Clinical Protocol

A Randomized, Observer-blind, Multicenter, Phase 3 Study to Evaluate the Lot Consistency, Immunogenicity, and Safety of a Plant-Derived Quadrivalent VLP Influenza Vaccine in Healthy Adults 18-49 Years of Age

CP-PRO-QVLP-011; 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 1.3

Date: 08 August 2017

SIGNATURE

Study Title: A Randomized, Observer-blind, Multicenter, Phase 3 Study to Evaluate the Lot Consistency, Immunogenicity, and Safety of a Plant-Derived Quadrivalent VLP Influenza Vaccine in Healthy Adults 18-49 Years of Age

Study Author(s): PPD

I confirm that Medicago R&D Inc. has approved the version 1.3 (dated 08 August, 2017) of the protocol CP-PRO-QVLP-011 and agree that it may be issued to the relevant authorized study personnel, independent ethics committees and regulatory authorities.

PPD

~~2018-08-0~~ 2017-09-28
Date

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2017-08-09

PPD

Date

Medicago

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PPD — Date

PPD — 2017-08-09 — Date

PPD — 2017-08-10 — Date

Medicago

INVESTIGATOR AGREEMENT

I have read the version 1.3 (dated 08 August, 2017) Protocol No. CP-PRO-QVLP-011 titled, "A Randomized, Observer-blind, Multicenter, Phase 3 Study to Evaluate the Lot Consistency, Immunogenicity, and Safety of a Plant-Derived Quadrivalent VLP Influenza Vaccine in Healthy Adults 18-49 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), 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 proteins (hemagglutinin) expressed as virus-like particles (VLPs) for the 2016-2017 influenza virus strains in the Northern hemisphere.
Protocol Title:	A Randomized, Observer-blind, Multicenter, Phase 3 Study to Evaluate the Lot Consistency, Immunogenicity, and Safety of a Plant-Derived Quadrivalent VLP Influenza Vaccine in Healthy Adults 18-49 Years of Age
Protocol Number:	CP-PRO-QVLP-011
Development Phase:	Phase 3
Study Center(s):	Multiple sites in Canada
Study Rationale:	This Phase 3 study is intended to assess the clinical lot-to-lot consistency in manufacturing by evaluating and comparing the immunogenicity of three consecutively manufactured lots of the Quadrivalent VLP Influenza Vaccine, during the 2016-2017 influenza season, in healthy adults 18-49 years of age. A single dose of one of three consecutive lots of Quadrivalent VLP Influenza Vaccine (30 µg/strain) will be administered to 1,200 subjects. The study is intended to support consistency of the manufacturing process and therefore support the licensure of the vaccine in Canada, the United States (USA), and Europe.
Planned Study Period:	The Day 0 (Screening/Vaccination) visit will occur between September and October 2017. The last study blood sample (Day 21) will be collected in November 2017.
Study Objectives **Primary Objective:**	• To assess the consistency of three consecutive manufacturing lots of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, as measured by the serum hemagglutination inhibition (HI) antibody titers on Day 0 and Day 21.

Secondary Objectives:	**Safety:** • To assess the safety and tolerability of a single dose of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain. **Immunogenicity:** • To assess the immunogenicity of a single dose of Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain against homologous influenza strains.
Number of Planned Subjects:	Approximately 1,200 subjects are planned for randomization in a 1:1:1 ratio to receive one of three lots of Quadrivalent VLP Influenza Vaccine at a dose of 30 µg/strain.
Sample Size Determination:	Based on data from the CP-Q14VLP-009 study, a sample size of 400 subjects per lot (a total of 1,200 subjects) will have a greater than 90 % power to detect consistency between the lots (i.e. to test that the pairwise comparisons of the two-sided 95 % confidence interval (CI) for adjusted geometric mean titer (GMT) ratios of the three lots being tested [lot 1/lot 2, lot 1/lot 3, lot 2/lot 3] fall within the equivalence range of 0.67 to 1.5 for all four homologous strains). A drop-out rate and exclusion from the per protocol (PP) population of approximately 10 % was assumed in the sample size calculation.
Study Population:	Healthy male and female subjects 18 to 49 years of age and with no clinically significant disease at the time of vaccination are to be included in this study. The subjects must understand and agree to comply with study procedures and be available throughout the study. Subjects must not have received any influenza vaccine in the last 24 months.
Dosage and Administration:	On Day 0, subjects will receive one intramuscular (IM) injection of 0.5 mL of their assigned vaccine lot (lot 1 or 2 or 3) of 30 µg/strain Quadrivalent VLP Influenza Vaccine.
Study Design:	This is a randomized, observer-blind, multicenter, Phase 3 lot consistency study. Subjects will participate in this study for approximately 21 days, 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 memory aid (MA), concomitant medications, and medical history; a visit will occur

	on Day 21 for blood sample collection for immunogenicity assessment.
Primary Evaluations and Endpoints:	**Immunogenicity:** Immunogenicity will be evaluated by the immune response, as measured by the serum HI antibody titers on Day 0 and Day 21: • GMTs of the three vaccine lots (21 days after vaccination) for all four vaccine strains.
Secondary Endpoints:	**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 treatment-emergent adverse events (TEAEs) for 21 days following study vaccine administration; • Occurrences of deaths, serious adverse events (SAEs), adverse events (AEs) leading to withdrawal, and new onset of chronic disease (NOCD) up to Day 21. **Immunogenicity:** • HI antibody response induced by the Quadrivalent VLP Influenza Vaccine (pooled data from the three lots) against the homologous influenza strains on Days 0 and 21; HI antibody titers will be analyzed using the following parameters: seroconversion (SC) rate, seroprotection (SP) rate, and geometric mean fold rise (GMFR).
Statistical Methods:	**Populations:** Statistical analyses will be performed on pre-defined population sets (the safety analysis set [SAS], the full analysis set [FAS], and the PP set) according to the statistical analysis plan (SAP). The analyses of the primary endpoint (Day 21 GMT), as well as the analyses of the secondary endpoints (SC rate, SP rate, and GMFR) for each strain will be performed using the PP set. The primary immunogenicity endpoint analyses will also be performed on the FAS to support results from the PP set. All safety analyses will be performed using the SAS.

