Clinical Protocol

A Randomized, Partially-Blinded, Active Comparator-Controlled, Dose-Ranging, Safety, Tolerability, and Immunogenicity Phase 1/2 Study of an Adjuvanted Seasonal Recombinant Quadrivalent VLP Influenza Vaccine in Adults 65 Years of Age and Older

CP-PRO-AdjQVLP-020; Phase 1/2

Adjuvanted Recombinant Quadrivalent VLP Influenza Vaccine

Name of Sponsor:	Medicago USA Inc. 7 Triangle Drive Durham (NC), United States 27713
Status:	Final version 5.0
Date:	23-Feb-2022

SIGNATURES

Study Title:	A Randomized, Partially-Blinded, Active Comparator-Controlled, Dose-Ranging, Safety, Tolerability, and Immunogenicity Phase 1/2 Study of an Adjuvanted Seasonal Recombinant Quadrivalent VLP Influenza Vaccine in Adults 65 Years of Age and Older
Study Author(s):	PPD

I confirm that Medicago USA Inc. has approved the version 5.0 (dated 23-Feb-2022) of the protocol CP-PRO-AdjQVLP-020 and agree that it may be issued to the relevant authorized study personnel, Independent Ethics Committees and Regulatory Authorities.

PPD PPD 2022-02-24 | 12:30 PM EST
Medicago Date (YYYY-MM-DD)

PPD PPD 2022-02-25 | 3:53 PM EST
Medicago Date (YYYY-MM-DD)

PPD PPD 2022-02-23 | 1:19 PM EST
Medicago Date (YYYY-MM-DD)

SIGNATURES (continued)

PPD PPD 2022-02-24 | 6:28 PM EST

PPD Date (YYYY-MM-DD)

Medicago

PPD PPD 2022-02-23 | 9:23 AM PST

PPD Date (YYYY-MM-DD)

Medicago

COORDINATING INVESTIGATOR SIGNATURE

Study Title:	A Randomized, Partially-Blinded, Active Comparator-Controlled, Dose-Ranging, Safety, Tolerability, and Immunogenicity Phase 1/2 Study of an Adjuvanted Seasonal Recombinant Quadrivalent VLP Influenza Vaccine in Adults 65 Years of Age and Older

I have read the version 5.0 (dated 23-Feb-2022) Protocol No. CP-PRO-AdjQVLP-020 titled, "A Randomized, Partially-Blinded, Active Comparator-Controlled, Dose-Ranging, Safety, Tolerability, and Immunogenicity Phase 1/2 Study of an Adjuvanted Seasonal Recombinant Quadrivalent VLP Influenza Vaccine in Adults 65 Years of Age and Older".

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

Coordinating Investigator:

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.

INVESTIGATOR AGREEMENT

I have read the version 5.0 (dated 23-Feb-2022) Protocol No. CP-PRO-AdjQVLP-020 titled, "A Randomized, Partially-Blinded, Active Comparator-Controlled, Dose-Ranging, Safety, Tolerability, and Immunogenicity Phase 1/2 Study of an Adjuvanted Seasonal Recombinant Quadrivalent VLP Influenza Vaccine in Adults 65 Years of Age and Older".

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

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

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

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

Principal Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

Telephone Number: _____

_____ _____

Signature Date (YYYY-MM-DD)

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

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SYNOPSIS

Sponsor:	Medicago USA Inc.
Investigational Product:	Adjuvanted Recombinant Quadrivalent VLP Influenza Vaccine (QVLP)
Active Substance(s):	Mix of recombinant H1, H3, and two B hemagglutinin proteins expressed as virus-like particles (VLP) for the 2020-2021 Northern Hemisphere influenza virus strains
Adjuvant	AS03 (produced by GlaxoSmithKline)
Control Products:	Active comparators: Fluzone® High-Dose Quadrivalent (produced by Sanofi Pasteur); 2020-2021 Northern Hemisphere influenza virus strains[1] (Fluzone HD Quad) QVLP (unadjuvanted) for the 2020-2021 Northern Hemisphere influenza virus strains
Protocol Title:	A Randomized, Partially-Blinded, Active Comparator-Controlled, Dose-Ranging, Safety, Tolerability, and Immunogenicity Phase 1/2 Study of an Adjuvanted Seasonal Recombinant Quadrivalent VLP Influenza Vaccine in Adults 65 Years of Age and Older
Protocol Number:	CP-PRO-AdjQVLP-020
Development Phase:	Phase 1/2
Study Center(s):	The study will be conducted at multiple sites.
Study Rationale:	This Phase 1/2 study is to assess the safety, tolerability, and immunogenicity of adjuvanted recombinant QVLP in healthy adults 65 years of age and older. One dose of the following vaccine formulations will be administered in this study: • 30 µg/strain of QVLP adjuvanted with AS03, or • 30 µg/strain of QVLP unadjuvanted, or • Fluzone HD Quad.

[1] Fluzone® High-Dose Quadrivalent is licensed in the US and expected to be commercially available for the 2020-2021 influenza season.

