous strains on Days 0 and 21, will be analysed using the following parameters: geometric mean area (GMA), SC rate, SP rate, and GMFR.
Exploratory Endpoints:	**Efficacy:** • Occurrences, per age stratum, of laboratory-confirmed influenza illnesses (≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are matched (and/or antigenically similar) to the strains covered in the vaccine formulations, according to protocol-defined respiratory illness; • Occurrences of laboratory-confirmed influenza illnesses (≥ 14 days post-vaccination) caused by mismatched influenza viral strains, according to protocol-defined respiratory illness; • Occurrences of respiratory illnesses ≥ 14 days post-vaccination (confirmed or not). **Safety:** • 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.

	Immunogenicity (subset of subjects): • CMI response induced by the Quadrivalent VLP Influenza Vaccine against homologous and heterologous strains on Day 21 (subset of 400 subjects).
Statistical Methods:	**Populations:** Statistical analyses will be performed on pre-defined population sets (the safety analysis set, the full analysis set, and the per protocol set) according to the Statistical Analysis Plan (SAP). The analyses of all efficacy endpoints will be performed using the efficacy per protocol (PP) population and the full analysis set (FAS) population. The analysis in the PP will be considered the primary analysis for these objectives. All safety analyses will be performed using the safety analysis set (SAS). The immunogenicity analyses will be performed using a subset of the PP that includes only subjects with valid immunogenicity samples collected within the specified time window.
	Statistical Analyses: In general, categorical data will be summarized using the number and percent of subjects in each category and continuous data will be summarized using descriptive statistics (mean or geometric mean, median, SD, minimum, and maximum). Immunogenicity endpoints will also be compared between the vaccine group and the placebo group. **Efficacy Analyses:** For the primary endpoint, vaccine efficacy (VE) will be evaluated as the relative risk of vaccinated versus unvaccinated subjects to become infected with laboratory-confirmed influenza caused by one or more vaccine-matched strains in a timeframe of 14 or more days following vaccination (i.e. the proportion of subjects with one or more episodes of respiratory illness shown to be caused by viral types/subtypes that are matched and/or antigenically similar to the strains covered in the vaccine formulation), as per the following formula: $VE=(1-ARV/ARU)*100\ \%$ Where: ARV = attack rate in vaccinated subjects; and ARU = attack rate in unvaccinated subjects.

	The VE success criterion for the primary endpoint is defined as a > 40 % lower limit of the two-sided 95 % CI against vaccine-matched influenza strains. VE against all influenza strains and against mismatched strains will also be calculated. **Safety Analyses:** Safety endpoints will be tabulated, listed, and compared with the placebo group using descriptive statistics. **Immunogenicity Analyses:** For the immunogenicity analysis of the HI assays against the homologous strains, the point estimates and the corresponding two-sided 95 % CI will be calculated to determine if the Center for Biologics Evaluation and Research (CBER) criteria for licensure for influenza vaccine are met.

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				
Vaccine administration	X				
Immediate surveillance (15 minutes)	X				
Provide eDiary 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				
Urine (dipstick) pregnancy test	X				
Oral digital thermometer and instructions on reactions and respiratory illness symptoms[4]	X				
Collection of solicited local/ systemic reactions	X	X	X	X	
Concomitant medications	At any time during the study period				
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 three times per week. At least one of these contacts each week will be through a scripted telephone call, with the remaining contacts via text messaging; a higher proportion of telephone contacts may be used if deemed appropriate by the clinic site (e.g. difficulty in obtaining responses via text messaging).				
Collection of NP swabs for laboratory confirmation of influenza[5]	From Day 14 until the end of the influenza surveillance period[1], NP swabs will be collected from subjects who report a new or a worsening respiratory illness (as defined in the protocol). 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[6]	For each case of respiratory illness (as defined in the protocol), a questionnaire on disease burden (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 (Section 19.3) to facilitate accurate reporting.				
AEs, SAEs, and NOCDs[7]	At any time during the study period				
Termination record					X

[1] The end of the surveillance period is targeted as approximately 30 April 2018; 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

[3] Only a subset of 400 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 memory aid and electronic data capture system (eDiary) provided for their use for recording reactions, adverse events, 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] 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. If the respiratory illness starts prior to Day 14, swabs are not to be collected, even if symptoms persist beyond Day 14.

[6] A questionnaire for the collection of disease burden is available in 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.

[7] Adverse events 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	0-1.5 Days	0-1.5 Days[1]	Monitoring[2]	30 (+ 7) Days[3]
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]		X		
Collection of reportable concomitant medications	X	X	X	X
Collection of information on respiratory illness symptoms [4]	X	X	X	X
Collection of disease burden and health care information				X

[1] 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).

[2] 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.

[3] 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.

[4] 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.

ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
ANOVA	analysis of variance
ARU	attack rate in unvaccinated subjects
ARV	attack rate in vaccinated subjects
BMI	body mass index
BP	blood pressure
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CMI	cell-mediated immune (response)
eCRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice
GMA	geometric mean area
GMFR	geometric mean fold rise or seroconversion factor
GMT	geometric mean titer
HI	hemagglutination inhibition
HR	heart rate
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ILI	influenza-like illness
IM	intramuscular
IEC	independent ethics committee
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
MN	microneutralization
NACI	National Advisory Committee on Immunization
NOCD	new onset of chronic disease
OT	oral temperature
PBMC	peripheral blood mononuclear cell
PP	per protocol
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
SP	seroprotection
SRH	single radial hemolysis
TEAE	treatment-emergent adverse event
VE	vaccine efficacy
VLP	virus-like particle
WHO	World Health Organization
US	United States

1 INTRODUCTION

Seasonal influenza is a potentially serious infection associated with a wide range of clinical outcomes across the entire human lifespan. The influenza virus genome is an eight-segment single-stranded RNA with high potential for *in situ* recombination and mutations for host adaptation. Two segments code for the hemagglutinin (H) and neuraminidase (N) antigens that play an essential role in virus infectivity. At present, 17 hemagglutinin and ten neuraminidase subtypes are known in bird populations and some subtypes routinely circulate in humans, such as the H1N1, H3N2, and B influenza viruses. When a new subtype acquires the capacity for human-to-human transmission, this can give rise to a major pandemic like the one caused by an H1N1 strain in 1918 referred to as the Spanish flu. Antibodies that bind to the hemagglutinin molecule can prevent or modify infection and are the basis on which influenza vaccines are formulated every year.

Despite continuing advances in understanding of the immune response to natural infection and immunization, the disease remains a major cause of morbidity and mortality worldwide. In the United States (US) alone, influenza is responsible for approximately 36,000 deaths per year and the WHO estimates that influenza causes three to five million cases of severe illness and 250,000 to 500,000 deaths per year (Palache, 2011). Influenza is also responsible for a massive economic burden, with a total cost for each winter influenza season estimated at over 87 billion dollars (Molinari et al., 2007) in the US alone.

The main strategy for prevention and control of seasonal and pandemic influenza is still vaccination. In 2012, the Advisory Committee on Immunization Practices (ACIP) issued the first recommendation of national universal seasonal influenza vaccination (Osterholm et al., 2012).

Licensure of influenza vaccines is based either on efficacy studies or on surrogate correlates of protection. The latter are primarily based on their ability to induce HI titers. Despite the existence of these surrogate correlates of protection, recent reviews and meta-analyses suggest that the overall efficacy of licensed trivalent vaccines is highly variable and depends, among other factors, on the 'match' between circulating strains and the strains used for vaccine production. One such analysis produced efficacy estimates from 43 % to 89 % in well-matched seasons and from 38 % to 85 % in poorly-matched seasons (< 25 % of isolates matched the vaccine strains) (DiazGranados et al., 2012), suggesting that there is still great room for improvement.

For the 2012-2013 influenza season, vaccine efficacy numbers were particularly discouraging. When stratified by age group, the overall vaccine efficacy against influenza A and B viruses ranged from 27 % in persons 65 and older to 64 % in children (aged six months to 17 years old). When specific strains and age groups were examined (e.g. H3N2 in the elderly), efficacy estimates could be as low as 9 % (95 % CI: -84 % to 55 %). Preliminary efficacy estimates for the H3N2 strain in the on-going 2014-2015 influenza season are even lower: hovering at or even below 0 % due to a significant mismatch between vaccine and circulating strains (Skowronski et al., 2015).

1.1 Quadrivalent VLP Influenza Vaccine

Medicago R&D Inc. has developed a plant-derived system (*Nicotiana benthamiana*) for transient expression of two Type A and two Type B influenza strains to produce the Quadrivalent VLP Influenza Vaccine intended for active immunization for the prevention of influenza disease caused by the influenza A subtype viruses and type B virus strains covered in the vaccine. This vaccine may be able to address some limitations of the currently licensed vaccines:

- The hemagglutinin proteins in each monovalent VLP is based on the genetic sequence of circulating human influenza viruses selected by the WHO; in contrast, influenza strains grown in embryonic eggs or tissue culture tend to mutate for optimal growth in these substrates;
- Medicago's clinical trial program has revealed that plant-made VLP vaccines induce long-lasting and cross-reactive T cell responses that could be pivotal for protection against both matched and diverse influenza strains, particularly in the elderly who often derive significant benefit from vaccination despite little evidence of a humoral response (McElhaney, 2011).

Nicotiana benthamiana is a non-transgenic plant that is a distant wild relative from Australia of the tobacco plant, *Nicotiana tabacum*. The transfer vector used to move targeted DNA constructs into the plant cells is the bacterium *Agrobacterium tumefaciens*. This vector then directs the expression of the protein(s) of interest, in this case the hemagglutinin protein. The hemagglutinin proteins are assembled into trimers in the intracellular secretory pathway, aligned at the plant plasma membrane via a transmembrane domain, and finally bud out of the plant plasma membrane in the form of VLPs. Thus, the viral hemagglutinin proteins are anchored in a lipid bilayer of plant cell origin. The VLPs accumulate in the space between the plasma membrane and plant cell wall.

1.2 Pre-clinical Studies

Medicago has conducted several preclinical studies in rats with monovalent, trivalent, and quadrivalent formulations. All strains included in the quadrivalent vaccine are immunogenic at doses ranging from 0.001 to 10 µg in the rat model.

For more comprehensive preclinical information regarding the safety and toxicity of the Quadrivalent VLP Influenza Vaccine, refer to the current Investigator's Brochure (IB).

1.3 Clinical Studies

Under the clinical development program for the Quadrivalent VLP Influenza Vaccine, Medicago has conducted five clinical trials to date (CP-Q12VLP-004, CP-Q13VLP-007, CP-Q13VLP-008, CP-Q14VLP-009, and CP-Q14VLP-010). Study designs and statuses are summarized in Table 3.

Table 3 Summary of Design of Clinical Studies Performed to Date with the Quadrivalent Influenza VLP Vaccine

Study / Status	Phase	Design	Population	N	Treatment groups
CP-Q12VLP-004 / Completed	1-2	Single-center, observer-blind, randomized, dose-ranging, placebo-controlled study	Healthy adults 18 to 49 years of age, both genders	90 (active; ratio 1:1:1); 30 (placebo)	3 µg VLP; 9 µg VLP; 15 µg VLP; placebo
CP-Q13VLP-007 / Completed	2A	Multicenter, observer-blind, randomized, dose-ranging, placebo-controlled study	Healthy adults 18 to 49 years of age, both genders	225 (active; ratio 1:1:1); 75 (placebo)	15 µg VLP; 30 µg VLP; 60 µg VLP; placebo
CP-Q13VLP-008 / Completed	2	Multicenter, observer-blind, randomized, dose-ranging, placebo-controlled study	Healthy subjects of 50 years of age or older, both genders	375 (active; ratio 1:1:1:1:1); 75 (placebo)	15 µg VLP; 30 µg VLP; 60 µg VLP; 7.5 µg VLP + Alhydrogel®; 15 µg VLP + Alhydrogel®; placebo
CP-Q14VLP-009 / Clinic portion completed	2	Multicenter, observer-blind, randomized, dose ranging, active-comparator clinical study	Healthy adults aged 18 to 64 years, both genders	604 (active; ratio 1:1); 296 (active comparator)	15 µg VLP; 30 µg VLP; 15 µg/strain dose of FluLaval® Tetra
CP-Q14VLP-010 / Clinic portion completed	2	Multicenter, observer-blind, randomized, dose ranging, active-comparator clinical study	Healthy subjects of 65 years of age or older, both genders	499 (active; ratio 1:1); 250 (active comparator 1) 252 (active comparator 2)	30 µg VLP; 60 µg VLP; 15 µg/strain dose of FluLaval® Tetra; 60 µg/strain dose of Fluzone® High Dose

Overall, a total of 1,793 normal healthy subjects have received a single dose of the Quadrivalent Influenza VLP vaccine: 1,106 subjects aged from 18 to 64 years and 687 subjects 65 years of age and older.

An overview of the available safety and immunogenicity findings from these studies are summarized in Section 1.3.1 and Section 1.3.2, respectively. For detailed information on these findings, please refer to the current version of the IB.

1.3.1 Safety Overview

This section summarizes the safety data obtained to date from the five clinical trials performed to date (CP Q12VLP-004, CP-Q13VLP-007, CP-Q13VLP-008, CP Q14VLP-009, and CP Q14VLP-010); see Table 3 for a description of the basic design of these studies, status, and exposure.