	Statistical Analyses: In general, continuous data will be summarized using descriptive statistics (i.e. mean or geometric mean, median, standard deviation, minimum, and maximum). Categorical data will be summarized using the number and percent of subjects in each category. **Immunogenicity Analyses:** The immunologic equivalence of three separate production lots of the Quadrivalent VLP Influenza Vaccine will be measured in terms of GMTs, as measured by HI assay, against all vaccine influenza strains. Lot-to-lot consistency is based on adjusted Day 21 GMT ratios for pairwise comparisons of the lots (lot 1/lot 2, lot 1/lot 3, and lot 2/lot 3). For each pairwise comparison of the lots, the lot-to-lot consistency will be demonstrated if the two-sided 95 % CIs on the adjusted Day 21 GMT ratios fall within the equivalence range of 0.67 to 1.5 for all four strains. For the secondary immunogenicity analysis (conducted on the pooled data of the three lots), the point estimates and the corresponding two-sided 95 % CI will be calculated to determine if the CI meets the USA Center for Biologics Evaluation and Research (CBER) criteria for SC rate and SP rate. The immunogenicity endpoints for all four homologous influenza antigens will be evaluated according to the CBER) criteria for SC rate and SP rate. **Safety Analyses:** Safety data will be summarized using descriptive statistics as pooled data of all three lots: • 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 study (Day 21).

Table 1 Time and Events Schedule

Visit Type	**Screening/ Vaccination**	**Post-vaccination Visits/Contacts**		
Study Day	**Day 0**	**Day 1 (+ 1)**	**Day 8 (- 1/+ 1)**	**Day 21 (- 2/+ 3)**
Visit Number	**1**	**Phone**	**Phone**	**2**
Informed consent	X			
Demographics	X			
Medical history/prior medication	X			
Vaccination history[1]	X			
Inclusion/exclusion criteria	X			
Randomization	X			
Vaccine administration	X			
Immediate surveillance (15 min)	X			
Serology for HI titers	X			X
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			X[2]
Urine (dipstick) pregnancy test	X			X
Memory aid (MA)[3] and digital thermometer instructions	X			
Collection of solicited local/ systemic reactions	X	X	X	
Concomitant medications	At any time during the study period			
AEs, SAEs, and NOCDs	X	X	X	X

[1] Information on past influenza vaccinations for two years prior to study entry; subjects who received an influenza vaccine within 24 months prior to study start are to be excluded from the study.

[2] History/symptom-directed physical examinations will be performed on Day 21 if deemed necessary by the Investigator. If a subject complains of arm and/or shoulder pain of the vaccinated arm or neck pain on the day of the visit, a direct examination of the lymph nodes for swelling (neck and axilla) will be performed by the Investigator.

[3] The MA must be verified with the subject for completeness. All corrections must be made by the subjects before leaving the clinic.

ABBREVIATIONS

AE	adverse event
BMI	body mass index
BP	blood pressure
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
DP	drug product
DS	drug substance
eCRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice
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
IEC	independent ethics committee
IM	intramuscular
IRB	institutional review board
IRT	interactive voice response system
MA	memory aid
MedDRA	Medical Dictionary for Regulatory Activities
NOCD	new onset of chronic disease
OT	oral temperature
PP	per protocol
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SAS®	Statistical Analysis System®
SC	seroconversion
SP	seroprotection
TEAE	treatment-emergent adverse event
VLP	virus-like particle
WHO	World Health Organization
USA	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 H and ten N 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 USA alone, influenza is responsible for approximately 36,000 deaths per year and the World Health Organization (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 USA alone.

The main strategy for prevention and control of seasonal and pandemic influenza is still vaccination. In 2012, the Advisory Committee on Immunization Practices 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 2014-2015 influenza season were even lower: hovering at or even below 0 % due to a significant mismatch between vaccine and circulating strains (Skowronski et al., 2015).

1.1 Background

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 viruses contained 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 version of the 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 2.

Table 2 Summary of Design of Clinical Studies Performed to Date with the Quadrivalent VLP Influenza 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 18-49 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 18-49 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 - 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 VLP Influenza 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 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 2 for a description of the basic design, status, and exposure for these studies.

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 VLP vaccine (all dose levels without adjuvant combined, N = 1,642) and three for subjects who received a single dose of adjuvanted VLP vaccine (both dose levels combined, N = 151). None of these SAEs were considered to be vaccine-related by the Investigator. 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 (with and without adjuvant) 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, 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. Few 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 be 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 five clinical trials conducted to date (CP-Q12VLP-004, CP-Q13VLP-007, CP-Q13VLP-008, CP-Q14VLP-009, and CP-Q14VLP-010). Studies CP-Q12VLP-004, CP-Q13VLP-007, and CP-Q14VLP-009 were conducted in an adult population (18 to 49 years for the first two studies and 18 to 64 years for CP-Q14VLP-009), CP-Q13VLP-008 was conducted in a combined adult and elderly population (50 years and older), and CP-Q14VLP-010 was conducted in an elderly population (65 years and older). See Table 2 for a description of the basic design, status, and exposure of these studies.

1.3.2.1 Antibody Response

Overall, the immunogenicity data from the studies conducted to date show that the Quadrivalent VLP Influenza 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. As a result, the 30 µg/strain dose level has been selected for the lot-to-lot consistency evaluation 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) studies, the 30 µg/strain dose level met the CHMP criteria for SC rate, SP rate, and GMFR against all four homologous 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 unbiased by the use of eggs for production (even when cell-based reagents are available, their history includes an initial expansion in embryonic-eggs). These reagents often include mutations of a 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 in these studies.