Planned Study Period:	The total planned study period is approximately 17 months. Subject enrollment will continue for approximately 4 to 5 months. Biological samples for immunogenicity assessments will be collected over 4 weeks post-vaccination, and long-term safety follow up and evaluation of durability of the immune responses will continue 6 and 12 months after administration of the vaccines.
Study Objectives **Primary Objectives:**	The primary objectives of the study are: **Safety:** • To assess the safety and tolerability of a single dose of QVLP (30 µg/strain) with AS03 adjuvant compared to QVLP (30 µg/strain) (unadjuvanted) and Fluzone HD Quad; **Immunogenicity:** • To assess the immunogenicity of a single dose of QVLP (30 µg/strain) with AS03 adjuvant compared to QVLP (30 µg/strain) (unadjuvanted) and Fluzone HD Quad, as measured by hemagglutination inhibition (HI) assay against homologous influenza strains.
Secondary Objectives:	The secondary objectives of this study are: **Immunogenicity:** • To assess the immunogenicity of a single dose of QVLP (30 µg/strain) with AS03 adjuvant compared to QVLP (30 µg/strain) (unadjuvanted) and Fluzone HD Quad, as measured by microneutralization (MN) assay against homologous influenza strains; • To assess the immunogenicity of a single dose of QVLP (30 µg/strain) with AS03 adjuvant compared to QVLP (30 µg/strain) (unadjuvanted) and Fluzone HD Quad, as measured by HI assay against heterologous influenza strains; • To assess the immunogenicity of a single dose of QVLP (30 µg/strain) with AS03 adjuvant compared to QVLP (30 µg/strain) (unadjuvanted) and Fluzone HD Quad, as measured by HI (homologous and heterologous influenza strains) and MN (homologous influenza strains) assays, stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination; • To evaluate the persistence of antibody responses, as determined by HI titers against homologous influenza strains, at 6 and 12 months post-vaccination; **Safety:** • To assess the safety and tolerability of a single dose of QVLP (30 µg/strain) with AS03 adjuvant compared to QVLP

	(30 µg/strain) (unadjuvanted) and Fluzone HD Quad, stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination.
Number of Planned Subjects:	Approximately 120 healthy adult subjects 65 years of age and older are planned for randomization in a 1:1:1 ratio to receive QVLP at a dose of 30 µg/strain with AS03 adjuvant or QVLP (30 µg/strain) (unadjuvanted) or Fluzone HD Quad.
Sample Size Determination:	The sample size up to approximately 120 subjects with 40 subjects in each treatment group will make it possible to perform the initial evaluation of vaccine immunogenicity and detect gross differences in rates of adverse events. The sample size is not large enough to detect all types of adverse reactions, including less frequent or rare events. The objective of this study is to quantify the type, percentage, duration, intensity, and relationship of common post-vaccination safety events to determine if they differ clinically among the treatment groups.
Study Population:	Healthy male and female subjects 65 years of age and older will be included in the study.
Dosage and Administration:	On Day 0, subjects will receive one intramuscular (IM) injection into the deltoid region of the non-dominant (if possible) arm, of their assigned treatment: • 30 µg/strain of QVLP adjuvanted with AS03, or • 30 µg/strain of QVLP unadjuvanted, or • Fluzone HD Quad. The volume of injection will be 0.7 mL for all treatments.
Study Design:	This is a randomized, partially-blinded, active comparator-controlled, multicenter, Phase 1/2 dose-finding, safety, tolerability and immunogenicity study. The influenza strain composition of the vaccines used in this study will be based on the recommended World Health Organization (WHO) strains for vaccination in the 2020-2021 season in the Northern Hemisphere. Approximately 120 healthy male and female subjects 65 years of age and older will be enrolled into three treatment groups: QVLP given at a dose level of 30 µg/strain with AS03 adjuvant or QVLP (30 µg/strain) (unadjuvanted) or Fluzone HD Quad.

	<table><tr><th>Treatment Group</th><th>Treatments</th><th>Dose Level</th><th>No. of Subjects</th></tr><tr><td>1</td><td>QVLP adjuvanted with AS03</td><td>30 µg/strain</td><td>40</td></tr><tr><td>2</td><td>QVLP unadjuvanted</td><td>30 µg/strain</td><td>40</td></tr><tr><td>3</td><td>Fluzone HD Quad</td><td>60 µg/strain</td><td>40</td></tr></table> The first 3 subjects per treatment group enrolled in the study will receive an IM injection of one of the three treatments listed in the table above. The vaccinations for the first three subjects in each treatment group will be staggered so that each vaccination must be performed at least 30 minutes apart. The seven-day safety data will be collected from these subjects and reviewed by the Independent Data Monitoring Committee (IDMC), prior to permitting the vaccination of the remaining subjects in these three treatment groups. Subjects will be screened up to seven days in advance of the vaccine administration and will demonstrate a satisfactory baseline medical assessment by medical history, general physical examination, urinalysis, haematological and blood biochemistry analyses, and serum screening for HIV, Hepatitis B and Hepatitis C markers. On Day 0, vaccine administration will occur. Phone contacts will be made one day and eight days after the vaccine administration, specifically for review of the subject's safety and concomitant medication data. Visits to the Investigator site will occur 3 days after the vaccine administration (Day 3) for key safety assessments and 28 days after the vaccine administration (Day 28) for key safety and immunogenicity assessments. Subjects will have monthly telephone calls after Day 28 up to the end of the study. Subjects will return to the Investigator site on Day 182 for immunogenicity and safety assessments (6-month follow-up) and on Day 365 for final immunogenicity and safety assessments (12-month follow-up). Subjects enrolled and vaccinated in the QVLP (15 µg/strain and 45 µg/strain) adjuvanted with AS03 adjuvant (full dose or half dose) and the QVLP (30 µg/strain) adjuvanted with AS03 adjuvant (half dose) treatment groups will complete study procedures as outlined above and will be followed for safety and immunogenicity assessments up to Day 365.
Blinding	In this study, a partially-blinded design is applied whereby the following individuals will not have access to treatment allocation (i.e. remain "blind") throughout the entire study duration: the subjects, the Investigators and all personnel involved in the clinical conduct of the study (except the staff