No deaths were reported for either the adults (N = 1,106) or the elderly subjects (N = 687) administered the Quadrivalent VLP Influenza vaccine. A total of 21 SAEs were reported for subjects who received the Quadrivalent VLP Influenza vaccine: 18 for subjects who received a single dose of non-adjuvanted VLP vaccine (all dose levels combined, N = 1,642) and three for subjects who received a single dose of adjuvanted VLP vaccine (both dose levels combined, N = 151). None were considered by the Investigator to be vaccine-related. No subject withdrew

from any of the studies due to a TEAE and none of the NOCDs reported for subjects who received the VLP vaccine were considered to be vaccine-related.

The incidence of local and systemic reactions observed within seven days post-vaccination in the five studies was consistent with the known safety profile for commercial influenza vaccines. The most frequently reported unsolicited TEAEs included nasopharyngitis, upper respiratory tract infection, aspartate aminotransferase increased (minor increase), headache, and oropharyngeal pain; no notable differences in the incidence of these events were observed between the VLP groups and the active comparators or placebo groups. No safety issues and no notable trends were observed with respect to vital signs, clinical laboratory, or physical examinations in any of the five studies conducted.

As a precaution, subjects were monitored for TEAEs with a hypersensitivity component. Based on the data from the five studies conducted to date, there is no evidence of anaphylactic reactions associated with use of the Quadrivalent VLP Influenza Vaccine in humans: a small number of subjects had potential hypersensitivity reactions judged to be related to vaccine administration (no more than 0.3 % of subjects in any given VLP treatment group experienced one of these events) and the events were distributed fairly evenly among treatment groups, including the placebo and the active comparator groups. However, since severe reactions are considered to be an important potential risk (based on the theoretical risk that using plants for the production of biotherapeutics may induce hypersensitivity) the sponsor will continue to require that appropriate medical treatment and supervision are available to manage any possible anaphylactic reactions.

Safety results from the five clinical trials performed to date show that the Quadrivalent VLP Influenza Vaccine was well-tolerated, with a safety profile similar to that of the active comparators and to the placebo for systemic reactions and TEAEs.

1.3.2 Immunogenicity Overview

This section summarizes the immunogenicity data obtained from the studies conducted to date with an adult population (up to 64 years of age): four clinical trials (CP-Q12VLP-004, CP-Q13VLP-007, CP-Q13VLP-008, and CP-Q14VLP-009). Studies CP-Q12VLP-004, CP-Q13VLP-007, and CP-Q14VLP-009 were conducted in an adult-only population (18 to 49 years for the first two studies and 18 to 64 years for CP-Q14VLP-009) and CP-Q13VLP-008 was conducted in a combined adult and elderly population (50 years and older); see Table 3 for a description of the basic design of these studies and exposure.

1.3.2.1 Antibody Response

Overall, the immunogenicity data from the studies conducted to date show that the Quadrivalent Influenza VLP Vaccine induced a strong antibody response in healthy adults (18 to 64 years). The 30 µg/strain dose level appeared to be the lowest dose to consistently meet the CBER criteria and the lowest dose to be the most comparable with the commercial licensed vaccines. As a result, the 30 µg/strain dose level has been selected for evaluation during this Phase 3 efficacy study to be conducted in an adult population.

A summary of the Day 21 HI response data for the 30 µg/strain dose level is presented below:

- In the combined immunogenicity results of the CP-Q13VLP-007 (all subjects) and CP-Q13VLP-008 (50 to 64 years old strata), the 30 µg/strain dose level met the CHMP criteria for SC rate, SP rate, and GMFR for all four tested influenza strains and the CBER criteria for both SC rate and SP rate against all four homologous strains;
- In study CP-Q14VLP-009, conducted in adults aged from 18 to 64 years, the 30 µg/strain VLP vaccine met the CBER criteria for both SC rate and SP rate, as well as the CHMP criterion for GMFR against all four homologous strains tested.

For all of these studies, the HI response may have been underestimated due to the limited availability of assay reagents unaffected by the use of eggs for production (even when cell-based reagents are available, their history often includes an initial expansion in embryonic-eggs). These reagents often include mutations of glycosylation site loss in the receptor binding domain, which, in turn can affect the assay results, particularly for the B strains. In consequence, the ability of the VLP vaccine to elicit an HI response against the B strains may have been underestimated.

Further assessment of the humoral immune response induced by the VLP vaccine included MN and SRH assays. No correlates of protection are currently available for these two assays and, as a result, data interpretation is limited. However, for both assays, the VLP vaccine showed notable Day 0 to Day 21 increases in GMT against all four of the homologous strains and the overall pattern of responses confirms the 30 µg/strain dose selected for this Phase 3 study.

In addition to the results above, HI and MN data from the studies conducted to date show that the Quadrivalent VLP Influenza Vaccine also elicits some cross-protective antibodies against heterologous influenza strains (current IB version).

1.3.2.2 Plant Glycans

Plant glycoproteins contain structural motifs not found on human glycoproteins (e.g. core β1-2 xylose and α1-3fucose). Since some of these motifs occur on known plant allergens, one theoretical risk of using plants for production of biotherapeutics was the induction of hypersensitivity. Medicago monitored allergic symptoms and the humoral response to plant glycans in previous clinical trials; based on the results obtained from these studies, in which there were no observed trends suggestive of safety concerns (current IB version), there is no need to include assessment of plant glycans in this study. Medicago will continue to monitor allergic-like reactions in this study.

1.3.2.3 Cell-mediated Immune Response

In order to further define immune response induced by the VLP vaccine, the CMI response was measured in a small subset of subjects in the five studies. In spite of the small sample sizes, a clear and consistent vaccine-related Day 21 poly-functional CD4+ T cell response was observed with the VLP vaccine against all four homologous strains in all studies and in both the adult and elderly populations. Overall, the 30 µg/strain dose level showed the highest response of the VLP vaccines; in contrast, an active comparator (FluLaval® Tetra) showed only a minimal response

against the H1N1 and H3N2 strains, although significant Day 0 to Day 21 differences were detected for most parameters against the two B strains for this vaccine. Further, the CMI response induced by the VLP vaccines appeared to be both durable (up to Day 201) and cross-reactive.

1.4 Overall Rationale for the Study

This Phase 3 study is intended to assess the efficacy of the Quadrivalent VLP Influenza Vaccine during the 2017-2018 influenza season in healthy adults 18-64 years of age. One dose of Quadrivalent VLP Influenza Vaccine (30 µg/strain) or of placebo will be administered to approximately 10,000 subjects. This study will support the licensure of the vaccine in the US, Canada, and Europe in the general adult population for whom ACIP and National Advisory Committee on Immunization (NACI) recommend annual influenza vaccination.

2 OBJECTIVES

2.1 Primary Objectives

- To evaluate the efficacy, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, against protocol-defined respiratory illness due to laboratory-confirmed influenza caused by vaccine matched strains.

2.2 Secondary Objectives

Efficacy:

- To evaluate the efficacy, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, against protocol-defined respiratory illness due to any laboratory-confirmed influenza strains;
- To evaluate the efficacy, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, against laboratory-confirmed protocol-defined influenza-like illness (ILI) caused by vaccine-matched strains;
- To evaluate the efficacy, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, against laboratory-confirmed protocol-defined influenza-like illness (ILI) caused by any influenza viral types/subtypes (matched, mismatched, and un-typed).
- To evaluate the efficacy, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, as measured by the incidence of subjects presenting with symptoms of protocol-defined ILI, regardless of laboratory results.

Safety:

- To assess the safety and tolerability, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain.

Immunogenicity:

- To assess, in a subset of 400 subjects, the immunogenicity of a single dose of Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain or placebo, as measured by hemagglutination inhibition (HI) assay, microneutralization (MN) assay, and single radial hemolysis (SRH) assay against homologous and heterologous (HI only) influenza strains.

2.3 Exploratory Objectives

Efficacy:

- To evaluate per age stratum, the efficacy, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, against laboratory-confirmed influenza caused by vaccine-matched strains;
- To evaluate the efficacy, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain against mismatched influenza strains;
- To evaluate the efficacy, relative to placebo, of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, as measured by the incidence of subjects presenting with symptoms of protocol-defined respiratory illness, regardless of laboratory results.

Immunogenicity:

- To assess the cell-mediated immune (CMI) response against homologous and heterologous strains on Days 0 and 21 in a subset of 400 subjects (same subset as the immunogenicity subset).

Safety:

- 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 given at a dose of 30 µg/strain, relative to subjects administered the placebo.

3 STUDY ADMINISTRATIVE STRUCTURE

Table 4 Study Administrative Structure

Role	Name and Address
Sponsor	Medicago R&D Inc. 1020, route de l'Église, bureau 600, Sainte-Foy (Qc) Canada G1V 3V9
PPD	

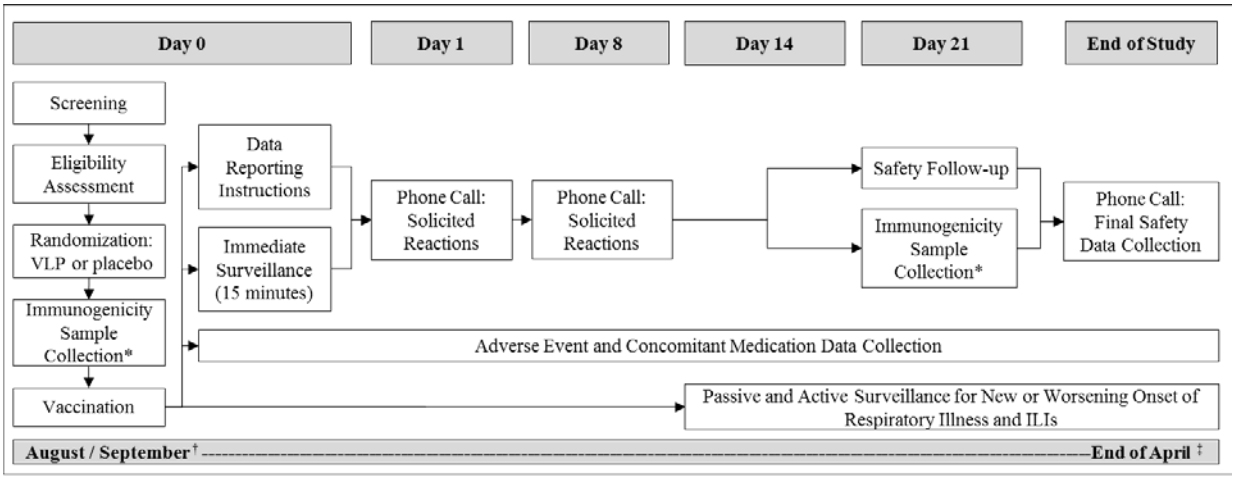
4 STUDY DESIGN AND RATIONALE

4.1 Overview of Study Design

This randomized, observer-blind, placebo-controlled multicenter, 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 for the 2017-2018 influenza virus strains (see Investigational Product Management Manual).

Approximately 10,000 healthy male and female subjects aged 18 to 64 years will be randomized in a 1:1 ratio into one of two parallel treatment groups, such that approximately 5,000 subjects will receive the Quadrivalent VLP Influenza Vaccine at a dose of 30 µg/strain and approximately 5,000 subjects will receive the placebo. Within the two treatment groups, subjects will be stratified by site and two age groups (18-49 years of age and 50-64 years of age in a 1:1 ratio).

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



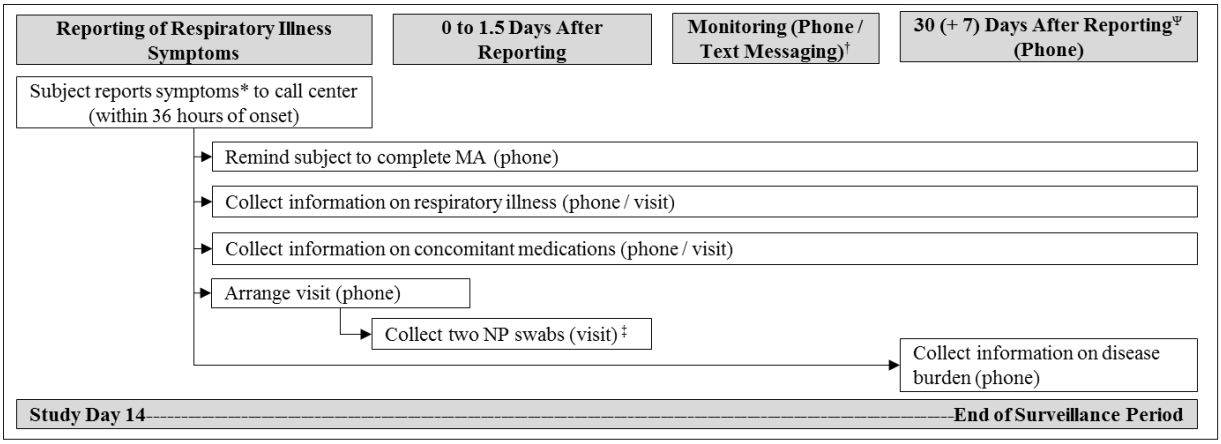
* Subset of 400 subjects for CMI and humoral assessments
† August / September for North America and Europe; approximately early November for Asia
‡ The duration of the surveillance period may be adjusted, based on the observed epidemiology during the season.