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 selection 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 (reference: 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 the clinical trials conducted to date; based on the results obtained from these studies, in which there were no observed trends suggestive of safety concerns (reference: current IB version), there is no need to include assessment of plant glycans in this study.

1.4 Overall Rationale for the Study

This Phase 3 study is intended to assess the clinical lot-to-lot consistency in manufacturing by comparing the immunogenicity of three separately manufactured lots of the Quadrivalent VLP Influenza Vaccine, during the 2017-2018 Influenza season, in healthy adults 18 to 49 years of age. One dose of Quadrivalent VLP Influenza Vaccine (30 µg/strain) will be administered according to the randomization code to each of the 1,200 trial participants. The study is intended to support consistency of the manufacturing process.

2 OBJECTIVES

2.1 Primary Objectives

- To assess the consistency of three consecutive manufacturing lots of the Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain, as measured by the serum hemagglutination inhibition (HI) antibody titers on Day 21.

2.2 Secondary Objectives

Safety:

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

Immunogenicity:

- To assess the immunogenicity of a single dose of Quadrivalent VLP Influenza Vaccine given at a dose of 30 µg/strain against homologous influenza strains.

3 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Table 3 Study Administrative Structure

Role	Name and Address
Sponsor PPD	Medicago R&D Inc., 1020, route de l'Église, bureau 600, Sainte-Foy (Qc) Canada G1V 3V9 PPD
Analytical Laboratories Serology (Immunogenicity):	 Medicago Inc., 1020, route de l'Église, bureau 600, Sainte-Foy (Qc) Canada G1V 3V9
Contract Research Organisation	CCI

4 STUDY DESIGN AND RATIONALE

4.1 Overview of Study Design

This randomized, observer-blind, multicenter, Phase 3 lot consistency study will be conducted at multiple sites in Canada.

The composition of the Quadrivalent VLP Influenza Vaccine used in this study includes two influenza A virus strains and two influenza B virus strains based on the 2016-2017 recommended WHO strains for vaccination in the Northern hemisphere.

Subjects will participate in this study for approximately 21 days, during which a first visit will be scheduled on Day 0 for screening, eligibility assessment, and vaccine administration; a phone contact will be made on Days 1 and 8 specifically for review of the MA, concomitant medications, and health status; a visit will occur on Day 21 for blood sample collection for immunogenicity assessment.

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 to enhance the validity of statistical comparisons across treatment groups.

4.2.2 Observer-blinding

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

4.2.3 Dose Selection

The dose of 30 µg/strain was selected based on data from previous studies.

4.2.4 Study Duration

The study duration of 21 days will allow for collection of immunogenicity data and the standard evaluation of immediate complaints, local and systemic reactions, and TEAEs. Given the modest sample size of this study compared to the planned phase 3 study, it was considered that monitoring of SAEs and NOCDs past Day 21 would not provide significant additional safety information on this vaccine in this subject population.

4.2.5 Immunogenicity Assessments

The primary immunogenicity assessment (Day 21 GMT measured by HI assay), is standard for this type of study. The secondary immunogenicity assessments (SC rate, SP rate, and GMFR measured by HI assay) are standard for immunogenicity evaluation in vaccine development.

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 be able to read, understand, and sign the informed consent form (ICF); complete study-related procedures; and communicate with the study staff at visits and by phone;
2. Subjects must be considered by the Investigator to be reliable and likely to cooperate with the assessment procedures and be available for the duration of the study;
3. Male and female subjects must be 18 to 49 years of age, inclusive, at the Screening/Vaccination visit (Visit 1);
4. Subjects have a body mass index (BMI) ≤ 40.0 kg/m^2 on Day 0 pre-vaccination;
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 six months prior to vaccination. Based on the Investigator's judgment, a subject with a 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 effective method of contraception for one month prior to vaccination and agree to continue employing adequate birth control measures for the duration of the study. 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 a sterilized partner (at least one year prior to vaccination);
   - Credible self-reported history of heterosexual vaginal intercourse abstinence until at least the Day 21 visit;
   - Female partner.

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. 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 six months prior to study vaccine administration unless the criteria outlined in inclusion criterion no. 5 can be met (i.e. the Investigator can justify inclusion based upon the innocuous nature of medical/surgical events and/or treatments);
   - Requiring any significant change in a chronic medication (i.e. drug, dose, frequency) during the three months prior to study vaccine administration due to uncontrolled symptoms or drug toxicity, unless the innocuous nature of the medication change meets the criteria outlined in inclusion criterion no. 5 and is appropriately justified by the Investigator.
2. Any medical or neuropsychiatric condition or any history of excessive alcohol use or drug abuse which, in the Investigator's opinion, would render the subject unable to provide informed consent or unable to provide valid safety observations and reporting;
3. Any autoimmune disease other than hypothyroidism with stable replacement therapy; or any confirmed or suspected immunosuppressive condition or immunodeficiency including known or suspected human immunodeficiency virus (HIV), hepatitis B or C infection, or the presence of lymphoproliferative disease;
4. Administration or planned administration of any non-influenza vaccine within 30 days prior to randomization and up to blood sampling on Day 21. Immunization on an emergency basis will be evaluated case-by-case by the Investigator;
5. Administration of any adjuvanted or investigational influenza vaccine within 24 months prior to randomization or planned administration prior to the completion of Day 21;
6. Administration of any "standard", non-adjuvanted influenza vaccine (e.g. live attenuated trivalent/quadrivalent inactivated influenza vaccine intranasal or split trivalent/quadrivalent inactivated influenza vaccine by either intradermal or IM route) within 24 months prior to randomization and up to completion of the Day 21 visit;
7. Use of any investigational or non-registered product within 30 days 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 the Day 21 visit. Participation in observational studies is permitted;