	involved in the preparation and administration of the study vaccine, the quality assurance auditor, and quality control reviewers), Medicago clinical staff and medical staff involved in safety evaluations (e.g. causality assessments), and all personnel involved in sample analysis at the central and testing (HI and MN) laboratories. The IDMC and the independent statistician involved in the preparation of the safety data summary for the IDMC reviews will have access to or be aware of treatment allocation (i.e. be "unblinded"). The IDMC will review safety data and will make recommendations for the entire duration of the study. In addition, select personnel of the third-party statistical team will have access to treatment allocation (i.e. be "unblinded") for the entire duration of the study since these personnel will be involved in the Day 28 data analysis and the Day 182 data analysis (see Statistical Methods section below). A small number of Medicago personnel will have access to the Day 28 and Day 182 data analyses (i.e. be "unblinded" to results and/or treatment allocation) and will be able to look at data throughout the study. The Medicago personnel will include senior personnel in Scientific and Medical Affairs, Biostatistics, Safety, Product Development, and Regulatory Affairs.
Safety Evaluations:	Clinical safety assessments will include repeated urine, blood chemistry and haematology testing. Safety and tolerability endpoints will include immediate adverse events (AEs) (30 minutes post-vaccination), solicited local and systemic AEs (up to seven days post-vaccination), unsolicited AEs up to Day 28, serious AEs (SAEs), AEs leading to withdrawal, AEs of special interest (AESIs), medically attended AEs (MAAEs), new onset of chronic diseases (NOCDs), and deaths up to the end of the study (Day 365).
Immunogenicity Evaluations:	Vaccine immunogenicity will be evaluated on Day 0, Day 28, Day 182, and Day 365, as measured by the serum HI and on Day 0 and Day 28 as measured by MN antibody titers.
Primary Endpoints:	**Safety:** The primary safety endpoints are: • Occurrences, intensity, and relationship to vaccination of immediate AEs (30 minutes post-vaccination);

	• Occurrences and intensity of solicited local and systemic AEs (for seven days following study vaccine administration); • Occurrences, intensity, and relationship of unsolicited AEs for 28 days following study vaccine administration; • Number and percentage of subjects with normal and abnormal, clinically significant urine, haematological and blood biochemistry values, and urinalysis at Days 0, 3, and 28; • Occurrences of SAEs, AEs leading to withdrawal, AESIs, MAAEs, NOCDs, and deaths up to Day 28; • Occurrences of SAEs, AEs leading to withdrawal, AESIs, MAAEs, NOCDs, and deaths from Day 29 up to Day 182; • Occurrences of SAEs, AEs leading to withdrawal, AESIs, MAAEs, NOCDs, and deaths from Day 183 up to the end of the study (Day 365). **Immunogenicity:** The primary immunogenicity endpoint is: • HI antibody response induced by adjuvanted and unadjuvanted QVLP and Fluzone HD Quad against the homologous influenza strains on Day 28, compared to Day 0 values. HI antibody titers will be analyzed using the following parameters: geometric mean titers (GMT), seroconversion (SC) rate, seroprotection (SP) rate, and geometric mean fold rise (GMFR).
Secondary Endpoints:	**Immunogenicity:** The secondary immunogenicity endpoints are: • MN antibody response induced by adjuvanted and unadjuvanted QVLP and Fluzone HD Quad against the homologous influenza strains on Day 28, compared to Day 0 values. MN antibody titers will be analyzed using the following parameters: GMT, SC rate, and GMFR; • HI antibody response induced by adjuvanted and unadjuvanted QVLP and Fluzone HD Quad against the heterologous influenza strains on Day 28, compared to Day 0 values. HI antibody titers will be analyzed using the following parameters: GMT, SC rate, SP rate, and GMFR. • HI antibody response (against homologous and heterologous influenza strains) and MN antibody response (against homologous influenza strains) induced by adjuvanted and unadjuvanted QVLP and Fluzone HD

	Quad on Day 28, compared to Day 0 values, stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination; • Durability of antibody responses, as determined by HI titers against homologous influenza strains (6 and 12 months post-vaccination); **Safety:** The secondary safety endpoints are: • Occurrences, intensity, and relationship to vaccination of immediate AEs (30 minutes post-vaccination), stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination; • Occurrences and intensity of solicited local and systemic AEs (for seven days following study vaccine administration), stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination; • Occurrences, intensity, and relationship of unsolicited AEs for 28 days following study vaccine administration, stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination; • Number and percentage of subjects with normal and abnormal, clinically significant urine, haematological and blood biochemistry values, and urinalysis at Days 0, 3, and 28, stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination; • Occurrences of SAEs, AEs leading to withdrawal, AESIs, MAAEs, NOCDs, and deaths up to Day 28, stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination; • Occurrences of SAEs, AEs leading to withdrawal, AESIs, MAAEs, NOCDs, and deaths from Day 29 up to Day 182, stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination;