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, concomitant medication use, and respiratory illness symptoms in their memory aid and eDiary (electronic data capture system), 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 will occur on Day 21 for a subset of 400 subjects for serology sampling and immunogenicity assessments (CMI, HI, MN, and SRH). From Day 14 until the end of the surveillance period, subjects will be instructed to report symptoms meeting the definition of a new or worsening respiratory illness and ILI (passive surveillance). In addition, active surveillance will be performed during this same period: symptoms of a new or worsening respiratory illness and ILI will be collected a minimum of three

times per week (at least one of these contacts each week will be through a scripted telephone call, with the remaining contacts via text messaging). A final phone contact will be made at the end of the surveillance period (approximately 30 April 2018; however, the duration of surveillance period may be adjusted, based on the observed epidemiology during the season in participating countries) for a safety assessment.

Reports of respiratory illness within the specified window will be followed up for the collection of information regarding symptoms, concomitant medication use, and disease burden and the collection of two nasopharyngeal swabs. 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
† 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
Ψ Data past Day 30 of onset of respiratory illness is not to be collected
‡ Swabs must be collected within 36 hours (preferably 24 hours) after reporting of symptoms and prior to the use of influenza antiviral treatment medication

Figure 2 Flowchart of Process of Respiratory Illness Report

Throughout the influenza season, the number of laboratory-confirmed influenza cases will be monitored and reviewed on a regular basis by selected members of Medicago and the CRO. In the event of an insufficient number of reported cases, the extension of enrollment or the extension of the study will be addressed in a protocol amendment.

4.2 Rationale of Study Design

4.2.1 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 age strata, and to enhance the validity of statistical comparisons across treatment groups.

4.2.2 Observer-blinding

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

4.2.3 Age Group Stratification

Subjects under each treatment group will be stratified by site and two age groups (18 to 49 years and 50 to 64 years in a 1:1 ratio). The use of a 1:1 ratio in this study provides equal weight to both age groups to facilitate a better comparison between the two strata and to allow for possible extrapolation of results to an elderly population.

4.2.4 Dose Selection

The dose of 30 µg/strain was selected based on data from previous studies as the lowest dose to consistently meet the CBER criteria and the lowest dose to be the most comparable with the commercial licensed vaccines.

4.2.5 Study Duration

The duration of this study will be approximately eight to ten months post-vaccination for all subjects.

4.2.6 Efficacy Assessments

The efficacy endpoint defined for this study (RT-PCR-confirmed influenza caused by influenza viral types/subtypes that are matched or similar to the strains covered in the vaccine formulation) is standard to demonstrate influenza vaccine efficacy.

5 STUDY POPULATION

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) below 40 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 18 to 64 (has not yet had his/her 65^{th} birthday) years of age, inclusive, at the Screening/Vaccination visit (Visit 1);
5. Subjects must be in good general health prior to study participation, with 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.

6. Female subjects must have a negative urine pregnancy test result at the Screening/Vaccination visit (Visit 1);
7. Female subjects of childbearing potential must use an acceptable method of birth control, as defined in Appendix 4 (Section 19.4);
8. Non-childbearing females are defined as:
   - Surgically-sterile (defined as bilateral tubal ligation, hysterectomy or bilateral oophorectomy performed more than one month prior to vaccination); or
   - Post-menopausal (absence of menses for 24 consecutive months and age consistent with natural cessation of ovulation).

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. Any subject whose medical condition(s) is sufficiently severe that annual influenza vaccination would be routinely recommended in the jurisdiction of recruitment, as per the Investigator's judgement;
2. According to the Investigator's opinion, history of significant acute or chronic, uncontrolled medical or neuropsychiatric illness. 'Uncontrolled' 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.
3. Any medical or neuropsychiatric condition or any history of excessive alcohol use or drug abuse which, in the Investigator's opinion, would render the subject unable to provide informed consent or unable to provide valid safety observations and reporting;
4. Any autoimmune disease other than hypothyroidism on stable replacement therapy (including, but not limited to rhematoid arthritis, systemic lupus erythematosus, Crohn's disease, 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;

5. History of chronic pulmonary (including asthma, bronchopulmonary dysplasia, and cystic fibrosis) or cardiovascular (except isolated hypertension), renal, hepatic, neurologic, hematologic (including anemia and hemoglobinopathy), or metabolic disorders (including diabetes mellitus);
6. Because this is a placebo-controlled study, any subjects in close contact with individuals considered to be at high risk for developing influenza-related complications (individuals considered at high risk for complications include adults and children who have chronic pulmonary or cardiovascular [except isolated hypertension], renal, hepatic, neurologic, hematologic, or metabolic disorders [including diabetes mellitus]), ;
7. 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;
8. Administration of any adjuvanted or investigational influenza vaccine within one year prior to randomization or planned administration prior to the completion of the study;
9. 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 IM route) within six months prior to randomization and up to completion of the study;
10. 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;
11. Treatment with systemic glucocorticoids at a dose exceeding 10 mg of prednisone (or equivalent) per day for more than seven consecutive days or for 10 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;
12. 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 325 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;
13. History of allergy to any of the constituents of the Quadrivalent VLP Influenza Vaccine or tobacco;
14. History of anaphylactic allergic reactions to plants or plants components;
15. Use of antihistamines with systemic absorption for more than 14 days in the four weeks prior to vaccination or use of antihistamines 48 hours prior to study vaccination (the use of topical antihistamines and nasal or inhaled steroids is acceptable);

16. 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. Any subject discovered to have taken a prophylactic medication to prevent or pre-empt symptoms due to vaccination within the 24 hours prior to planned randomization must be delayed until at least the 24 hours period is met;
17. Planned use of influenza antiviral treatment medication before the collection of NP swabs (e.g. oseltamivir, zanamivir, rapivab);
18. Have a rash, dermatological condition, tattoos, muscle mass, or any other abnormalities at the injection site that may interfere with injection site reaction rating;
19. Subjects who have received a blood transfusion within 90 days prior to study vaccination;
20. Any female subject who has a positive or doubtful pregnancy test result prior to vaccination or who is lactating;
21. Subjects with abnormal vital signs (systolic blood pressure [BP] > 140 mmHg and/or diastolic BP ≥ 90 mmHg, 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);
22. Presence of any febrile illness (including an oral temperature [OT] ≥ 38.0 ˚C within 24 hours prior to vaccination. Such subjects may be re-evaluated for enrolment after resolution of illness;
23. 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;
24. 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, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study or any employee of Medicago;
25. Subjects with a history of Guillain-Barré Syndrome.

5.3 Prior and Concomitant Therapy

Any new or changed medications reported by the subject post-vaccination and through to the end of the study will be recorded in the electronic case report form (eCRF) as a concomitant medication. Since AEs may be secondary to new medications, the Investigator will explore the reasons for the change or for the new medication intake and document these AEs, if any.

Concomitant medications must be reported in the eCRF (reason for use, dates of administration, dosage, and route) if the use meets the following conditions:

- Within 30 days preceding vaccination: any treatments and/or medications specifically contraindicated (e.g. influenza vaccines, any immunoglobulins or other blood products, or any immune modifying drugs, etc.);

- From randomization to Day 21, inclusive: any medication (including, but not limited to, over-the-counter medicines such as aspirin or antacids), vitamins, and mineral supplements;
- From Day 22 to the end of the study, inclusive: any concomitant medication(s) administered to treat a NOCD (see Section 13.1.4 for definition of NOCD), SAE, or AE leading to withdrawal; any concomitant medication used to treat an AE that occurred before Day 21 and that is still being used afterwards (i.e. on-going use); and any concomitant medications used to treat a protocol-defined respiratory illness or ILI;
- Any concomitant medication used to treat conditions reported as medical history;
- Any investigational medication or vaccine; any vaccine not foreseen in the study protocol.

Please refer to the eCRF completion guidelines for details of data entry requirements.

Given that an important objective of this study is to evaluate the tolerability of the study vaccine, the use of prophylactic medications to prevent or pre-empt symptoms due to vaccination is specifically prohibited up to Day 7 (end of collection of solicited symptoms). A prophylactic medication is a medication administered in the absence of ANY symptom and in anticipation of a reaction to the vaccination (e.g. an antipyretic is considered to be prophylactic when it is given in the absence of fever or any other symptoms, to prevent fever from occurring, vitamins used to boost immune system, etc.).

The use of influenza antiviral treatment (e.g. oseltamivir, zanamivir, rapivab) is not permitted until the NP swab is collected.

5.4 Prohibited Therapy

Please refer to Section 5.2 (exclusion criteria numbers 4, 7, 8, 9, 10, 11, 12, 15, 16, 17, and 23) for details on medications or therapies prohibited prior to randomization, prior to NP swab collection, and/or during the conduct of this study.

6 TREATMENT ALLOCATION AND BLINDING

6.1 Randomization

Randomization will be stratified by site and age group (18 to 49 years of age and 50 to 64 years of age in a 1:1 ratio). 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.

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.

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.

6.2 Blinding

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.

Although there may be some visual differences in the VLP vaccine and placebo preparations, 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 reactogenicity of the subjects following vaccination.

This study is blinded through to the end of the surveillance period of the last subject. The RT-PCR samples corresponding to influenza cases that might lead to the unblinding of 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 biostatistical team from the contract research organization (CRO) and selected individuals from Medicago and the CRO. The selected individuals 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 a blinded 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.

7 DOSAGE AND ADMINISTRATION

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 placebo). The volume of injection will be 0.5 mL for both the vaccine and placebo.

8 SPECIMENS AND CLINICAL SUPPLIES

8.1 Management of Samples

A urine sample will be collected during the screening/vaccination visit for a dipstick pregnancy test to be performed during the same visit for females of childbearing potential.

Between vaccination and the end of the surveillance period, NP swabs will be collected from any subject who reports a new or a worsening respiratory illness (as defined in Section 10.2.1); these swabs will be collected each time a subject reports such an event (i.e. multiple collections may be required from a subject). Two swabs will be collected per subject per event.

On Days 0 and 21, a blood sample for CMI (peripheral blood mononuclear cell [PBMC] assay) and humoral immunity analysis will be collected for a pre-defined subset of 400 subjects.

Refer to the Study Procedure Manual for complete information on the handling, storage, and shipment of all laboratory samples.

8.2 Clinical Supplies

Each study center will be provided with supplies for NP swabs and selected centers will be provided with serologic supplies (e.g. aliquot tubes, aliquot labels, aliquot storage, shipping boxes, and accompanying manifests). Sites will be authorized to use their own materials if agreed to by Medicago (or its designee).

9 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. Study drug supplies for each subject will be inventoried and accounted for throughout the study (refer to Study Procedures Manual for details).

10 STUDY EVALUATIONS

10.1 Study Procedures

10.1.1 Overview

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 (as defined in Section 10.2.1).

Most subjects will have no blood sampled; the subset of subjects included in the immunogenicity analyses and who complete the study will have blood volumes drawn of 120 mL (Table 5).

Table 5 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 400 subjects.

10.1.2 Screening/Vaccination (Visit 1)

Emergency equipment must be available on site and appropriate treatment must be instituted as soon as possible in the event of anaphylaxis or any other immediate hypersensitivity reaction. The Investigator will be on-site on vaccine administration days and for the duration of the observation period for the last subject dosed on that day. The Investigator will be available on call for the remainder of the study. A physician should be immediately available at the clinical site to administer treatment or to apply procedures for any immediate AEs/SAEs.

10.1.2.1 Prior to Vaccination

The following procedures will be performed on Day 0 (Visit 1) prior to vaccination:

- Review and proceed with the signature of the ICF. The Investigator or his/her designee, will fully inform the subject of the nature and scope of the study, potential risks and benefits of participation, and the study procedures involved and will answer all questions prior to requesting the subject's signature on the ICF. The subject's consent must be obtained prior to performing any study-related procedures; this must be clearly recorded and a copy of the signed ICF retained in the source documents. A copy of the ICF must be provided to the subject;
- Collect and review demographics (gender, date of birth, age, race, and ethnicity) and body measurements (BMI, weight [kg or lbs], and height [cm or inches]) data. BMI is to be calculated as body weight (kg) divided by the square of height (m); the BMI result will be rounded to one decimal place using the standard convention. For the measurement of body weight, subjects will be lightly clothed, without shoes;
- Collect and review medical history, including the grade of any medical conditions. The medical history should record significant problems active at the time of screening and present within the preceding six months. Problems that have been clinically inactive for more than six months preceding screening, but which might alter the subject's current or future medical management, should also be noted (e.g. known mitral valve prolapse or a remote history of a seizure disorder);
- Review and record current and previous medication use (up to 30 days prior to study vaccine administration);
- Record influenza vaccinations received within 24 months prior to the administration of the study vaccine;

- Perform a vital signs measurement, including resting BP, HR, and OT. OT will be collected in degrees Celsius or Fahrenheit using a digital thermometer. The OT measurement should not be collected immediately following consumption of a hot or cold beverage or after smoking. The BP will be taken after the subject has been in a seated position as per the site's standard procedure. The BP should be taken by cuff (manual or automated are both acceptable). BP and HR may be repeated once if judged necessary. All measurements (including any repeats) will be recorded in the source documents. Inclusion of subjects with an out-of-range BP or HR measurement will be based on the Investigator's judgment;
- Perform a history- or symptom-directed physical examination. The physical exam will be performed by the Investigator;
- Collect a urine sample for female subjects of childbearing potential and perform a urine dipstick pregnancy test. No study vaccine must be administered to a childbearing potential female until a negative result is obtained and documented;
- Review the inclusion and exclusion criteria and determine the subject's eligibility to participate in this study. The eligibility must be confirmed by the Investigator;
- Register the subject in the interactive voice/web response system (IRT); the subject's treatment group will be automatically assigned by this system;
- Subjects for humoral and Day 0 CMI immunogenicity analyses only: collect baseline blood samples for CMI, HI, MN, and SRH assessments and prepare and store these samples until shipment to the analytical laboratory.