8. Treatment with systemic glucocorticoids at a dose exceeding 10 mg of prednisone (or the equivalent) per day for more than seven consecutive days or for ten or more days in total, within one month of study vaccine administration; or any other cytotoxic or immunosuppressant drug, or any immunoglobulin preparation within three months of vaccination and until the completion of the Day 21 visit. Low doses of nasal or inhaled glucocorticoids and topical steroids are permitted;
9. 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.
10. History of allergy to any of the constituents of the Quadrivalent VLP Influenza Vaccine or a tobacco allergy;
11. History of anaphylactic allergic reactions to plants or plants components;
12. Any history of serious asthma (e.g. status asthmaticus, hospitalization for asthma control) in the last three years;
13. Use of antihistamines 48 hours prior to study vaccination;
14. The 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. Subjects 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-hour period is met;
15. Subjects who have a dermatological condition at the injection site that may interfere with injection site reaction rating;
16. Subjects who have received a blood transfusion within 90 days prior to study vaccination;
17. Any female subject who has a positive or doubtful pregnancy test result prior to vaccination or who is lactating;
18. Presence of any febrile illness (including oral temperature [OT] $\geq$ 38.0 ˚C within 24 hours prior to vaccination). Such subjects may be re-evaluated for enrolment after resolution of illness;
19. Cancer or treatment for cancer within three years of study vaccine administration. Persons with a history of cancer who are disease-free without treatment for three years or more are eligible. Individuals with treated and uncomplicated basal cell carcinoma of the skin or with non-treated, non-disseminated local prostate cancer are eligible;
20. 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. Immediate family members of the Investigator or employees of a clinical site can participate in the study at

another clinical site, as long as the Investigator or employees are not involved in the study at that site;

21. Subject 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. Any AEs associated with the new or changed medication use must also be documented.

Concomitant medications must be reported in the eCRF (reason for use, dates of administration, dosage, frequency, 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;
- Any concomitant medication use 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.

5.4 Prohibited Therapy

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. 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.).

Please refer to Section 5.2 (exclusion criteria numbers 3, 4, 5, 6, 7, 8, 9, 13, 14, and 19) for details on medications or therapies prohibited prior to randomization and/or during the conduct of this study.

6 TREATMENT ALLOCATION AND BLINDING

6.1 Randomization

Randomization will be stratified by site. Subjects will be randomized to one of three treatment groups, based on a computer-generated randomization schedule prepared by or under the supervision of Medicago before the study. The randomization system will assign the treatment group.

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. 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.

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 or designee as soon as possible after the unblinding to discuss the case.

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 AEs or reactogenicity of the subjects following vaccination.

This study is blinded through to the end of the study.

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 (one of three lots of 30 µg/strain of Quadrivalent VLP Influenza Vaccine). The volume of injection will be 0.5 mL for all treatments.

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.

On Days 0 and 21, a serology sample for HI response analysis will be collected for all 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 serologic measures (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.

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. 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 Investigational Product Management Manual for details).

10 STUDY EVALUATIONS

10.1 Study Procedures

10.1.1 Overview

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

Subjects who complete the study will have blood volumes of 20 mL drawn (Table 4).

Table 4 Estimated Blood Volume Drawn

Type of Sample	Volume per Sample (mL)	Number of Samples per Subject	Total Volume of Blood per Subject (mL)
HI titers	10	2	20

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. They 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 must be 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, and height) data in metric units. 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 include significant problems active at the time of Screening and present within the preceding year. Problems that have been clinically inactive for more than one year 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 blood pressure (BP), heart rate (HR), and OT. The OT will be collected in degrees Celsius using a digital thermometer and 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). The 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 an Investigator;
- Collect a urine sample for all female subjects and a perform urine dipstick pregnancy test. No study vaccine must be administered 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 response system (IRT); the subject's treatment group will be automatically assigned by this system;
- Collect a baseline blood sample for HI assessment and prepare and store the sample 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, using a 25 gauge needle of sufficient length to reach the substance of the muscle (at least 1 inch or 2.5 cm or longer). Needle length will be based on the subject's BMI: for subjects with a BMI > 30 kg/m^2, the use of a 1.5 inch or 3.8 cm needle is recommended. 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 arm used for 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 an MA, a measurement device template for measuring (in mm) solicited local reactions of erythema (redness) and swelling, and a digital thermometer for recording daily temperature (in degrees Celsius). Each subject will be provided with the following instructions:
  - How to collect his/her OT in degrees Celsius with the provided digital thermometer (the preferred route for temperature measurement is oral):
    - From Day 0 to Day 7, the subject will measure his/her OT at approximately the same time (preferably in the evening) and will record the results in the MA;
    - 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 MA. In the event that a temperature ≥ 38.0 °C 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). The subject is to document medication intake in the MA, 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 from Day 0 to Day 7 (preferably in the evening); the results will be recorded in the MA. 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 5;
- How to grade, on a daily basis from the Day 0 to Day 7 (preferably in the evening), each of the solicited systemic reactions and their severity (as per the same guidance used for solicited local reactions; see Table 5) (FDA, 2007) and to record the worst grade of the day for each of these solicited systemic reaction in the MA. The instructions will include how to examine and grade swelling in the neck and axilla and to record any unusual feeling and/or swelling in the MA;
- To use their MA to support their recall in providing information during the scheduled phone interview conducted on Days 1 and 8 and to bring their MA with them to the Day 21 clinic visit. The staff will review the MA entries and grade these entries with the subject;
- To record new use of medication in their MA, in addition to each intake of PRN drugs;
- 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;
- 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 at least 15-minute observation period (allowed window of + 15 minutes) is completed, measure vital signs (BP, HR, and OT) as described in Section 10.3.1.3. 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 (preferably in the evening) each day from Day 0 to Day 7;
- 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;