	• Occurrences of SAEs, AEs leading to withdrawal, AESIs, MAAEs, NOCDs, and deaths from Day 183 up to the end of the study (Day 365), stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination.
Statistical Methods:	**Populations:** Statistical analyses will be performed on pre-defined population sets (the safety analysis set [SAS], the intention-to-treat [ITT] set, and the per protocol [PP] set) according to the Statistical Analysis Plan (SAP). All safety analyses will be performed using the SAS. The analyses of all immunogenicity endpoints will be performed using the PP set and the ITT set. The analysis in the PP set will be considered the primary analysis for these objectives in order to collect information regarding the immunogenicity responses that most closely reflect the scientific model underlying the protocol. ITT set will be used as sensitivity analysis.
	Day 28 and Day 182 Data Analyses: The third-party statistical team will perform data analyses after Day 28 (last subject) and Day 182 (last subject). The data analyses will involve select individuals from the third-party statistical team and Medicago who will be unblinded (as described in Blinding section above). The Day 28 and Day 182 data analyses will allow discussions of the clinical data to inform study design decisions of the subsequent study, without having to wait until after the end of the follow-up period for study completion. **Statistical Analyses:** All descriptive and inferential statistical analyses will be performed using Statistical Analysis System® (SAS®) software (version 9.4 or higher). In general, categorical data will be summarized using the number and percent of subjects in each category and continuous data will be summarized using descriptive statistics (mean or geometric mean, median, standard deviation, minimum, and maximum). Analyses of the immunogenicity and safety endpoints will include each group as a whole as well as comparisons by prior influenza vaccination status, if >25% of the enrolled subjects

	have received a standard influenza vaccine during the 12 months prior to study vaccination. **Safety Analyses:** Safety and tolerability endpoints will be summarized by treatment using descriptive statistics. **Immunogenicity Analyses:** For both HI and MN, point estimates and two-sided 95 % CI for all immunogenicity endpoints and responses for the treatment groups will be calculated. GMT will be compared among treatment groups by using Analysis of Variance (ANOVA) on log-transformed data. GMFR will be derived by using Analysis of Covariance (ANCOVA) to model the difference in the log of the titer values between Day 28/182/365 and Day 0 for the HI assay and between Day 28 and Day 0 for the MN assay, with treatment group as main effect and baseline titer as covariate. For GMT and GMFR comparisons, Tukey's test will be performed to show p-values for the pairwise comparisons between treatment groups. Fisher's exact tests or chi square tests will be used to compare SC among treatment groups.

Table 1 Time and Events Schedule: General Information

Visit Type	Screening	Vaccination	Post-vaccination Visits/Contacts						
Study Day	Day -7 to 0	Day 0	Day 1 (+ 1)	Day 3 (± 1)	Day 8 (+ 1)	Day 28 (± 2)	Monthly Calls[8] (± 14)	Day 182 (± 14)[10]	Day 365 (± 14)
Visit Number	1	2	Phone	3	Phone	4	Phone	5	6
Informed consent	X								
Demographics	X								
Medical history/prior medication[7]	X	X[1]							
Inclusion/exclusion criteria[7]	X	X							
Physical examination[2]	X	X		X					
Vital Signs[7]	X	X[3]		X		X		X	X
Height, weight, and BMI[7]	X	X							
Urinalysis	X			X		X			
Blood chemistry and Hematology	X[9]			X		X			
Serum for HIV, Hepatitis B, and Hepatitis C	X								
Serum sample for HI and MN		X				X		X[11]	X[11]
Randomization		X							
Vaccine administration		X							
Immediate surveillance (30 minutes)		X							
Provide diary and memory aid instructions (manual or electronic)		X							
Oral digital thermometer and instructions on AEs[4]		X							
Collection of solicited local/systemic AEs		X	X	X	X				
Concomitant medications[5]		At any time during the study period							
AEs, SAEs, AESI, MAAEs, and NOCDs[6]		At any time during the study period							
Termination record									X

[1] Record any changes in medical history and medications and confirmation that the subject continues to meet all inclusion and no exclusion criteria since screening.

[2] A limited physical examination will occur at screening, Day 0, and Day 3. History/symptom-directed physical examinations may be at Day 28, Day 182, and Day 365 visits if 1) new complaints or concerns are raised by either the study subject or study staff and 2) deemed to be necessary by the Investigator.

[3] Record prior to study vaccine, after the observation period and as deemed necessary.

[4] After vaccination, subjects will be instructed on the diary and memory aid (manual or electronic) provided for their use for recording AEs and concomitant medication use.

[5] After the Day 28 visit, concomitant medication collection will be limited to those used to treat a NOCD, SAE, AE leading to withdrawal, AESIs, MAAEs, or an AE that occurred before Day 28; any vaccine not foreseen in the study protocol; and prohibited medications.

[6] AEs will be collected up to Day 28; SAEs, AEs leading to withdrawal, AESIs, MAAEs, and NOCDs will be collected through to the end of the study. Specific contacts for the collection of information regarding all these events will occur on Day 365 (during the Day 365 final visit) for SAEs, AEs leading to withdrawal, AESIs, MAAEs, and NOCDs.

[7] If screening and vaccination occur on the same day (Day 0), then this test and/or procedure should only be performed once prior to randomization.