10.1.2.2 Vaccination

Once all pre-vaccination procedures have been completed and subject eligibility determined, the study vaccine will be administered (on Day 0) IM into the deltoid muscle of the non-dominant (if possible) arm. A 25 gauge needle of one inch or 2.5 cm in length should be used for vaccination for subjects with a BMI under 35; for subjects with a BMI of 35 and over, the use of a 25 gauge needle (when available) of 1.5 inches or 3.8 cm in length is required to reach the muscle. For subjects with BMI greater than or equal to 35, if the longer 25 gauge needle is not available, then a long 23 gauge needle (1.5 inches; 3.8 cm) can be used. In order to prevent possible confounding of vaccination site reactions, whenever possible, blood samples will not be collected from the same arm as the one used for vaccination. The arms used, both for blood collection and vaccination, will be documented in the source documents.

10.1.2.3 Fifteen Minutes Post-vaccination

The following safety observation procedures will be performed for all subjects immediately following study vaccine administration:

- Subjects will remain in the clinic for at least 15 minutes post-vaccination for observation. The observation period will include an assessment of immediate solicited local and systemic reactions. Any unusual signs or symptoms reported during the initial 15 minutes post-vaccination will result in continued close monitoring. Based on their condition,

subjects may be asked to remain in the clinic for their safety for more than 15 minutes after vaccination (the reason will be recorded in the source documents). All data (including the assessment of solicited local and systemic reactions) will be recorded in the source documents during and after the observation period. Refer to Section 10.3.1 for details regarding the assessment of AEs and/or solicited local and systemic reactions;

- During the observation period, subjects will be provided with a measurement device template for measuring (in mm) solicited local reactions of erythema (redness) and swelling and an oral digital thermometer for recording daily temperature (in degrees Celsius or Fahrenheit). Subjects will be shown how to enter their data in their eDiary. Each subject will be provided with the following instructions on the measurements they are to make:
  - How to collect his/her OT in degrees Celsius or Fahrenheit with the provided digital thermometer:
  - From the evening of Day 0 to the evening of Day 7, the subject will measure his/her OT at approximately the same time each evening and will record the results;
  - The OT should not be collected immediately following consumption of a hot or cold beverage or after smoking.
  - The subject is to also take his/her OT if he/she feels feverish and to record the highest temperature of the day. In the event that a temperature ≥ 38.0 °C or ≥ 100.4 °F is obtained, the subject will be allowed to take over-the-counter antipyretics (e.g. acetaminophen/paracetamol, aspirin, naproxen, or ibuprofen) and will be advised to increase the frequency of OT measurements to approximately every four hours, until he/she is no longer febrile (fever is defined as a temperature of ≥ 38.0 ºC or ≥ 100.4 °F). The subject is to document medication intake, which will be reviewed by the site personnel;
  - How to measure any solicited local reactions, including erythema (redness) and swelling diameter at the injection site using the measurement template supplied for this purpose; subjects will also be requested to evaluate pain at the injection site. Local reactions will be assessed every day starting in the evening of Day 0 and up to the evening of Day 7 and the results will be recorded. The severity of solicited local reactions will be graded according to the Food and Drug Administration (FDA) Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA, 2007), as presented in Table 6.
  - How to grade, on a daily basis from the evening of Day 0 through to the evening of Day 7, each of the solicited systemic reactions and their severity (as per the same guidance used for solicited local reactions; see Table 6) (FDA, 2007) and to record the worst grade of the day for each of these solicited systemic reaction. The instructions will include how to examine and grade swelling in the neck and axilla and to record any unusual feeling and/or swelling;
  - Subjects will be advised that they will be asked about the occurrence of any symptoms or events requiring medical attention and the use of any concomitant medication during the 21-day post-vaccination period and until the end of the surveillance period;

- Subjects will be instructed to contact the clinical site for any unsolicited AEs and/or solicited local and systemic reactions of greater than Grade 2 (moderate). Based on their condition, the Investigator may request that the subject return to the clinic for evaluation;
- Subjects will be advised on emergency contact information and instructions for contacting study personnel. Subjects will be advised to immediately contact the Investigator (or his/her designee) in the event of an SAE or a medical emergency. Subjects will be provided with a phone contact number and be instructed to call if any suspected reaction to the vaccination is felt to be significant or of concern;
- Subjects will be advised to notify their health care professional(s) (e.g. primary care physician) that they are participating in a clinical research study of an influenza vaccine;

- After the 15-minute observation period (allowed window of + 15 minutes) is completed, measure vital signs (BP, HR, and OT) as described in Section 10.3.1.4. Any out-of-range measurements will be assessed by the Investigator (or his/her designee) and any further action will be determined upon his/her medical decision;
- Instruct the subjects to perform measurements of local and systemic reactions at approximately the same time each day from Day 0 to Day 7 (preferably in the evening);
- Provide appointments (date and time) for the next planned visit to the clinical site (Day 21) and also for the Days 1 and 8 phone contacts and passive and active surveillance periods;
- The subject will be released from the clinical site once all Day 0 post-vaccination procedures have been completed and the subject is in stable condition.

10.1.3 Day 1 and Day 8 (Telephone Contact)

The following procedures will be performed during the phone contact (acceptable interval of + 1 day for Day 1 and ± 1 day for Day 8):

- Ask the subjects about any difficulties in recording their data, any change in health, any visits to health care facilities and/or medical practitioners, and any use of concomitant medications. Record the information in the source documents;
- For any unsolicited AEs and/or solicited local and systemic reactions of greater than Grade 2 (moderate), the Investigator should be informed within 48 hours of the time the clinical site is made aware of the event. The Investigator may request that the subject return to the clinic for evaluation;
- Advise subjects to immediately contact the Investigator (or his/her designee) in the event of any AE that requires medical attention. Subjects will be provided with a phone contact number and be instructed to call if any suspected reaction to the vaccination is felt to be significant or of concern;
- Remind the subjects how to measure and record any solicited local and systemic reactions. Subjects should also be reminded to record any changes in health, including changes in AEs and changes in medications;

- Remind subjects to immediately report any new or a worsening respiratory illness, as defined in Section 10.2.1. Ensure that subjects have the reminder aid listing the respiratory illness symptoms and contact information for the study site;
- Remind subjects to immediately report any symptoms that meet the definition of an ILI, as defined in Section 10.2.1. Ensure that subjects have the reminder aid listing the symptoms of ILI and contact information for the study site;
- Remind subjects of their next appointment (date and time) for the clinical visit and/or the next phone contact. Subjects will also be reminded to record their data in the electronic system in a timely manner.

In the event that a subject cannot be reached via phone, he/she may be contacted by text message or via email (if these contacts are available). However, the phone should be the initial and preferred means of communication.

10.1.4 Surveillance for Respiratory Illness

From Day 14 following randomization and vaccination, passive and active surveillance will be performed until the end of the end of the surveillance period:

- Passive surveillance: subjects will be instructed to contact the clinical site within 24 hours in case of any new or worsening respiratory illness as defined in Section 10.2.1;
- Active surveillance: subjects will be contacted a minimum of three times per week. At least one of these contacts each week will be through a scripted telephone call, with the remaining contacts via text messaging; a higher proportion of telephone contacts may be used if deemed appropriate by the clinic site (e.g. difficulty in obtaining responses via text messaging).

Note: An episode of respiratory illness is considered to extend from the first day of the first symptom to the last day of the last symptom. In most cases, 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. However, some degree of site investigator discretion will be permitted in defining new episodes (e.g. a non-productive cough and fatigue persisting for ten days from one episode, with a new onset of myalgia, headache, and sore throat would constitute the onset of a valid new episode).

If a subject reports a new or worsening respiratory illness:

- Collect information regarding the respiratory illness, including all applicable symptoms and the onset date:
  - The onset date is defined as the first date when one or more of the qualifying symptoms (see above) occurred and persisted for at least 12 hours;
  - Symptoms collected should also include 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);
- Collect information on any associated concomitant medication use;

- Schedule a time when the subject can return to the clinic site for the collection of NP swabs. The NP swabs are to be collected within 36 hours (preferably within 24 hours) after reporting of the respiratory symptoms;

- Respiratory illnesses that start on or after Day 14 will be followed up for 30 days after the illness start date, including occurrences of any of the following in association with any respiratory illness: 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 the diagnoses associated with those instances. This follow-up will be conducted via the planned active surveillance contacts (telephone and text messaging). Information from more than 30 days from respiratory illness onset does not need to be collected. As part of this follow up, the following information will be needed:
  - Collect any new information regarding the evolution of the respiratory illness, including symptoms and any associated concomitant medication use;
  - Collect data regarding the end date (if resolved). The end date is defined as the date on which the last symptom resolved;
  - Collect information regarding disease burden and health care information:
    - Document whether the illness required consultation at a clinic or with a general practitioner or family physician and if so, how many consultations;
    - Document whether the illness required consultation at an emergency department and if so, how many consultations;
    - Document whether the illness required hospitalization and if so, for how many days;
    - Document any other medical interventions associated with the illness;
    - Document whether the illness resulted in missed work days and if so, how many;
    - Document any disease sequelae (including long-term);
- Ask subjects if they have any ILI symptoms, as defined in Section 10.2.1;
- Ensure subjects have the reminder aid listing the symptoms of ILI and contact information for the study site.

In case a subject cannot be reached via phone, he/she may be contacted by text message or via email (if these contacts are available). However, other than for planned text message contacts, the phone should be the initial and preferred means of communication.

10.1.5 Day 21

For all subjects a safety follow-up will be performed on or shortly after Day 21 (- 2/+ 3 days):

- Review the subject's safety data and ensure all updates on concomitant medication usage and any changes in the subject's health (AEs, SAEs, or NOCDs) are recorded appropriately;

- Advise the subjects to immediately contact the Investigator or his/her designee, in the event of any AE that requires a visit to an emergency room and/or hospitalization;
- Remind the subjects of their next phone contact.

Note: This safety follow-up will be performed during one of the surveillance telephone contacts either on or shortly after Day 21. For the subset of subjects participating in the CMI and humoral immunity assessment, this follow-up can be done during the Day 21 visit.

The following procedures will be performed during the Day 21 (- 2/+ 3 days) visit for the subset of 400 subjects included in the immunogenicity analyses:

- Collect blood samples for CMI, HI, MN, and SRH assessments and prepare and store these samples until shipment to the analytical laboratory;
- Perform Day 21 safety follow-up (as described above) if it is to be done during this visit.

Note: This visit might replace one of the phone contacts planned for that week.

10.1.6 End of Surveillance (Telephone Contact)

The following procedures will be performed during the end of surveillance telephone contact (approximately 30 April 2018 (the duration of surveillance period may be adjusted, based on the observed epidemiology during the season in participating countries); acceptable interval of ± 3 days):

- Record updates on any change in the subject's health and report any SAEs or NOCDs;
- Record updates on any changes in concomitant medications used to treat conditions reported in the subject's medical history, AEs that started before Day 21 and were still ongoing after Day 21, SAEs, AEs leading to withdrawal from the study, or NOCDs as well as prohibited medication use (if any);
- Confirm that the subject has continued to comply with protocol requirements (e.g. no use of prohibited concomitant medications, use of an adequate contraceptive method, reporting of any respiratory illness or ILI symptoms).

Any subject who withdraws consent from the study will be asked to participate in the final telephone contact within two weeks of withdrawal, if the subject agrees.

10.2 Efficacy

10.2.1 Efficacy Evaluations

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 reminder 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: respiratory illness symptoms will be solicited a minimum of three times per week. At least one of these contacts each week will be through a scripted telephone call, with the remaining contacts via text messaging; a higher

proportion of telephone contacts may be used if deemed appropriate by the clinical site (e.g. difficulty in obtaining responses via text messaging).

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. As outlined in Section 10.1.4, 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 nasopharyngeal (NP) swabs from the subject (two per subject per event). 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. One 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), the second swab will be used 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. 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 (Section 19.2); subjects will be provided with a memory aid (Section 19.3) 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.

10.2.2 Efficacy Endpoints

10.2.2.1 Primary Endpoint

- Occurrences of protocol-defined respiratory illness due to laboratory-confirmed influenza (≥ 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.

10.2.2.2 Secondary Endpoints

- Occurrences of protocol-defined respiratory illness due to laboratory-confirmed influenza (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes (matched, mismatched, and un-typed);
- Occurrences of laboratory-confirmed influenza (according to protocol defined ILI) illnesses (≥ 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;
- Occurrences of laboratory-confirmed influenza (according to protocol defined ILI) illnesses (≥ 14 days post-vaccination) caused by any influenza viral types/subtypes (matched, mismatched, and un-typed);
- Occurrences of protocol-defined ILI ≥ 14 days post-vaccination (confirmed or not).

10.2.2.3 Exploratory Endpoints

- Occurrences, per age stratum, of laboratory-confirmed influenza (≥ 14 days post-vaccination) caused by influenza viral types/subtypes that are matched (and/or antigenically similar) to the strains covered in the vaccine formulations, according to protocol-defined respiratory illness;
- Occurrences of laboratory-confirmed influenza illnesses (≥ 14 days post-vaccination) caused by mismatched influenza viral strains, according to protocol-defined respiratory illness;

- Occurrences of respiratory illness ≥ 14 days post-vaccination (confirmed or not).