- 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 Day 1 (+ 1 day) and Day 8 (- 1 day/+ 1 days) phone contact:

- Ask the subjects to use their MA to support their recall in providing information during the scheduled phone interview;
- Ask the subjects about any difficulties in completing the MA, 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 and to record this information on the appropriate MA pages. Remind the subjects to record PRN intake;
- 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 bring back the MA for their Day 21 visit;

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 Day 21 (Visit 2)

The following procedures will be performed during the Day 21 (-2/+3 days) visit:

- Collect and review the MA content with the subject to ensure appropriate completion. Corrections must be made by the subject him/herself and all corrections must be initialed and dated. In the event that a subject is not able to make the correction him/herself, the site personnel will be authorized to enter a clarification in the comments section of the MA with a proper explanation. The original MA will be kept in subject's chart;
- Record any changes in the subject's health, any complaints of lymphadenopathy, any visits to health care facilities and/or medical practitioners, and any concomitant medication use

(including any vaccines received) since the Day 8 phone contact and confirm that the subject has continued to comply with the protocol requirements (e.g. no use of prohibited concomitant medications, use of an adequate contraceptive method);

- Perform a lymphadenopathy examination if the subject complains of arm or shoulder pain of the vaccinated arm or neck pain at the time of the visit (a directed exam for lymph node swelling of the neck and axilla). In addition, a history/symptom-directed physical examination can also be performed, based on the Investigator's opinion. These examinations should be performed by the Investigator;
- Collect a blood sample for HI assessment and prepare and store the sample until shipment to the analytical laboratory;
- Collect a urine sample for all female subjects and a perform urine dipstick pregnancy test.

Any subject who withdraws consent from the study prior to completion of the Day 21 visit will be asked to return their MA to the clinic site and to provide an update on their health status and concomitant medication usage (if the subject agrees).

10.2 Immunogenicity

10.2.1 Evaluations

Immunogenicity will be evaluated by the humoral immune response (HI assay) induced in subjects on Day 0 and Day 21.

10.2.2 Immunogenicity Endpoints

10.2.2.1 Primary Immunogenicity Endpoints

- GMTs of the three vaccine lots (21 days after vaccination) for all four vaccine strains:
  - Lot-to-lot consistency is based on adjusted GMT ratios for pairwise comparisons of the lots (lot 1/lot 2, lot 1/lot 3, and lot 2/lot 3). Lot-to-lot consistency will be demonstrated if the two-sided 95 % CI limit falls between 0.67 and 1.5 for all four strains.

10.2.2.2 Secondary Immunogenicity Endpoints

- HI antibody response induced by the Quadrivalent VLP Influenza Vaccine (pooled data from the three lots) against the homologous influenza strains on Days 0 and 21; HI antibody titers will be analyzed as follows:
  - SC rate: the proportion of subjects 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 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: 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 for SC rate and SP rate.

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), and unsolicited SAEs, NOCDs, and AEs up to 21 days post-vaccination.

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 Day 0 to Day 7 (preferably in the evening), subjects will measure and record their local and systemic reactions in their MA.

The intensity of the solicited local and systemic reactions will be graded as: mild (1), moderate (2), severe (3) or potentially life threatening (4), as defined below in Table 5. 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 5 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

Symptoms	Severity				
	None	**Grade 1 (Mild)**	**Grade 2 (Moderate)**	**Grade 3 (Severe)**	**Grade 4 (Potentially life-threatening)**
Solicited Systemic Reactions					
Fever (ºC)	< 38.0 ºC	38.0 - 38.4 ºC	38.5 - 38.9 ºC	39.0 - 40.0 ºC	> 40.0 ºC
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 recorded in the source documents or MA and reported in the "Adverse Event" form in the subject's eCRF, irrespective of intensity or whether or not they are considered to be vaccination-related.

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 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.

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

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

10.3.1.4 Physical Examinations

A history/symptom-directed physical examination will be performed by the Investigator as part of screening procedures (prior to eligibility assessment on Day 0) and on Day 21 (if deemed necessary by the Investigator). In addition, on Day 21, a lymphadenopathy examination (a directed exam for lymph node swelling of the neck and axilla) will be performed for subjects who complain of arm or shoulder pain of the vaccinated arm or neck pain at the time of the visit.

10.3.2 Pregnancy

A urine dipstick pregnancy test will be performed prior to vaccination and during the Day 21 visit. 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 or elective termination of a pregnancy for non-medical reasons are not considered to be an AE or 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 to be 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

- 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 Day 21.

10.3.4 Memory Aid

The MA is considered to be a critical source document that facilitates and ensures accurate reporting of reactions and illnesses by subjects through the inclusion of both the space for subjects to record data and instructions on what and how to record information. These documents will be collected by the clinical sites on Day 21 and kept with each subject's study chart. Review of the MA will be done by clinic site staff. Any required corrections noted at the time of the Day 21 visit may be made by the subjects; otherwise clinic staff will make corrections after confirmation by the subject (when appropriate). In the event the MA is lost by the subject, information collected by the coordinator or designee and information recalled by the subject will serve as the source data for this subject. The recalled information will be captured in the source documents.

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 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 who 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 who have signed the ICF and are eligible for enrolment, but who were either not randomized or randomized and not treated.

Tracking 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 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 the 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 prior to completion of the Day 21 visit, for whatever reason. Withdrawal subjects will not be replaced. Withdrawal subjects who received the study medication will be asked to return to the clinical site for a final assessment. The procedures performed for the final assessment will comprise those of the Day 21 visit, 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.

11.3.1 Follow-up of Discontinuations

All subjects who receive a study vaccine will be followed for safety until the end of the Day 21 visit, 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 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 immunogenicity and safety data is outlined below. Complete details will be provided in the SAP.

12.1 Analysis Populations

12.1.1 Safety Analysis Set

The SAS is defined as all subjects who received one of the study treatments. All safety analyses will be performed using the SAS, according to the treatment the subjects actually received (when applicable).