Visit Type	Screening	Vaccination	Post-vaccination Visits/Contacts						
Study Day	Day -7 to 0	Day 0	Day 1 (+ 1)	Day 3 (± 1)	Day 8 (+ 1)	Day 28 (± 2)	Monthly Calls[8] (± 14)	Day 182 (± 14) [10]	Day 365 (± 14)
Visit Number	1	2	Phone	3	Phone	4	Phone	5	6

[8] Subjects should be reached once a month with no more than 45 days between phone contacts (use Day 28 date as starting reference).

[9] Sample blood collection at screening should be performed under fasting conditions (approximately 12 hours) for cholesterol and triglyceride analyses. Cholesterol and triglyceride analysis will only be performed at screening.

[10] For some subjects, the Day 182 visit may occur during the time the subject may want to receive the 2021-2022 seasonal influenza vaccine. Hence, the tests/procedures (including immunogenicity sample collection) originally planned for the Day 182 visit will be collected at the Day 182 timepoint or immediately prior to administration of the 2021-2022 seasonal influenza vaccine (whichever comes first).

[11] Only HI assay will be performed on the serum sample collected at Day 182 and Day 365.

ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
ANOVA	analysis of variance
BMI	body mass index
BP	blood pressure
CBER	Center for Biologics Evaluation and Research
CI	confidence interval
CMI	cell-mediated immune (response)
eCRF	electronic case report form
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
ITT	intention-to-treat
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MN	microneutralization
NACI	National Advisory Committee on Immunization
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
SRH	single radial hemolysis
TEAE	treatment-emergent adverse event
VLP	virus-like particle

WHO	World Health Organization
US	United States

1 INTRODUCTION

Seasonal influenza is a potentially serious infection associated with a wide range of clinical outcomes across the entire human lifespan. The influenza (A and B) 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 and neuraminidase antigens that play an essential role in virus infectivity. At present, 17 hemagglutinin and ten neuraminidase subtypes are known in bird populations and some subtypes routinely circulate in humans, such as the A (H1N1), A (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 viral entry into host cells or modify the severity of the infection and are the basis on which influenza vaccines are formulated every year.

Despite continuing advances in understanding of the immune response to natural infection and immunization, the disease remains a major cause of morbidity and mortality worldwide. In the United States (US) alone, influenza is responsible for approximately 36,000 deaths per year and the WHO estimates that influenza causes three to five million cases of severe illness and up to 650 000 deaths per year [Palache 2011, WHO 2018]. Influenza is also responsible for a massive economic burden, with direct medical costs for each winter influenza season estimated at over 10 billion dollars [Molinari 2007] in the US alone.

The main strategy for prevention and control of seasonal and pandemic influenza is still vaccination. In 2012, the Advisory Committee on Immunization Practices (ACIP) issued the first recommendation of national universal seasonal influenza vaccination in the US [Osterholm 2012]. Currently, various health and disease monitoring agencies around the world continue to recommend annual influenza vaccinations and communicate that it is the most effective way to prevent influenza [European Centre for Disease Prevention and Control (ECDC) 2018a, Grohskopf 2019, NACI 2019].

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 of vaccine efficacy studies suggest that the overall efficacy of currently licensed inactivated trivalent and quadrivalent vaccines is highly variable and depends, among other factors, on the “match” between circulating strains and the strains used for vaccine production [Lewnard 2018]. Although mismatches are not unique to A (H3N2) viruses, the rapid evolution of this family of viruses and risk of mutations with egg-based platforms have resulted in serious problems in several recent influenza seasons.

Indeed, the 2014-2015 Northern Hemisphere influenza season was a critical reminder of how the efficacy of commercially available vaccines can be affected by strain mismatch. In that year, vaccine effectiveness in North America for A (H3N2) viruses ranged from 19 % [Flannery 2015] to 0 % [Skowronski 2015]. The A (H3N2) viruses were once again problematic in the 2017-2018 influenza season, generally considered to be one of the worst in decades. In Canada,

the season was characterized by co-circulation of influenza A (H3N2) and B (Yamagata) viruses [Public Health Agency of Canada (PHAC) 2018]. Europe experienced an unusually long influenza season characterized by high levels of influenza infection with a significant proportion of B / Yamagata strains [ECDC 2018b]. The US experienced a flu season that was mostly dominated by A (H3N2) strains [CDC 2018]. In both North America and Europe, the 2017-2018 flu season was also characterized by reported low effectiveness of influenza vaccines at preventing medically-attended influenza-like illness (ILI) ranging from 18 to 54 % overall and from 7 to 33 % for A (H3N2) strains [ACIP 2018, Rondy 2018, Shoubaki 2018, Skowronski 2018]. This low effectiveness was attributed to antigenic mismatch of the A (H3N2) vaccine-strain virus produced in embryonic eggs and circulating strains as well as continued evolution (i.e., drift) of wild-type A (H3N2) viruses [Paessler 2017].

1.1 Quadrivalent VLP Influenza Vaccine

Medicago USA Inc. has developed a plant-based system (*Nicotiana benthamiana*) for transient expression of two type A and two type B influenza strains to produce QVLP intended for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine. This vaccine may be able to address several limitations of the currently licensed vaccines:

- The hemagglutinin proteins in each of the four monovalent VLPs are based on the genetic sequences 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;
- Plant-based VLP manufacturing does not require the use of live viruses. Thus, inactivation by chemicals and then splitting by a detergent before injection into humans are not needed, as is the process for living non-attenuated viruses. These processes are known to influence antigenicity, and antigens displayed on the VLPs are not impacted by the potentially denaturing treatments;
- The plant-based technology used for QVLP produces hemagglutinin proteins from the selected influenza strains without introducing undesirable mutations that can occur when influenza viruses are grown in egg- and cell-based production platforms [Parker 2016, Wu 2017, Zost 2017]. Very few microbial pathogens can infect both plants and humans so the risk of exposure to potentially pathogenic adventitious agents is greatly reduced;
- Medicago's previous clinical data suggests that plant-made VLP vaccines induce not only antibodies, but also strong CD4+ T cell immunity which may be important for both the persistence of immunity and the provision of better protection in older subjects, who often derive significant benefit from vaccination despite little evidence of a humoral response [Haq 2014].