10.3 Safety

10.3.1 Evaluations

Safety and tolerability will be evaluated by solicited local and systemic reactions (immediate complaints within 15 minutes post-vaccination and reactions up to seven days post-vaccination), unsolicited AEs up to 21 days post-vaccination, and SAEs and NOCDS up to the end of the surveillance period.

10.3.1.1 Solicited Local and Systemic Reactions

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 eDiary.

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 6). 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 for a definition of these causal relationships.

Table 6 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

10.3.1.2 Adverse Events

All 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 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 for a definition of these causal relationships.

10.3.1.3 Clinical Laboratory Tests

As part of screening procedures, a urine sample will be collected for female subjects of childbearing potential for a urine dipstick pregnancy test that will be performed prior to the eligibility assessment on Day 0.

10.3.1.4 Vital Signs

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

OT will be collected in degrees Celsius or Fahrenheit using a digital thermometer. The OT measurement should not be collected immediately following consumption of a hot or cold beverage or after smoking.

BP will be taken after the subject has been in a seated position as per the site's standard procedure. BP should be taken by cuff (manual or automated are both acceptable). BP and HR may be repeated once if judged necessary. All measurements (including any repeats) will be recorded in the source documents.

10.3.1.5 Physical Examinations

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

10.3.2 Pregnancy

Female subjects who become pregnant during the study will be followed for safety. The Investigator, or his/her designee, will collect pregnancy information on any subject who becomes pregnant while participating in this study. The Investigator or his/her designee will record pregnancy information on the Pregnancy Report Form (for the template of the form, refer to Study Procedures Manual) and submit it to the Sponsor Safety Contact (see Section 13.1.6) within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to the Sponsor Safety Contact, if available. Generally, follow-up will be no longer than six to eight weeks following the estimated delivery date.

While pregnancy itself and elective termination of a pregnancy for non-medical reasons are not considered to be an AE/SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded in the Pregnancy Report Form or as an SAE and will be followed. A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and considered reasonably related in time to receipt of the investigational product by the Investigator, will be reported to the Sponsor Safety Contact. While the Investigator is not obligated to actively seek this information from former study subjects, he/she may learn of a pregnancy through spontaneous reporting. Information on pregnancies identified during the screening phase/prior to vaccine administration do not need to be collected; this information need not be communicated to Medicago (or its designee).

10.3.3 Safety Endpoints

10.3.3.1 Secondary Endpoints

- Percentage, intensity, and relationship to vaccination of immediate complaints (15 minutes post-vaccination);

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

10.3.3.2 Exploratory Endpoint

- 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.

10.4 Immunogenicity

10.4.1 Immunogenicity Evaluations

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 400 subjects (300 from the VLP vaccine group and 100 from the placebo group) from selected sites. The North American sites selected for this subset of 400 subjects will be pre-defined prior to study start and will target providing a representative age distribution.

10.4.2 Immunogenicity Endpoints

10.4.2.1 Secondary Endpoints

- HI antibody response induced by the Quadrivalent VLP Influenza Vaccine against the homologous and heterologous influenza strains on Days 0 and 21 in a subset of 400 subjects. HI antibody titers will be analyzed as follows:
  - GMTs of HI antibody on Days 0 and 21;
  - 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;
  - 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);
  - GMFR: the geometric mean of the ratio of GMTs (Day 21/Day 0).

  The immunogenicity endpoints for all four homologous influenza antigens will be evaluated according to the CBER criteria.
- MN antibody response induced by the Quadrivalent VLP Influenza Vaccine against the homologous influenza strains on Days 0 and 21, in the subset of 400 subjects, will be analysed as follows:

- GMTs of MN antibody on Days 0 and 21;
- SC rate on Day 21 (as defined above for HI);
- GMFR (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 400 subjects, will be analysed 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 diameter ≥ 25 mm^2 following vaccination (Day 21);
  - GMFR: the geometric mean of the ratio of GMAs (Day 21/Day 0).

10.4.2.2 Exploratory Endpoint

- CMI response induced by the Quadrivalent VLP Influenza Vaccine against homologous and heterologous strains on Day 21 (in the subset of 400 subjects).

11 SUBJECT COMPLETION/WITHDRAWAL

11.1 Temporary Contraindications

Some exclusion criteria that render subjects ineligible for the study may be temporary in nature:

- Temperature ≥ 38.0 ºC or ≥ 100.4 ºF within 24 hours prior to randomization;
- Acute cold symptoms such as upper respiratory tract infection symptoms, with or without fever, that resolve at least 48 hours prior to randomization.

Following the resolution of such conditions, a subject may be considered eligible by the Investigator and be enrolled in the study.

11.2 Screening Failures

Screening failures are subjects who have signed the study-specific ICF but are not eligible for enrolment (subjects who were not randomized), due to failure on one or more of the inclusion or exclusion criteria or because the subject withdrew consent prior to randomization. Eligible/not treated subjects are subjects that have signed the ICF and are eligible for enrolment, but were either not randomized or randomized and not treated.

Recording of screening failures and eligible/not treated subjects will be carried out in the study records maintained at the participating clinical sites. Neither of these subject classes will receive a safety follow-up.

A screening failure subject can be rescreened once, with prior authorization from Medicago or its designee. If the subject is rescreened, a new subject number will be allocated.

11.3 Removal of Subjects from Treatment or Assessment

Subjects will be advised that they are free to withdraw from the study at any time without prejudice to their future medical care by the physician or the institution. Subjects who withdraw or are withdrawn from the study after vaccination will not be replaced.

Every reasonable effort will be made to ensure that each subject complies with the protocol and completes all study visits. However, a subject may withdraw or be withdrawn from participation if:

- The subject withdraws consent;
- The subject displays non-compliance to the terms of their participation in the clinical study (based on Investigator's or Medicago's [or its designee's] opinion);
- Safety reasons as judged by the Investigator and/or Medicago (or its designee);
- Medicago or the regulatory authority(ies) terminates the clinical study.

Withdrawal subjects will be those who leave the study before the end of the surveillance period, for whatever reason; withdrawal subjects will not be replaced. Any subject who withdraws consent from the study will be asked to participate in the final telephone contact within two weeks of withdrawal, if the subject agrees. The procedures performed for the final assessment will comprise those for the end of surveillance telephone contact, if permitted by the subject. All withdrawal subjects must be reported to Medicago (and/or its designee). The reason for withdrawal should be documented in the subjects' records and in the appropriate section of the eCRF. The eCRF must be completed up to and including the time of the drop-out/final assessment.

11.3.1 Follow-up of Discontinuations

All subjects who receive a study vaccine will be followed for safety until the end of the surveillance period, if permitted by the subject.

11.3.2 Lost to Follow-up Procedures

Every attempt will be made to contact study subjects who are lost to follow-up. At least three contacts will be attempted and recorded in the source documents. As a last resort, one registered letter requesting contact with the site will be sent to any subject with whom the clinic staff no longer has contact. All attempts at contact will be documented in the subject's source documents.

11.4 Interruption of the Study

The Investigator (in consultation with Medicago [or its designee]), Medicago, or Regulatory Authorities may interrupt or terminate this study for any reason. The Investigator will immediately, on discontinuance of the clinical study at the clinical site, inform both the study subjects and the Institutional Review Board (IRB) responsible for the study of the discontinuance, provide them with reasons for the discontinuance and advise them in writing of any potential health risks to the subjects themselves or to other persons. It is Medicago's (or its

designee's) responsibility to report discontinuance of the study to the local regulatory agencies within the appropriate timeframe, providing them with the reasons for the discontinuance and advising them in writing of any potential health risks to the study subjects or to other persons. Medicago (or its designee) must then inform the Investigator that the appropriate notifications were done.

12 STATISTICAL METHODS

A general description of the statistical methods used to analyze the efficacy, safety, and immunogenicity data is outlined below. Complete details will be provided in the SAP, which will be finalized prior to database lock.

12.1 Analysis Populations

12.1.1 Safety Analysis Set

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

12.1.2 Full Analysis Set

The 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.

12.1.3 Per Protocol Set

The 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 vaccine or placebo. 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.

The immunogenicity PP 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 placebo. 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.

12.2 Sample Size Determination

The sample size of approximately 10,000 subjects (5,000 subjects per treatment group) was selected based on the assumption that the Quadrivalent VLP Influenza Vaccine would have a VE of at least 70 % and that the ARU would be 2 % or greater for laboratory-confirmed influenza caused by vaccine-matched strains. The sample size was chosen to have 90 % power to determine whether the lower bound of the two-sided 95 % CI for the primary endpoint would be greater than 40 %, assuming a 10 % attrition rate.

If the ARU is lower than 2 %, but greater than or equal to 1.5 %, this sample size will have an 80 % power to determine whether the lower bound of the two-sided 95 % CI for the primary endpoint (VE) would be greater than 40 %, assuming a 10 % attrition rate.

A protocol amendment will be issued to address changes to the enrolment plan in the event of insufficient ARU.

12.3 Efficacy Analyses

Efficacy endpoints are described in Section 10.2.2.

All descriptive and inferential statistical analyses will be performed using Statistical Analysis System® (SAS®) software (version 9.3 or higher). Details of the statistical analyses are provide in the SAP.

Analyses of primary and secondary endpoints will include each group as a whole as well as comparisons by age strata (18 to 49 years and 50 to 64 years).

12.3.1 Analysis of Primary Endpoint

The primary efficacy endpoint is defined in Section 10.2.2.1.

For the primary endpoint, VE will be evaluated as the relative risk of vaccinated (30 µg/strain VLP vaccine) and unvaccinated (placebo) subjects to become infected with protocol-defined respiratory illness caused by one or more vaccine-matched strains in a timeframe of 14 or more days following vaccination (i.e. the proportion of subjects with one or more episodes of respiratory illness shown to be caused by viral types/subtypes that are matched and/or antigenically similar to the strains covered in the vaccine formulation).

VE will be calculated using the following formula:

$$VE=(1-ARV/ARU)*100\ \%$$

Where:

ARV = attack rate in vaccinated subjects; and

ARU = attack rate in unvaccinated subjects.

The VE success criterion is defined as a > 40 % lower limit of the two-sided 95 % CI.

12.3.2 Analysis of Secondary Endpoints

The secondary efficacy endpoints are defined in Section 10.2.2.2.

VE will be calculated for the following endpoints, using the same formula indicated for the primary efficacy analysis:

- The relative risk of vaccinated (30 µg/strain VLP vaccine) and unvaccinated (placebo) subjects to become infected with protocol-defined respiratory illness caused by any influenza strain in a timeframe of 14 days or more following vaccination (i.e. the proportion of subjects with one or more episodes of respiratory illness shown to be caused by any influenza strain [matched, mismatched, and un-typed with the strains covered in the vaccine formulation]);
- The relative risk of vaccinated (30 µg/strain VLP vaccine) and unvaccinated (placebo) subjects to become infected with laboratory-confirmed ILI caused by one or more vaccine-matched strains in a timeframe of 14 or more days following vaccination (i.e. the proportion of subjects with one or more episodes of ILI shown to be caused by viral types/subtypes that are matched and/or antigenically similar to the strains covered in the vaccine formulation);
- The relative risk of vaccinated (30 µg/strain VLP vaccine) and unvaccinated (placebo) subjects to present with ILI in a timeframe of 14 days or more following vaccination, regardless of the laboratory results (i.e. the proportion of subjects with at least one episode of protocol-defined ILI).

12.3.3 Analysis of Exploratory Endpoints

The exploratory efficacy endpoints are defined in Section 10.2.2.3.

VE will be calculated for the following endpoints, using the same formula indicated for the primary efficacy analysis:

- The relative risk, per age stratum, of vaccinated (30 µg/strain VLP vaccine) versus unvaccinated (placebo) subjects with laboratory-confirmed influenza caused by one or more vaccine-matched strains in a timeframe of 14 days or more following vaccination (i.e. the proportion of subjects in each age stratum with one or more episodes of respiratory illness shown to be caused by viral types/subtypes that are matched and/or antigenically similar to the strains covered in the vaccine formulation);
- The relative risk of vaccinated (30 µg/strain VLP vaccine) and unvaccinated (placebo) subjects to become infected with laboratory-confirmed influenza caused by a mismatched influenza strain in a timeframe of 14 days or more following vaccination (i.e. the proportion of subjects with one or more episodes of respiratory illness shown to be caused by viral types/subtypes that are not antigenically similar to the strains covered in the vaccine formulation);

- The relative risk of vaccinated (30 µg/strain VLP vaccine) and unvaccinated (placebo) subjects to present with respiratory illness symptoms in a timeframe of 14 days or more following vaccination regardless of the laboratory results (i.e. the proportion of subjects with at least one episode of protocol-defined respiratory illness).

12.4 Baseline and Subject Disposition

Demographic data and influenza immunization history will be presented in listings and summarized by treatment. Continuous variables including age, weight, height, and BMI will be summarized with mean, median, standard deviation, minimum, and maximum. Count and percentage of subjects will be presented for categorical variables such as sex, race, ethnicity, and immunization history.

The number of subjects in different study disposition statuses will be summarized by number and, when applicable, percentage (based on vaccinated subjects). Subjects' completion/discontinuation status will be listed (including subject identifier, date of completion/early discontinuation and, for those who discontinued early, the specific reason(s) for discontinuation).