12.1.2 Full Analysis Set

The FAS will consist of the subset of subjects in the SAS with Day 0 and Day 21 immunogenicity assessments.

Subjects who receive the wrong treatment will be analyzed as randomized.

12.1.3 Per Protocol Set

The PP set will consist of the subjects with no major deviations related to the analyses and with Day 0 and Day 21 immunogenicity assessments. Subjects who had blood samples for immunogenicity collected outside of the time window are to be excluded from the PP set. Subjects who received the wrong vaccine, but for whom the treatment received can be unequivocally confirmed, will be analyzed in the PP set as treated, provided they have no other deviations that could compromise their data. The PP set will be the primary analysis population for the primary immunogenicity endpoint.

12.2 Sample Size Determination

Based on data from the CP-Q14VLP-009 study, a sample size of 400 subjects per lot (a total of 1,200 subjects) will have a greater than 90 % power to test the consistency criterion between the lots (i.e. to test that the pairwise comparisons of the two-sided 95 % CI limit for adjusted GMT ratios of the three lots being tested [lot 1/lot 2, lot 1/lot 3, lot 2/lot 3] fall within the equivalence range of 0.67 to 1.5 for all four vaccine strains).

A drop-out rate and exclusion from the PP set of approximately 10 % was assumed in the sample size calculation.

12.3 Immunogenicity Analyses

Immunogenicity 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). In general, continuous data will be summarized using descriptive statistics (i.e. mean or geometric mean, CI, median, standard deviation, minimum, and maximum). Categorical data will be summarized using the number and percent of subjects in each category.

12.3.1 Analysis of Primary Endpoints

The primary immunogenicity endpoint is defined in Section 10.2.2.1.

The immunologic equivalence of three consecutive production lots of the Quadrivalent VLP Influenza Vaccine will be measured in terms of GMTs, as measured by HI assay, for all vaccine influenza strains. Lot-to-lot consistency is based on adjusted Day 21 GMT ratios for pairwise comparisons of the lots (lot 1/lot 2, lot 1/lot 3, lot 2/lot 3); for each pairwise comparison of the lots, the lot-to-lot consistency will be demonstrated if the two-sided 95% CIs on the adjusted Day 21 GMT ratios fall within the equivalence range of 0.67 to 1.5 for all four vaccine strains in the investigational product. The adjusted Day 21 GMT ratios and the 95 % CI of the ratios will be calculated via an analysis of covariance (ANCOVA) model and back-transformation.

12.3.2 Analysis of Secondary Endpoints

The secondary immunogenicity endpoints are defined in Section 10.2.2.2.

The secondary immunogenicity analysis will be conducted on the pooled data of the three lots. The point estimates and the corresponding two-sided 95 % CI will be calculated to determine if the CI meets the CBER criteria for SC rate and SP rate.

12.4 Baseline and Subject Disposition

Demographic data will be presented in listings and summarized by vaccine lot (treatment group). 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, and ethnicity.

The frequency of subjects for 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.

Safety and tolerability endpoints (immediate complaints, solicited local and systemic reactions, and TEAEs, SAEs, and NOCDs) will be summarized using descriptive statistics by individual vaccine lot and as pooled data of all three lots. Listings of safety data will be provided.

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 a post-vaccination onset will be included in the safety analyses.

Additional attention will be given to the safety data from those subjects who die, who discontinue from the study due to an AE, who experience a severe AE or 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).

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 puts 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 (e.g. any cases of newly diagnosed cancer).

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 recorded in the source documents or MA and reported in the "Adverse Event" form in the subject's eCRF, irrespective of intensity or whether or not they are considered to be vaccination-related.

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 study 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. Few 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 be 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.

Any NOCDs will be collected from vaccination on Day 0 to the end of the Day 21 visit 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

Any 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 Day 21 visit. 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 designee) within 24 hours of the Investigator learning of the event. The

Investigator must also complete, sign, and date the SAE report form, and send, via e-mail, a copy to the safety e-mail address:

Medicago-Safety@medicago.com

Sponsor Safety Contact: PPD

13.1.7 Follow-up Reporting by the Investigator

All SAEs, regardless of relationship to study vaccination, 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 Detection Period or Study Termination

All SAEs occurring during the study will be followed until resolution or for a period of 30 days from the final subject's visit, regardless of conclusion of the study.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE detection period (after the Day 21 visit). 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.

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

13.1.10 Reporting of SAEs to Health Authorities and IRB

Medicago 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 IRB as soon as possible, and will also provide the IRB with any safety reports prepared by Medicago.

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 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 2016-2017 influenza virus strains in the Northern hemisphere, assembled into VLPs, and produced in a plant-based (*Nicotiana benthamiana*) transient expression system. The transfer vector used to insert the plasmids (containing the constructs for proteins of interest) into the plant for expression is a bacterium, *Agrobacterium tumefaciens*. The hemagglutinin protein sequences utilized in the expression constructs are all obtained from viruses isolated from humans, not from egg- or cell-grown viruses.

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 indicated virus strains, in a phosphate buffered saline 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 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 for a final dose of 30 µg/strain.

14.1.2 Independence between Vaccine Lots

Three lots of the quadrivalent VLP drug product (DP) will be used in this study. Each DP lot will be manufactured separately and will be obtained by mixing four strains of monovalent VLP drug substance (DS). Each DS lot within a DP lot represents the recombinant hemagglutinin proteins expressed as VLPs of one of the four influenza virus strains recommended by WHO for the 2016-2017 season in the Northern hemisphere. Each DS lot will be manufactured separately.

14.1.3 Preparation and Administration of Study Vaccine

The study treatments will be prepared by staff members at the clinical site as described in the Investigational Product Management Manual. The study treatment will subsequently be administered to subjects by a staff member at the clinic site.