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 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.

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. Moreover, a repeated-dose toxicity study in rats assessing the safety and immunogenicity of QVLP with or without the adjuvant AS03 was performed to support this Phase 1/2 clinical study.

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

1.3 Clinical Studies

Under the clinical development program for QVLP, Medicago has conducted nine clinical trials (eight completed; one ongoing) that included testing with unadjuvanted QVLP over a wide range of doses (CP-Q12VLP-004, CP-Q13VLP-007, CP-Q13VLP-008, CP-Q14VLP-009, CP-Q14VLP-010, CP-PRO-QVLP-011, CP-PRO-QVLP-012, CP-PRO-QVLP-013, and CP-PRO-QVLP-014). Among these trials, one trial included testing QVLP with an adjuvant (CP-Q13VLP-008). Study designs and statuses are summarized in Table 2.

Table 2 Summary of Design of Clinical Studies Performed to Date with QVLP

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

Study / Status	Phase	Design	Population	N	Treatment groups
CP-Q14VLP-010 / 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
CP-PRO-QVLP-013 / Clinic completed; Data analysis ongoing	2	Single-site, observer-blind, randomized, active comparator-controlled study	Healthy adults 18 to 49 years of age and 65 years of age or older, both genders	Age: 18-49 years: 25 (VLP); Age: ≥ 65 years: 25 (VLP); 25 (active comparator 1); 25 (active comparator 2)	30 µg VLP; 15 µg/strain dose of Fluzone® Tetra; 60 µg/strain dose of Fluzone® High Dose
CP-PRO-QVLP-011 / Completed	3	Multicenter, observer-blind, randomized, lot consistency study	Healthy adults of 18 to 49 years of age, both genders	1200 (VLP; 1:1:1 ratio to one of three lots)	30 µg VLP (three lots)
CP-PRO-QVLP-012 / Completed	3	Multicenter, observer-blind, randomized, placebo-controlled efficacy study	Healthy adults of 18 to 64 years of age, both genders	5064 (VLP); 5072 (placebo)	30 µg VLP; Placebo
CP-PRO-QVLP-014 / Completed	3	Multicenter, observer-blind, randomized, placebo-controlled efficacy study	Healthy adults of ≥ 65 years of age, both genders	6352 (VLP); 6366 (commercial IIV comparator)	30 µg VLP; 15 µg QIV (Fluarix® Quadrivalent)

Among the eight completed studies, 14 258 subjects have been exposed to unadjuvanted QVLP and 151 subjects have been exposed to adjuvanted QVLP (adjuvanted with Alhydrogel®). Of those exposed to unadjuvanted QVLP, 7295 subjects were 18-64 years of age, while 6963 subjects were 65 years of age and above and of those exposed to adjuvanted QVLP, 75 subjects were 50-64 years of age, while 76 subjects were 65 years of age and above. In total, 12 616 of these subjects received the 30 µg/strain dose selected for Phase 3 evaluation of the vaccine; 6264 subjects were 18-64 years of age and 6352 subjects were 65 years of age and above.

An overview of the available safety and immunogenicity findings from these studies are summarized in Section **Error! Reference source not found.** 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 for QVLP

This section summarizes the safety data obtained from the eight completed clinical trials performed with unadjuvanted QVLP (CP-Q12VLP-004, CP-Q13VLP-007, CP-Q13VLP-008, CP-Q14VLP-009, CP-Q14VLP-010, CP-PRO-QVLP-011, CP-PRO-QVLP-012, and CP-PRO-QVLP-014) and adjuvanted QVLP (CP-Q13VLP-008); see Table 2 for a description of the basic design of these studies, status, and exposure. The incidence of local and systemic reactions observed within seven days post-vaccination in these eight studies was consistent with the known safety profile for commercial influenza vaccines. The most frequently reported (≥ 1.0 % of subjects) unsolicited TEAEs within 21 days of vaccine administration included arthralgia, back pain, diarrhea, fatigue, headache, musculoskeletal pain, myalgia, nasal congestion, nasopharyngitis, nausea, oropharyngeal pain, pain in extremity, rhinorrhea, and upper respiratory

infection. No notable differences in the incidence of these events were observed between the QVLP 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 eight completed studies.

In these eight completed clinical trials, the incidence of subjects with at least one SAE during the overall study period was < 5.0 % in the QVLP groups. No apparent trends with respect to the number or types of SAEs were noted. However, there were more SAEs reported among the elderly subjects 65 years of age and older compared to the adult subjects 18 to 64 years old. Only three SAEs were considered by the site Investigator to be related to the study treatment (all in the elderly subjects 65 years of age and older group) and only one of these was for the QVLP group: a possible anaphylactic reaction in one subject in the 30 µg/strain QVLP group. There were fifteen subjects in the QVLP group who had treatment-emergent adverse events (TEAEs) leading to withdrawal from the study and all these subjects received the 30 µg/strain dose and were 65 years and older. Only one NOCD for adult subjects 18 to 64 years old who received QVLP and only six NOCDs for elderly subjects 65 years and older who received QVLP were reported that were considered by the site investigators to be vaccine-related.