12.5 Safety Analyses

The safety endpoints are defined in Section 10.3.3.

12.5.1 Analysis of Secondary Endpoints

The secondary safety endpoints are defined in Section 10.3.3.1.

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 using descriptive statistics.

The original terms used in the eCRFs by Investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). 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 (see Section 13.1.3).

Analyses of secondary safety endpoints will include each group as a whole as well as comparisons by age strata (18 to 49 years and 50 to 64 years).

12.5.2 Analysis of Exploratory Endpoint

The exploratory safety endpoint is defined in Section 10.3.3.2.

The occurrences of medical visits, hospitalizations, and workdays missed will be summarized by treatment using descriptive statistics.

12.6 Immunogenicity Analyses

12.6.1 Analysis of Secondary Endpoints

The secondary immunogenicity endpoints are defined in Section 10.4.2.1.

For the immunogenicity analysis of the HI assays against the homologous strains, the point estimates and the corresponding two-sided 95 % CI will be calculated to determine if the CBER criteria for licensure for influenza vaccine are met. The following analyses for the HI assay (homologous strains) will be performed on the immunogenicity PP:

- GMT (Day 21): 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;
- SC rate (Day 0 and Day 21): The point estimates and the corresponding two-sided 95 % CI for subjects achieving SC by treatment group and strain will be calculated to determine whether the lower bound of the CI will meet or exceed 40 %;
- SP rate (Day 21): The point estimates and the corresponding two-sided 95 % CI for subjects achieving SP by treatment group and strain will be calculated to determine whether the lower bound of the CI will meet or exceed 70 %.

The analyses for the MN and SRH assays (homologous strains) will be performed on the immunogenicity PP. The GMTs, GMFRs, and SC rates of 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 or chi square tests will be used. GMT and GMFR for MN and GMA and GMFR for SRH will be compared using appropriate analysis of variance (ANOVA) models.

Analyses of secondary immunogenicity endpoints will include each group as a whole as well as comparisons by age strata (18 to 49 years and 50 to 64 years).

12.6.2 Analysis of Exploratory Endpoint

The exploratory immunogenicity endpoint is defined in Section 10.4.2.2.

The CMI response will be compared between the treatment groups using appropriate non-parametric (Wilcoxon) models. Additional details will be provided in the SAP.

13 ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, Investigators, and the Sponsor, and are mandated by regulatory agencies worldwide.

13.1 Definitions

13.1.1 Serious Adverse Events

An SAE is any untoward medical occurrence (whether or not considered to be related to the study vaccine) that, at any dose:

- Results in death;
- Is life-threatening (at the time of the event);

  Note: the term "life-threatening" in the definition of an SAE refers to an event that put the subject at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe;

- Requires inpatient hospitalization (≥ 24 hours) or prolongation of existing hospitalization (elective hospitalizations/procedures for pre-existing conditions that have not worsened are excluded);
- Results in persistent or significant disability/incapacity;
- Is a congenital abnormality/birth defect;
- Is another medically important event.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but that may jeopardize the subject's health or may require an intervention to prevent one of the other outcomes listed in the definition above. These events should be considered serious. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or the development of drug dependency or drug abuse. See Section 13.1.6 for initial SAE reporting by the Investigator.

13.1.2 Adverse Events

An AE or adverse experience is defined as any untoward medical occurrence in a subject or clinical investigation subject who was administered a pharmaceutical product, with or without a causal relationship with the treatment. An AE can be any favorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to a medicinal product.

Information such as the date and time of onset and resolution (duration), intensity (defined below), seriousness, any required treatment or action taken, outcome, relationship to the investigational vaccine, and whether the AE caused withdrawal from the study will be collected.

The intensity of all AEs will be graded as mild (1), moderate (2) severe (3), or potentially life threatening (4), according to the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (FDA, 2007) and the following definitions:

Mild (Grade 1):	The AE is easily tolerated and does not interfere with usual activity;
Moderate (Grade 2):	The AE interferes with daily activity, but the subject is still able to function;
Severe (Grade 3):	The AE is incapacitating and the subject is unable to work or complete usual activity;
Potentially life-threatening (Grade 4):	The AE is likely to be life-threatening if not treated in a timely manner.

The Investigator will be instructed to closely monitor each subject who experiences an AE (whether ascribed to the investigational product or not) until the outcome of the AE has been determined.

If any of the solicited local or systemic reactions persist beyond Day 7, these will also be recorded as AEs. In this case, the AE start will be set as eight days post-vaccination. The subject will be requested to note when the AE resolves and to report this information to the Investigator or clinic staff at the next visit at the clinical site or contact.

The clinical importance of AEs will be determined based upon the Investigator's judgment. The Investigator must ensure that any sample obtained to follow-up on an AE is properly labeled and stored. The Investigator and others responsible for care of the subjects should institute any supplementary investigations of significant AEs based on the clinical assessment of the likely causative factor. This may include seeking the opinion of a specialist in the field of the AE.

All AEs occurring within 21 days after vaccination must 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 through to the end of the surveillance period, SAEs, AEs leading to withdrawal, and NOCDs (see Section 13.1.4 for definition) will be monitored and reported in the eCRF. Additional details on eCRF entries can be found in the eCRF completion guidelines.

The SAEs and NOCDs will be followed up until complete resolution or stabilization. Follow-up of unresolved SAEs, AEs leading to withdrawal, or NOCDs after the end of the surveillance period will continue under the discretion of the Investigator.

13.1.3 Adverse Events of Special Interest

Based on the data from the five studies conducted to date, there is no evidence of anaphylactic reactions associated with use of the Quadrivalent VLP Influenza Vaccine in humans: a small number of subjects had potential hypersensitivity reactions judged to be related to vaccine administration (no more than 0.3 % of subjects in any given VLP treatment group experienced one of these events) and the events were distributed fairly evenly among treatment groups,

including the placebo and the active comparator groups. However, since severe reactions are considered to be an important potential risk (based on the theoretical risk that using plants for the production of biotherapeutics may induce hypersensitivity) the sponsor will continue to require that appropriate medical treatment and supervision are available to manage any possible anaphylactic reactions.

To collect additional data on these events, Medicago will closely monitor and assess allergic or allergic-like reactions as AEs of special interest. Thus, to collect specific data under this protocol, the Investigator should, whenever possible, take a picture of any occurrence of allergic or allergic-like reactions and send the anonymized images to Medicago as described in the Study Procedure Manual.

13.1.4 New Onset of Chronic Disease

In the context of this study, all NOCDs that may plausibly have an allergic, autoimmune or inflammatory component are to be reported. Plausibility should be interpreted broadly however; the only clear exceptions are degenerative conditions such as osteoarthritis, age-related physiologic changes (e.g. benign prostatic hypertrophy) and life-style diseases (e.g. alcohol-associated cirrhosis, bronchitis in a smoker, etc.). In this context, most cancers, cardiac conditions and kidney diseases should be reported.

NOCDs will be collected from vaccination on Day 0 to the end of the surveillance period and reported as an AE or SAE, as applicable.

13.1.5 Expectedness of an Adverse Drug Reaction

An “unexpected” adverse reaction is one in which the nature or severity of the event is not consistent with information in the current version of the IB. Expedited reporting to the regulatory authorities is required if an SAE occurs that is both unexpected and considered possibly, probably, or definitely related to the study vaccine.

13.1.6 Initial SAE Reporting by the Investigator

SAEs related to pre-treatment study procedures will be reported from the time the ICF is signed. All post-vaccination SAEs (treatment-emergent SAEs) will be reported from the time of receiving the study vaccine on Day 0 through to the end of the surveillance period (final scheduled phone contact). The Investigator (or designee) must report, by phone or email, all SAEs, whether considered related to the study vaccine or not, and whether considered unexpected or expected (as defined in Section 13.1.1), to Medicago (or its designee) within 24 hours of the Investigator learning of the event. The Investigator must also complete the AE screen of the eCRF page for SAE reporting. If the eCRF is not available, the Investigator must use a paper SAE report form, and send, via e-mail, a copy to the Medicago safety e-mail address and the appropriate regional (Americas or EU/APAC) e-mail address:

Medicago Safety e-mail address: Medicago-Safety@medicago.com
Americas SAE e-mail address: CCI [redacted]

EU/APAC SAE e-mail address: CCI

Sponsor Safety Contact: PPD

13.1.7 Follow-up Reporting by the Investigator

All SAEs, regardless of causality, will be followed as described in Section 13.1.2. When appropriate, documentation of any medical tests or examinations performed will be provided to document resolution/stabilization of the event.

13.1.8 Reporting of SAEs Occurring after Surveillance Period or Study Termination

All SAEs occurring during the safety follow up period will be followed until the end of the surveillance period.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE detection period (post surveillance period). Active follow-up for AEs or SAEs will continue until the end of the surveillance period for all subjects. However, after the end of the surveillance period, if the Investigator learns of any SAE, including death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the investigational product, the Investigator will promptly notify the Sponsor Safety Contacts for Reporting SAEs.

13.1.9 Causal Relationship

The Investigator must make the determination of relationship to the study vaccine for each AE. The Investigator should decide whether, in his/her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational vaccine. If there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational vaccine and the occurrence of the AE, then the AE should be considered “definitely related”, “probably related”, or “possibly related”. Otherwise, if no valid reason exists for suggesting a possible relationship, then the AE should be classified as “probably not related” or “definitely not related”. The following guidance should be followed:

Definitely Not Related:	The AE is clearly not related to the administration of the study vaccine. Another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study vaccine administration; and/or a causal relationship is considered biologically implausible.
Probably Not Related:	There is no medical evidence to suggest that the AE is related to the study vaccine. The event can be readily explained by the subject’s underlying medical condition or concomitant therapy or lacks a

	plausible temporal relationship to the study vaccine.
Possibly Related:	A direct cause and effect relationship between the study vaccine and the AE has not been demonstrated but there is a reasonable possibility that the event was caused by the study vaccine.
Probably Related:	There probably is a direct cause and effect relationship between the AE and the study vaccine. A plausible biologic mechanism and temporal relationship exist and there is no more likely explanation.
Definitely Related:	There is a direct cause and effect relationship between the AE and the study vaccine. Reactions at the injection site (redness, swelling, and pain) will automatically be entered as definitely related to the study vaccine.

AE outcomes will be classified as recovered/resolved, not recovered/not resolved, recovered/resolved with sequelae, recovering/resolving, or death.

13.1.10Reporting of SAEs to Health Authorities and IRB

Medicago or its designee will be responsible for reporting SAEs that are deemed both possibly related to the study vaccine and considered to be unexpected (‘unexpected’ refers to events that do not appear in the package labeling or in the study vaccine IB) to the regulatory authorities in an expedited manner.

The Investigator will be responsible for reporting the SAEs that meet IRB reporting requirements directly to the relevant ethical review board as soon as possible, and will also provide the ethical review board with any safety reports prepared by Medicago or its designee.

All SAEs that are suspected, unexpected serious adverse reactions (SUSARs) should be reported to regulatory authorities by phone or by facsimile transmission as soon as possible but, in no event, later than seven calendar days for deaths and 15 calendar days for other SAEs after Medicago's (or its designee’s) initial receipt of the information. These events should be followed to resolution, stabilization, or return to baseline, regardless of conclusion of the study.

14 INVESTIGATIONAL PRODUCT INFORMATION

14.1 Identity of Investigational Product

The study vaccine is a Quadrivalent VLP Influenza Vaccine composed of recombinant H1, H3, and two B proteins (hemagglutinin) expressed as VLPs for the 2017-2018 influenza virus strains.

14.1.1 Study Vaccine Composition

The Quadrivalent VLP Influenza Vaccine is a sterile transparent to opalescent colorless to slightly yellowish liquid suspension consisting of a mix of VLPs from four strains, each bearing the hemagglutinin of one of the recommended virus strains , in a phosphate buffered saline (PBS) solution (100 mM $NaKPO_4$, 150 mM NaCl) and 0.01 % polysorbate 80 at pH 7.4). The Quadrivalent VLP Influenza Vaccine will be supplied in a one-millilitre borosilicate pre-filled syringes (type 1). The hemagglutinin protein concentration in the provided syringes will be

60 µg/strain/mL in a volume of approximately 0.6 mL; the syringes were designed to deliver 0.5 mL, for a final dose of 30 µg/strain.

14.1.2 Placebo

The control product (placebo) will be composed of a phosphate-buffered saline (PBS) solution (100 mM $NaKPO_4$, 150 mM NaCl) and 0.01 % polysorbate 80 at pH 7.4. The placebo will be provided in one-millilitre borosilicate pre-filled syringes (type 1). According to the randomization scheme, 0.5 mL of placebo will be administered to subjects.

14.1.3 Preparation and Administration of Study Vaccine

The study treatment (including both the VLP Vaccine and placebo) will be prepared by unblinded staff members at the clinical site as described in the Investigational Product Management Manual. The prepared study treatment will subsequently be administered to subjects by an unblinded staff member.

> Note: The personnel responsible for treatment preparation can also perform the vaccination (if certified and qualified to do it) as this person would already be unblinded. The unblinded staff members must not be involved in the evaluation of any AEs or reactogenicity evaluations following vaccination.