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 individual 30 µg/strain vaccine dose lots, the site will use a pre-filled syringe labelled with study protocol CP-PRO-QVLP-011, the lot number/treatment number identification, an indication that the product is for clinical use only, the concentration of 60 µg/strain/mL, and with the dose of 0.5 mL (30 µg/strain).

The 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 one of the three lots of Quadrivalent VLP Influenza Vaccine (30 µg/strain) 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.

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 is completed by Medicago (or its designee), all study treatments (used and unused syringes) will be returned to Medicago in accordance with instructions provided in the Investigational Product Management Manual. When the site is authorized by Medicago to destroy study drug supplies on site, this must be documented. Instructions will be provided by Medicago, when applicable.

Further specific information relating to treatment preparation, storage, and shipment will be 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 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.

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 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 used and 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.

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.

The GCP standard 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) or 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 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 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 regulatory authority, as applicable. A study may not be initiated until all 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 and AEs 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 will be provided for each subject who is randomized and receives a dose of study drug. Screening failures will also be entered in an eCRF; the 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 a 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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McElhaney, J.E. (2011). Influenza Vaccine Responses in Older Adults. Ageing Res Rev, 10(3), 379-388. doi:10.1016/j.arr.2010.10.008

Molinari, N. A., Ortega-Sanchez, I. R., Messonnier, M. L., Thompson, W. W, Wortley, P. M., Weintraub, E., & Bridges, C. B. (2007). The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine, 25(27), 5086-5096.

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19 APPENDICES

19.1 Appendix 1 – Sample Memory Aid Diary (Day 0 to Day 21)

MEMORY AID (DAY 0 to DAY 21)	
Study Name	A Randomized, Observer-blind, Multicenter, Phase 3 Study to Evaluate the Lot Consistency, Immunogenicity, and Safety of a Plant-Derived Quadrivalent VLP Influenza Vaccine in Healthy Adults 18-49 Years of Age
Protocol Number	CP-PRO-QVLP-011
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

SYMPTOMS (pages 4 to 6):

- Complete the table referring to the following periods:
  - For the 1st column: the period between the vaccination and the 15 minutes post-dose
  - For the 2nd column: to the period between the vaccination and the evening
  - For the remaining columns: the period since the previous evaluation of the symptoms
- If the symptom is not present, indicate 0.
- If the symptom is present, a grade should be indicated.
- Use the measuring tool given to you at the site to estimate the size of the red/swollen area around the injection site. Indicate the grades for the Redness and Swelling at injection site on the next page.
- Evaluate the grade of all other symptoms according to the definitions:
  - **0= No symptom**
  - **1= Mild: Does not interfere with activity**
  - **2= Moderate: Repeated use of non-narcotic pain reliever (e.g. Advil, Tylenol) >24 hours or interferes with activity**
  - **3= Severe: Any use of narcotic pain reliever (e.g. codeine, morphine) or prevents daily activity**
  - **4= Potentially life-threatening: Visit to Emergency room or hospitalization**
- List any other problems (not listed on pages 4 to 6) on page "side effects (symptoms)".
- Symptoms listed on pages 4 to 6 which persist longer than 7 days after study vaccine administration should also be listed on page "side effects (symptoms)".

SIDE EFFECTS (Symptoms) and MEDICATION:

- Use the space provided to record important information that you want to tell us about changes in your health. Note any health problems you experience, worsening of previous problems, or new medicines you take. Examples may include prescription drugs (including vaccines), over-the-counter drugs, herbal supplements and/or vitamins.
- It is especially important that you make a note of problems that required a visit to your doctor, a hospital stay, or a visit to emergency room.
- It is also important that you make a note of changes in your medications.
- Each medication must be associated to a problem, but each problem does not require a medication associated with it.
- Indicate the start and stop date (when available) for each symptom and medication. However, if it is still ongoing at the Day 21 visit, you will be required to tick the ongoing checkbox.

You received the study vaccine on: |_|_| |_|_|_| |_|_|_|_| (dd mmm yyyy) at: |_|_| : |_|_| (hh mm)

MEMORY AID (DAY 0 to DAY 21)										
Day 0 to Day 7		**15 min, Post-dose**	**Evening, day of dose**	**1 Day after dose**	**2 Day after dose**	**3 Day after dose**	**4 Day after dose**	**5 Day after dose**	**6 Day after dose**	**7 Day after dose**
Date (dd-mmm-yyyy)										
Oral Temperature	°C									
	Causality									
Redness where the injection was given	Grade									
	Use the measuring tool given to you at the site to estimate the size of the red area around the injection site and indicate the grade above.									
Swelling where the injection was given	Grade									
	Use the measuring tool given to you at the site to estimate the size of the swollen area around the injection site and indicate the grade above.									
Pain at vaccine injection site	Grade									
	0= No symptom; **1= Mild**: Does not interfere with activity; **2= Moderate**: Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity; **3= Severe**: Any use of narcotic pain reliever or prevents daily activity; **4= Potentially life-threatening**: Visit to Emergency room or hospitalization.									
MD initials and date:	dd mmm yyyy									
Comments: ❑ N/AP										

MEMORY AID DIARY (DAY 0 to DAY 21)										
Day 0 to Day 7		**15 min, Post-dose**	**Evening, day of dose**	**1 Day after dose**	**2 Day after dose**	**3 Day after dose**	**4 Day after dose**	**5 Day after dose**	**6 Day after dose**	**7 Day after dose**
Headache	Grade									
	Causality									
Muscle aches	Grade									
	Causality									
Joint aches	Grade									
	Causality									
Fatigue	Grade									
	Causality									

GRADES **0= No symptom**; **1= Mild**: Does not interfere with activity; **2= Moderate**: Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity; **3= Severe**: Any use of narcotic pain reliever or prevents daily activity; **4= Potentially life-threatening**: Visit to Emergency room or hospitalization.