Among the 14 409 subjects who were vaccinated with QVLP (with or without adjuvant), 13 deaths (neoplasm malignant, myocardial infarction (acute and non-acute), urosepsis, pneumonia complications, complications from Alzheimer's disease, septic endocarditis, cerebrovascular accident, acute heart failure, gastrointestinal haemorrhage, and completed suicide) were reported after vaccination of 30 µg/strain QVLP. The site Investigators assessed all of these events as definitely not related to the study vaccine, with the exception of two events (septic endocarditis and completed suicide) that were assessed as probably not related to the study vaccine.

As a precaution, subjects were monitored for TEAEs with a hypersensitivity component (reported events were searched using both narrow and broad standardized Medical Dictionary for Regulatory Activities (MedDRA®) queries for a possible hypersensitivity component). Based on the data from the eight completed studies, there is no definitive evidence of anaphylactic reactions associated with use of QVLP in humans. However, a single case of possible, truncated anaphylactic reaction in one subject has been reported. A small number of subjects had potential hypersensitivity reactions judged to be related to vaccine administration (no more than 0.5 % of subjects administered a QVLP treatment experienced one of these events) and the events were distributed fairly evenly among treatment groups, including the placebo and the active comparator groups. However, since severe reactions are considered to be an important potential risk (based on the theoretical risk that using plants for the production of biotherapeutics may induce hypersensitivity) the Sponsor will continue to require that appropriate medical treatment and supervision are available to manage any possible anaphylactic reactions.

Safety results from eight completed clinical trials performed show that QVLP was well-tolerated, with a safety profile similar to that of the active comparators and to the placebo for systemic reactions and TEAEs.

1.3.1.1 Safety Overview for AS03

The adjuvant AS03 is an established effective adjuvant used in the formulations for Arepanrix™ and Pandemrix™ and is manufactured by GlaxoSmithKline. Data from clinical trials with over 55 000 vaccinated subjects showed that AS03-adjuvanted influenza vaccines exhibited an acceptable safety profile [Cohet 2019, Garcon 2012, Vaughn 2014]. Increased reactogenicity, both local and general, is consistently noted for AS03-adjuvanted vaccines compared with the corresponding unadjuvanted vaccines [Garcon 2012, Launay 2013, Nolan 2014, Waddington 2010]. Most symptoms were mild to moderate in intensity and of short duration. An increased risk of narcolepsy was observed in some individuals after the vaccination campaign with Pandemrix™ in 2009-2010. A similar risk of narcolepsy was not identified with other non-adjuvanted influenza vaccines or other AS03-adjuvanted vaccines, like Arepanrix™ [Montplaisir 2014, Cohet 2015]. Current data suggest that cases of narcolepsy seen immediately following the 2009-2010 pandemic were most likely the result of an immune cascade, triggered by CD4 T cell cross-reactivity to HA proteins from the H1N1 virus itself and hypocretin. Research is continuing to assess whether either of the main components of the 2009/2010 flu pandemic vaccine (e.g., the viral proteins in the form used in the vaccine or the AS03 adjuvant) may have contributed to the reaction.

1.3.2 Immunogenicity and Efficacy Overview for QVLP

This section summarizes the immunogenicity data obtained from eight studies conducted with adult (18 to 64 years of age) and/or elderly (65 years of age and older) populations. Studies CP-Q12VLP-004, CP-Q13VLP-007, CP-Q14VLP-009, CP-Q14VLP-011, and CP-Q14VLP-012 were conducted in an adult-only population (18 to 49 years for CP-Q12VLP-004, CP-Q13VLP-007, and CP-Q14VLP-011, and 18 to 64 years for CP-Q14VLP-009 and CP-Q14VLP-012), CP-Q13VLP-008 was conducted in a combined adult and elderly population (50 years and older), and CP-Q14VLP-010 and CP-PRO-QVLP-014 were conducted in an elderly-only population (65 years of age and older). In addition, efficacy data was obtained from two studies conducted with adult (18 to 64 years of age) and elderly (65 years of age and older) populations: studies CP-PRO-QVLP-012 and CP-PRO-QVLP-014, respectively. All of these clinical studies were performed with unadjuvanted QVLP with the exception of study CP-Q13VLP-008 which was performed with both unadjuvanted and adjuvanted QVLP. See Table 2 for a description of the basic design of these studies and exposure.

Overall, the immunogenicity data from the studies conducted show that QVLP induced a substantial antibody response in healthy adult (18 to 64 years) and elderly (65 years of age and older) populations. The 30 µg/strain dose level appeared to be the lowest dose to elicit a consistent antibody response and be the most comparable with the commercial licensed vaccines. As a result, the 30 µg/strain dose level was selected for evaluation during Phase 3 efficacy studies in adult and elderly populations. The antibody response to QVLP, as determined by HI, MN, and single radial hemolysis (SRH) assays, was generally equivalent or lower compared to licensed influenza vaccines. As occurs with all licensed vaccines, the antibody responses induced by QVLP in the elderly population tended to be lower than those observed in the younger healthy

adult population. QVLP also elicited some cross-protective antibodies against heterologous influenza strains (current IB version).