The pre-filled syringes to be used for study treatment administration will be handled in a clean environment in an aseptic manner for preparation for injection as follows:

- For the administration of the 30 µg/strain vaccine dose, the site will use a pre-filled syringe labelled with study protocol CP-PRO-QVLP-012 and identified with a concentration of 60 µg/strain/mL and with a dose of 0.5 mL (30 µg/strain);
- For the administration of the placebo, the site will use a pre-filled syringe labelled with study protocol number CP-PRO-QVLP-012 and identified with the word “Placebo” and the lot number.

All study treatments will be administered IM. The needle to be used for the injection should be of sufficient length to reach the substance of the muscle. According to randomization scheme, subjects will receive either the Quadrivalent VLP Influenza Vaccine (30 µg/strain) or the placebo in the deltoid muscle of (preferably) the non-dominant arm. Whenever possible, the injection will be given in the opposite arm from which blood samples are drawn, when applicable.

The dose administered will be recorded in the Investigational Product Accountability Records form (refer to Investigational Product Management Manual) by the clinical site, which will be separate from the study medication record for drug preparation. After drug accountability monitoring and reconciliation has been completed by the site and Clinical Research Associate, all study treatments (used and unused syringes) will be destroyed locally upon Medicago’s approval or returned to Medicago (or its designee) in accordance with instructions provided in the Investigational Product Management Manual.

Further specific information relating to treatment preparation, storage, and shipment is provided in the Investigational Product Management Manual.

14.1.4 Preparation, Handling, Storage, and Precautions for Use

The study treatment should be stored in an access-restricted area between 2 ºC and 8 ºC; the vaccine should, however, be at room temperature before administration (i.e. the vaccine should not be administered cold). In the event of a storage temperature deviation outside of the permitted window of 2 ºC to 8 ºC, the study treatment should be quarantined (at the required storage temperature) and Medicago (or its designee) contacted immediately.

Note: The vaccine must NEVER be frozen, since freezing destroys activity; any vaccine that has been frozen must not be used.

Note: The vaccine must NEVER be shaken or vortexed.

Note: The treatments must NOT be administered intravenously, subcutaneously, or intradermally.

The Investigational Product Management Manual provides additional details on treatment preparation, handling and storage.

14.2 Packaging

The study drug will be packaged in boxes containing pre-filled syringes of the same treatment.

14.3 Labeling

The pre-filled syringes will have a product and study-specific label containing information that meets the applicable regulatory requirements. The study dispensing labels will contain dosing instructions, treatment, storage conditions, and a unique subject-specific treatment number.

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/placebo.

14.4 Drug Accountability

The Investigator is responsible for ensuring that all study treatments received at the site are inventoried and accounted for throughout the study. The dispensing of study treatment to each subject must be documented on the Investigational Product Accountability Records form.

The study treatments or drugs must be handled in strict accordance with the Investigational Product Management Manual and the syringe label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. All unused study drugs must be available for verification by Medicago's (or its designee's) unblinded site monitor during on-site monitoring visits. The return of all unused study drugs to Medicago (or its designee) for destruction will be documented on the Drug Return Form. When the site is authorized by Medicago (or its designee) to destroy study drug supplies on site, this must also be documented.

The study drug should be dispensed under the supervision of the Investigator or a qualified member of the investigational staff. The study drug will be supplied only to subjects participating in the study. Returned study drugs may not be relabeled or reassigned for use for other subjects. The Investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study centers agreed upon with Medicago (or its designee).

15 STUDY-SPECIFIC MATERIALS

The Investigator will be provided with the following:

- eCRF;
- Source documents (when applicable);
- Forms and questionnaires for special assessments;
- Thermometers and measurements template;
- Study manuals.

16 ETHICAL ASPECTS

16.1 Study-Specific Design Considerations

On-going medical review will be performed by Medicago (or its designee) throughout the duration of the study; subjects will be given any new information that may affect their decision to continue participation in the study.

The use of a placebo might raise ethical concerns since these research participants would not be receive an effective vaccine that would have decreased their risk of becoming infected with seasonal influenza. However, for this study, the use of a placebo control is considered to be justified and ethical for a number of reasons:

1. Although seasonal influenza vaccination is now widely recommended for all individuals aged six months and older (who do not have contraindications to the vaccine), the individuals at highest risk or with the highest burden of illness from seasonal influenza are considered to be individuals ≥ 65 years of age, children under five years of age, and individuals with medical conditions that place them at an increased risk for complications from influenza (CDC, 2016b; NACI, 2016; WHO, 2016). The population selected for this study (adults 18 to 64 years of age) are considered to be at relatively low risk for complications from seasonal influenza;
2. Even in high income countries, a large proportion of the target population typically remains unvaccinated (e.g. in the US vaccination is recommended for everyone aged six months and older, however, the Centers for Disease Control and Prevention [CDC] reports the amount of vaccine distributed for each influenza season to be less than 50 % of the population). Based on historical data, the proportion of healthy adults who do not fall into one of the major risk categories (for either themselves or their close contacts) and who go unvaccinated is lower than that of individuals considered to be at high risk (e.g. 22 % and 33.5 % of healthy adults were vaccinated against seasonal influenza in Canada in the 2013-2014 season (Gionet, 2015) and in the US in the 2015-2016 season (CDC, 2016a),

respectively. In consequence, a large proportion of the target population of this study would likely go unvaccinated, irrespective of this study;

3. The size of the currently planned placebo-controlled trial (approximately 10,000 subjects) is based on an ARU of ≥ 2 % and it is understood that if the ARU falls below 1.5 %, a second season may be required in order to have sufficient power for hypothesis testing. The use of an active comparator as a control would impact the attack rate estimate that was used in the sample size calculation in two ways, both of which could render the trial non-viable in terms of cost and/or duration:
   - A lower attack rate estimate would be required for an active comparator-controlled study design, resulting in an unrealistic sample size to have adequate power for hypothesis testing;
   - The attack rate estimate for an active comparator control would be significantly more unpredictable, since the efficacy of the currently available seasonal influenza vaccines can range greatly from one season to another (DiazGranados et al., 2012). This unpredictability can, in turn, independent of an increased sample size, lead to a longer study duration in order to achieve sufficient power for hypothesis testing.

Blood samples will be collected from a subset of subjects for humoral immunogenicity analysis, although not all will be analysed. Since blood sample collection is a minimally invasive procedure and the amount of blood collected will be a relatively small amount (Table 5), the benefits of obtaining this data outweigh the small level of risk associated with the collection of samples that may not require analysis.

16.2 Regulatory Ethics Compliance

16.2.1 Investigator Responsibilities

The Investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Conference on Harmonisation (ICH) guidelines on good clinical practice (GCP), and applicable regulatory and country-specific requirements.

GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are reliable.

16.2.2 Independent Ethics Committee or Institutional Review Board

Before the start of the study, the Investigator (or Medicago, where required) will provide the Independent Ethics Committee (IEC)/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments to the protocol;
- Sponsor-approved ICF (and any other written materials to be provided to the subjects);

- IB (or equivalent information) and amendments/addenda;
- Sponsor-approved subject recruiting materials;
- Information on compensation for study-related injuries or payments to subjects for participation in the study, if applicable;
- Investigator's *curriculum vitae* or equivalent information (unless not required, as documented by the IEC/IRB);
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects;
- Any other documents that the IEC/IRB requests to fulfill its obligation.

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative in nature, with no consequences for subjects, data, or study conduct), the ICF, applicable recruiting materials, and subject compensation programs, and Medicago (or its designee) has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved. In addition, the Investigator must wait for written confirmation from Medicago (or its designee) that the study can be started.

During the study, the Investigator (or Medicago [or its designee], where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments;
- Revision(s) to ICF and any other written materials to be provided to subjects;
- If applicable, new or revised subject recruiting materials approved by Medicago;
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable;
- New edition(s) of the IB and amendments/addenda;
- Summaries of the study at intervals stipulated in guidelines of the IEC/IRB (at a minimum, annually);
- Reports of AEs that are serious, unlisted/unexpected, and associated with the study drug (when applicable);
- New information that may adversely affect the safety of the subjects or the conduct of the study;
- Deviations from or changes to the protocol to eliminate immediate hazards to subjects;
- Reports of deaths of subjects under the Investigator's care;
- Notification if a new Investigator is responsible for the study at any of the sites;
- Development Safety Update Report and Line Listings, where applicable;
- Any other requirements of the IEC/IRB.

At least once a year, the IEC/IRB will be asked to review and reapprove this study. The reapproval should be documented in writing. At the end of the study, the Investigator (or Medicago [or its designee], where required) will notify the IEC/IRB of study completion.

16.2.3 Informed Consent

Each subject who participates in the study must first give written consent according to local requirements after the nature of the study has been fully explained, including the risks and requirements of the study. The consent form must be signed before performing any study-related activity. The consent form that is used must have been approved by regulatory authorities, Medicago, and the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Medicago policy. During the study, subjects will be given any new information that may affect their decision to continue their participation in the study. They will be told that their consent to participate is voluntary and that it may be withdrawn at any time, with no reason given, and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study and who provide their consent voluntarily will be enrolled.

16.2.4 Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to support the development, registration, and future marketing of the investigational product. The data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be in place. Medicago (or its designee) personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

17 ADMINISTRATIVE REQUIREMENTS

17.1 Protocol Amendments

Neither the Investigator nor Medicago will modify this protocol without a formal amendment. All protocol amendments must be issued and approved by Medicago, and signed and dated by the Investigator. Protocol amendments must not be implemented without prior IEC/IRB approval or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary in order to eliminate an immediate hazard to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the Investigator and IEC/IRB must be provided to Medicago or its designee.

Note that administrative changes may be implemented without prior IRB approval; however, the Investigator or Medicago, as applicable, must notify the IRB of any administrative change and ensure that IRB acknowledges receipt of the administrative changes.

The Investigator is responsible for notifying the IRB of all protocol amendments and ensuring that the IRB has approved any amendments when local IRBs are used. When a central IRB is used, Medicago or its designee will inform the IRB on behalf of the sites.

During the course of the study, in situations where a departure from the protocol is unavoidable, the Investigator or other physician in attendance will contact the appropriate Medicago representative or its designee (see Contact Information pages provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with Medicago or its designee must be made as soon as possible to discuss the situation and to agree on an appropriate course of action. The data recorded in the eCRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances that made a deviation necessary.

17.2 Regulatory Documentation

17.2.1 Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, as applicable. A study may not be initiated until all local regulatory requirements are met.

17.3 Source Documentation

At a minimum, source documentation must be available for the following information:

- Subject identification, eligibility, and study identification;
- ICF discussion and date of informed consent;
- Dates of visits;
- Results of safety and study procedures as required by the protocol;
- Record of all reactions, AEs, respiratory illnesses, ILIs, and associated follow ups;
- Concomitant medication;
- Drug receipt, dispensing, and return records;
- Study drug administration information;
- Date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

It is recommended that the author of an entry in the source documents be identifiable.

At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific

details required as source data for the study will be reviewed with the Investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

17.4 Case Report Form Completion

Electronic case report forms (eCRFs) will be provided for each subject who is randomized and receives a dose of study drug. Screening failures will also be entered in an electronic case report form; data entered should include date of birth and reason for screening failure.

Data must be entered into the eCRFs in English. The Investigator must verify that all data entries in the eCRFs are accurate and correct. All eCRF entries, corrections, and alterations must be made by the Investigator or other authorized study-site personnel.

17.5 Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and Medicago (or its designee) procedures, the site will be contacted prior to the study start to review the protocol and study requirements with the clinical study staff. Medicago (or its designee) will review their responsibilities to satisfy regulatory, ethical, and company (Medicago) requirements.

The Investigator or institution, if applicable, will authorize and provide direct access to all relevant documents to allow review of the appropriate conduct of the study by Medicago's (or its designee's) monitor. The Investigator(s) must allocate their time and the time of their staff to the monitors, discuss any findings or issues, and take appropriate actions to maintain the quality and integrity of the study data and conduct.

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.

17.6 Quality Assurance

To ensure compliance with GCP and all other applicable regulatory requirements, Medicago (or its designee) may conduct quality assurance assessments and/or an audit of the site. Regulatory agencies may conduct regulatory inspections at any time during or after completion of the study. If an audit or an inspection is conducted, the Investigator and/or institution (if applicable) must agree to grant auditors or inspectors direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study and any findings or issues, and to implement corrective and/or preventative actions to address any findings or issues identified.

17.7 Record Retention

Following closure of the study, the Investigator must maintain all site study records in a safe and secure location. The records must be easily accessible when needed (e.g. for a Medicago [or its designee] audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

When permitted by local laws and regulations or institutional policy, some or all of the records may be maintained in a format other than a hard copy (e.g. scanned electronic). The Investigator must ensure that all reproductions are legible and are a true and accurate copy of the original.

The Investigator must follow the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws and regulations, Medicago (or its designee) standard operating procedures (SOPs), and/or institutional requirements. The Investigator must contact Medicago (or its designee) prior to the disposal of any study documents at the end of the retention period.

If the responsible Investigator retires, relocates, or, for any other reason, withdraws from the responsibility of keeping the study records, custody must be transferred to another person who will accept the responsibility. Medicago (or its designee) must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents without having obtained prior written approval from Medicago (or its designee).

If it becomes necessary for Medicago or the appropriate regulatory authority to review any documentation relating to this study, the Investigator must permit access to such reports.