MD initials and date: |__|__| |__|__|__| |__|__|__|__|
dd mmm yyyy

Comments: ❑ N/AP

MEMORY AID DIARY (DAY 0 to DAY 21)

Day 0 to Day 7		15 min, Post-dose	Evening, day of dose	1 Day after dose	2 Day after dose	3 Day after dose	4 Day after dose	5 Day after dose	6 Day after dose	7 Day after dose
Chills	Grade									
	Causality									
Feelings of general discomfort or uneasiness	Grade									
	Causality									
Feeling of swelling in the neck	Grade									
	Causality									
Feeling of swelling in the axilla	Grade									
	Causality									

GRADES **0= No symptom**; **1= Mild**: Does not interfere with activity; **2= Moderate**: Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity; **3= Severe**: Any use of narcotic pain reliever or prevents daily activity; **4= Potentially life-threatening**: Visit to Emergency room or hospitalization.

MD initials and date: ☐☐ ☐☐☐ ☐☐☐☐ (dd mmm yyyy)

Comments: ❑ N/AP

MEMORY AID DIARY (DAY 0 to DAY 21)

Day 0 to Day 21 ❑ Nothing to report

#	Side Effects (symptoms)	Grade (See below)	Date and time it started	Date and time it ended	Did you receive medical care?	Validated with subject
			dd mmm yyyy hh : mm	dd mmm yyyy hh : mm ❑ Ongoing at Day 21	❑ Yes ❑ No	❑
			dd mmm yyyy hh : mm	dd mmm yyyy hh : mm ❑ Ongoing at Day 21	❑ Yes ❑ No	❑
			dd mmm yyyy hh : mm	dd mmm yyyy hh : mm ❑ Ongoing at Day 21	❑ Yes ❑ No	❑

GRADES	**0= No symptom**; **1= Mild**: Does not interfere with activity; **2= Moderate**: Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity; **3= Severe**: Any use of narcotic pain reliever or prevents daily activity; **4= Potentially life-threatening**: Visit to Emergency room or hospitalization.

Comments: ❑ N/AP

MEMORY AID DIARY (DAY 0 to DAY 21)

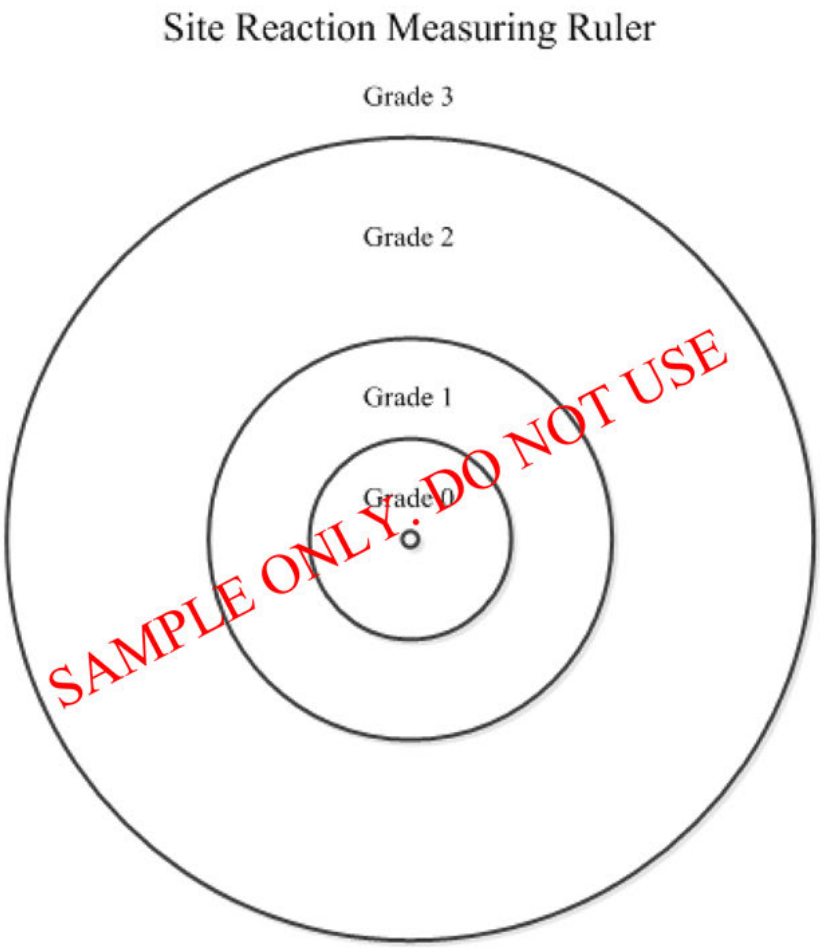
Day 0 to Day 21 ❑ Nothing to report

#	Medication (Name, Dose, Route and Frequence)	Date and Time		Reason(s) why you are taking this medication?	Validated with subject
		Started	Stopped		
		dd mmm yyyy hh : mm	dd mmm yyyy hh : mm ❑ Ongoing at Day 21		❑
		dd mmm yyyy hh : mm	dd mmm yyyy hh : mm ❑ Ongoing at Day 21		❑
		dd mmm yyyy hh : mm	dd mmm yyyy hh : mm ❑ Ongoing at Day 21		❑

Dose			Route			Frequency		
Capsule	mg/kg	Teaspoon	Intraocular	Intravenous	Topical	As needed	Every hour	Intermittent
g	mL	Unit/kg	Intramuscular	Nasal	Transdermal	Once	Every 2 hours	Continuous
IU	Puff Tablespoon	Units	Inhalation	Oral	Vaginal	Once a day	1x per week	Unknown
mcg	Tablet	Unknown	Intralesional	Rectal	Intrauterine	Twice a day	2x per week	
mg			Intraperitoneal	Subcutaneous	Unknown			

Comments: ❑ N/AP

19.2 Appendix 2 – 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