17.8 Study Completion/Termination

17.8.1 Study Completion

The study will be considered to be completed with the last contact with the last subject participating in the study. The final data from the investigational site will be sent to Medicago (or designee) after completion of the final subject visit at that site. Investigational sites will be closed after study completion. An investigational site is considered closed when all required documents and study supplies have been collected, all data have been entered, monitored, locked, and signed and a site closure visit has been performed.

17.8.2 Study Termination

Medicago (or its designee) reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of Medicago. Investigational sites will be closed after study termination once Medicago (or its designee) has completed all study related tasks. Reasons for the early closure of an investigational site by Medicago (or its designee) or the Investigator may include, but are not limited to:

- Failure of the Investigator to comply with the protocol, Medicago's (or its designee's) procedures, or GCP guidelines;
- Inadequate recruitment of subjects by the Investigator;
- Discontinuation of further drug development.

The Investigator may initiate site closure at any time, provided there is reasonable cause and

sufficient notice is given in advance of the intended closure.

Site closure following an Investigator request can only be performed when all active study subjects have completed the study period, Medicago (or its designee) has collected all required documents and study supplies, and all data have been entered, monitored and locked.

17.9 Registration of Clinical Studies and Disclosure of Results

Study information from this study will be posted on publicly available clinical trial registries in countries where applicable and will include information required by law. In addition, the results summary will be posted to the same clinical trial registries, to the extent specified by law, and will include information required by regulatory authorities.

18 REFERENCES

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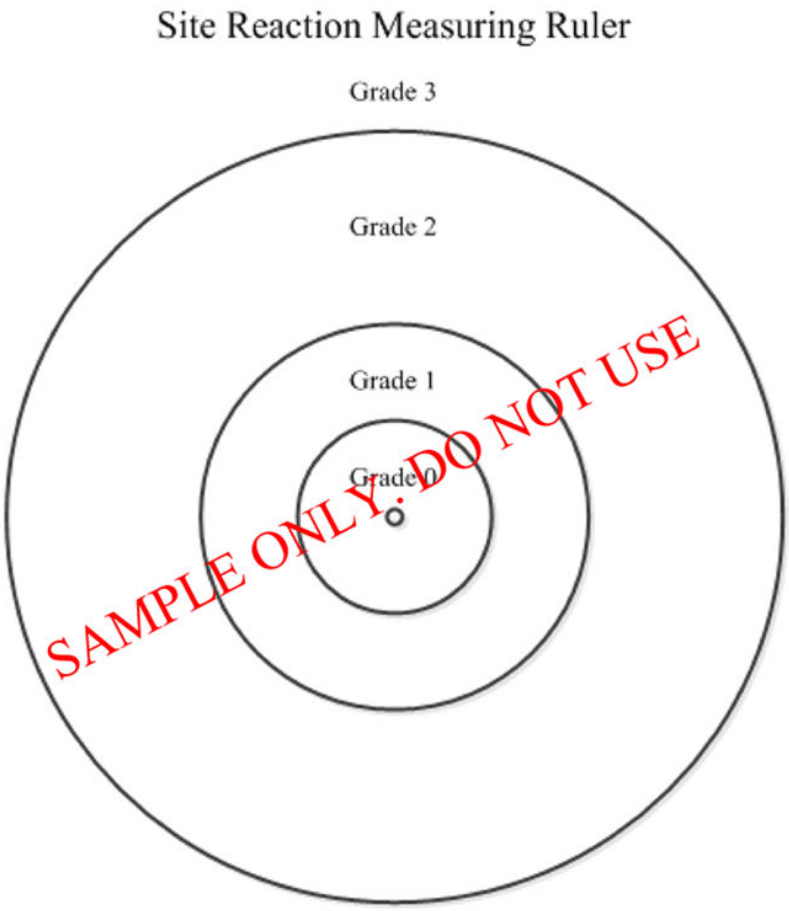
19 APPENDICES

19.1 Appendix 1 – Sample Ruler to Measure Local Reactions



Grading for erythema and swelling where the vaccine was given	
Grade 0	None or less than 25 mm
Grade 1	Between 25 mm and 50 mm
Grade 2	Between 51 and 100 mm
Grade 3	More than 100 mm
Grade 4	Skin/tissue loss at the injection site (blister or ulcer formation) of any size

19.2 Appendix 2 – Burden of Disease Questionnaire

Burden of Disease Questionnaire

This form is to be completed for each case of respiratory illness (there may be more than one questionnaire per subject). Preferably, this questionnaire should be completed at the end of the 30-day follow-up period for the respiratory illness to ensure the capture of all information.

Only complete this questionnaire for cases that meet the definition (as provided in the protocol) of respiratory illness.

1. Indicate the number of consultations with a **general practitioner** (for example, family doctor) for the respiratory illness: *(Do not leave any of the fields blank; if no visits of the indicated type occurred, enter "0").*	Doctor's Office* Home Visit Telephone	☐ ☐ ☐
2. Indicate the number of **non-hospital** consultations with a **specialist** (for example, a pneumologist or a ears, nose, and throat specialist) for the respiratory illness: *(Do not leave any of the fields blank; if no visits of the indicated type occurred, enter "0").*	Doctor's Office Home Visit Telephone	☐ ☐ ☐
3. Indicate the number of consultations at a **hospital** (this does not include any visits to the office of a general practitioner or non-hospital specialist consultations, which should have been indicated in Question 1 or 2). *(Do not leave any of the fields blank; if no visits of the indicated type occurred, enter "0").*	Emergency Specialist	☐ ☐
4. Indicate the number of days of hospitalization for the respiratory symptoms. *(Do not leave any of the fields blank; if no hospitalizations of the indicated type occurred, enter "0").*	General Intensive Care	☐ ☐
5. Did the respiratory illness result in pneumonia (medical diagnosis)? *(Check only one.)*	Yes No	☐ ☐
6. Did the respiratory illness result in a new or a worsened pre-existing cardio-respiratory condition? *(Check only one.)*	Yes No	☐ ☐
7. Were there any other medical diagnoses associated with the respiratory illness? If 'yes' indicate them in the space below. Other diagnoses:	Yes No	☐ ☐

* includes office visits at a clinic or hospital

Burden of Disease Questionnaire (continued)	
8. Indicate the number of days of missed work or school as a result of the respiratory illness. *(Do not leave any of the fields blank; if there were no missed days of the indicated type, enter "0").*	Work ☐ School ☐
9. Indicate the number of days that another person (or people) had to interrupt their daily activities to provide care as a result of this respiratory illness. *(Do not leave any of the fields blank; if care from another person was not required, enter "0").*	Family Member ☐ Paid Individual ☐
10. Was medication taken because of the respiratory illness? *(Check only one. If 'yes', ensure that the details of the type of medication are entered in the Memory Aid.)*	Yes ☐ No ☐
11. Indicate the current state of recovery from the respiratory illness (in comparison to the first few days of the illness). *(Check only the most applicable field)*	Fully recovered ☐ Close to recovering ☐ Improved, but still quite ill ☐ Unimproved or worse ☐

19.3 Appendix 3 – Subject Memory Aid

MEMORY AID	
Study Name	A Randomized, Observer-blind, Placebo-controlled, Multicenter, Phase 3 Study to Assess the Efficacy, Safety, and Immunogenicity of a Plant-Derived Quadrivalent VLP Influenza Vaccine in Adults 18-64 Years of Age
Protocol Number	CP-PRO-QVLP-012
Sponsor	Medicago R&D Inc. 1020, route de l'Église, bureau 600 Québec (Qc), Canada G1V 3V9
Clinical site Address	
Principal Investigator Name	
Clinical Research Coordinator	
24-hour Emergency Number	

INSTRUCTIONS

The Memory Aid is to help you keep track of information needed during this study. It should not be considered to replace data entry into your eDiary.

You will need to refer to this Memory Aid during the telephone contacts.

From vaccination:

- **To Day 7:** - Reactions collected in the eDiary (temperature, swelling, redness, and pain at injection site, headache, fatigue, muscle aches, joint aches, chills, general discomfort/uneasiness, swelling in the axilla and the neck) should not be recorded here.
- **To Day 21**: - Side effects (symptoms) should all be recorded. You do NOT need to collect reactions that you had to report in the eDiary (listed in the previous point).
  - All medication should also be recorded. Examples may include prescription drugs (including vaccines), over-the-counter drugs, herbal supplements and/or vitamins. Indicate each intake of medication you are usually taking as needed.

From Day 14 to the end of the study:

- Record below Respiratory Illness and Influenza-like Illness symptoms.
- Any medication taken for respiratory illness and influenza-like illness symptoms should also be recorded.

From Day 22 to the end of the study:

- Record health problems that required a visit to your doctor, a hospital stay, or a visit to an emergency room.
- Record any medication taken for these health problems or health problems you had before entering the study, or any medication taken for side effect that has started before Day 21.

NOTE: Each medication must be associated to a problem, but each problem does not require a medication associated with it.

You received the study vaccine on: |__|__| |__|__|__| at: |__|__| : |__|__|
dd mmm yyyy hh mm

Day 7	Day 14	Day 21
|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|	|__|__| |__|__|__| |__|__|__|__|
dd mmm yyyy	dd mmm yyyy	dd mmm yyyy

SIDE EFFECTS (SYMPTOMS)						
Side Effects (symptoms)	**Grade** (See below)	**START**		**STOP**		**Did you receive medical care?**
		Date	**Time**	**Date**	**Time**	
						❑ Yes ❑ No
						❑ Yes ❑ No
						❑ Yes ❑ No
						❑ Yes ❑ No
						❑ Yes ❑ No
						❑ Yes ❑ No
						❑ Yes ❑ No
						❑ Yes ❑ No
						❑ Yes ❑ No
						❑ Yes ❑ No

GRADES **1**= Does not interfere with activity; **2**= Some interference with activity not requiring medical intervention; **3**= Prevents daily activity and requires medical intervention; **4**= Visit to Emergency room or hospitalization.

MEDICATION			
Medication (Name, Dose, Route and Frequency)	**Start date**	**Stop date**	**Reason(s) why you are taking this medication?**

Dose			Route			Frequency		
Capsule	Tablespoon	g	Oral	Intramuscular	Ophthalmic	Once a day	Every other day	Continuous
Tablet	Teaspoon	mcg	Topical	Nasal	Intra-articular	Twice a day	Every 3 days	Intermittent
Ring	Puff	mg	Inhalation	Intravenous	Rectal	3 times/day	Every 2 weeks	Once
Application	Drops	IU	Intrauterine	Transdermal	Sublingual	1x per week	Every 6 months	As needed
Lozenge	mL	Units	Vaginal	Subcutaneous	Unknown	2x per week	Every hour	Unknown
Syringe	%	Unknown				Once a month	Once a year	

RESPIRATORY ILLNESS & INFLUENZA-LIKE ILLNESS SYMPTOMS

From Day 14 to the end of the study, record your symptoms when you experience one of the following.
Use a checkmark ("√") for each symptom you do have.
If you have a checkmark for any of the seven symptoms shaded in grey, call the site as soon as possible.

START		Sneezing	Stuffy / Runny Nose	Sore Throat	Cough	Sputum	Wheezing	Difficulty Breathing	Chills	Tiredness	Headache	Muscle Aches	Fever*	List if one of the following: feeling feverish, nausea, vomiting, or diarrhea
Date	Time													

* Fever: indicate a checkmark if your oral temperature is > 99 °F or > 37.2 °C

19.4 Appendix 4 – Acceptable Contraceptive Methods

Germany

Female subjects of childbearing potential must use an effective method of contraception for one month prior to vaccination and agree to continue employing adequate birth control measures for at least 60 days post-vaccination. Moreover, female subjects must have no plan to become pregnant for at least two months post-vaccination. The following relationship or methods of contraception are considered to be effective:

- Hormonal contraceptives (e.g. oral, injectable, topical [patch], or estrogenic vaginal ring);
- Intra-uterine device with or without hormonal release;
- Sterilized partner (at least one year prior to vaccination);
- Credible self-reported history of heterosexual vaginal intercourse abstinence until at least 60 days post-vaccination;
- Female partner.

United Kingdom

Female subjects of childbearing potential must use an effective method of contraception for one month prior to vaccination and agree to continue employing adequate birth control measures for at least 60 days post-vaccination. Moreover, female subjects must have no plan to become pregnant for at least two months post-vaccination. The following relationship or methods of contraception are considered to be effective:

- Hormonal contraceptives (e.g. oral, injectable, topical [patch], or estrogenic vaginal ring);
- Intra-uterine device with or without hormonal release;
- Male partner using a condom plus spermicide or sterilized partner (at least one year prior to vaccination);
- Credible self-reported history of heterosexual vaginal intercourse abstinence until at least 60 days post-vaccination;
- Female partner.

All Other Regions

Female subjects of childbearing potential must use an effective method of contraception for one month prior to vaccination and agree to continue employing adequate birth control measures for at least 60 days post-vaccination. Moreover, female subjects must have no plan to become pregnant for at least two months post-vaccination. Abstinent subjects should be asked what method(s) they would use should their circumstances change, and subjects without a well-defined plan should be excluded. The following relationship or methods of contraception are considered to be effective:

- Hormonal contraceptives (e.g. oral, injectable, topical [patch], or estrogenic vaginal ring);
- Intra-uterine device with or without hormonal release;

- Male partner using a condom plus spermicide or sterilized partner (at least one year prior to vaccination);
- Credible self-reported history of heterosexual vaginal intercourse abstinence until at least 60 days post-vaccination;
- Female partner.