In all the studies conducted, clear and consistent vaccine-related Day 21 poly-functional CD4+ T cell responses were observed with QVLP against all four homologous strains present in the vaccines in both the adult and elderly populations. Overall, the 30 µg/strain dose level showed the highest T cell response induced by QVLP that was at least equivalent (B virus antigens) or generally superior (A virus antigens) compared to licensed influenza vaccines. Further, the cell-mediated immune (CMI) response induced by QVLP appeared to be both durable (up to Day 201) and cross-reactive.

QVLP demonstrated statistically significant protection against respiratory illness and influenza-like illness, caused by influenza A and B strains, in adults aged 18 to 64 years (CP-PRO-QVLP-012) that was well-maintained for at least five to six months after vaccination. In the elderly population (65 years of age or older), QVLP showed non-inferiority compared to a licensed influenza vaccine in the prevention of ILI caused by any influenza strain (CP-PRO-QVLP-014). Moreover, it is important to note that there was no decline in protection with QVLP among the older age cohorts in either of these two studies and QVLP displayed the greatest protection in the oldest subjects (≥ 75 years of age) in study CP-PRO-QVLP-014.

1.3.2.1 Immunogenicity and Efficacy Overview for AS03

The AS03-adjuvanted pandemic influenza vaccines have been shown to be more immunogenic than non-adjuvanted vaccines. High efficacy and effectiveness have been demonstrated for AS03-adjuvanted H1N1 pandemic influenza vaccines in a wide range of populations [Garcon 2012]. Clinical data with AS03-adjuvanted antigen-sparing formulations have shown that immunization against influenza caused by the potential pandemic subtypes H5N1, H1N1, H7N1, H7N9, and H9N2 has demonstrated satisfactory immunogenic potency, as measured by haemagglutinin-inhibition titers, with reduced antigen doses in adults [Baz 2013, Jackson 2015, Lansbury 2017, Leroux-Roels 2007, Madan 2017, Madan 2017a, Madan 2017b, McElhaney 2013, Yang 2013, Yin 2011]. Also, AS03-adjuvanted H5N1 vaccines were shown to induce cross-clade neutralizing antibody responses [Leroux-Roels 2007] and antibody affinity maturation [Khurana 2018].

1.4 Overall Rationale for the Study

Given the relatively modest antibody responses elicited by QVLP against some strains and because the HI antibody response is well recognized by Regulatory Agencies to be a correlate of efficacy, Medicago will study the possible advantage of administering QVLP with an adjuvant used in licensed vaccine products (AS03).

This Phase 1/2 study is to assess the safety, tolerability, and immunogenicity of adjuvanted recombinant QVLP in healthy adults 65 years of age and older. One dose of the following vaccine formulations will be administered in this study:

- 30 µg/strain of QVLP adjuvanted with AS03, or
- 30 µg/strain of QVLP unadjuvanted, or
- Fluzone HD Quad.

2 OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

Safety:

- To assess the safety and tolerability of a single dose of QVLP (30 µg/strain) with AS03 adjuvant compared to QVLP (30 µg/strain) (unadjuvanted) and Fluzone HD Quad;

Immunogenicity:

- To assess the immunogenicity of a single dose of QVLP (30 µg/strain) with AS03 adjuvant compared to QVLP (30 µg/strain) (unadjuvanted) and Fluzone HD Quad, as measured by HI assay against homologous influenza strains.

2.2 Secondary Objectives

The secondary objectives of this study are:

Immunogenicity:

- To assess the immunogenicity of a single dose of QVLP (30 µg/strain) with AS03 adjuvant compared to QVLP (30 µg/strain) (unadjuvanted) and Fluzone HD Quad, as measured by MN assay against homologous influenza strains;
- To assess the immunogenicity of a single dose of QVLP (30 µg/strain) with AS03 adjuvant compared to QVLP (30 µg/strain) (unadjuvanted) and Fluzone HD Quad, as measured by HI assay against heterologous influenza strains;
- To assess the immunogenicity of a single dose of QVLP (30 µg/strain) with AS03 adjuvant compared to QVLP (30 µg/strain) (unadjuvanted) and Fluzone HD Quad, as measured by HI (homologous and heterologous influenza strains) and MN (homologous influenza strains) assays, stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination;
- To evaluate the persistence of antibody responses, as determined by HI titers against homologous influenza strains, at 6 and 12 months post-vaccination;

Safety:

- To assess the safety and tolerability of a single dose of QVLP (30 µg/strain) with AS03 adjuvant compared to QVLP (30 µg/strain) (unadjuvanted) and Fluzone HD Quad,

stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination.

3 STUDY ADMINISTRATIVE STRUCTURE

Table 3 Study Administrative Structure

Role	Name and Address
Sponsor	Medicago USA Inc. 7 Triangle Drive Durham (NC), United States 27713
PPD	PPD
PPD	PPD
PPD	PPD
PPD	PPD
PPD	PPD

4 STUDY DESIGN AND RATIONALE

4.1 Overview of Study Design

This randomized, partially-blinded, active comparator-controlled multi-center, dose-finding, Phase 1/2 study will be conducted at multiple sites. The composition of QVLP to be used in this study includes a mix of recombinant H1, H3, and two B hemagglutinin proteins expressed as VLPs and will be based on the 2020-2021 recommended WHO strains for vaccination in the Northern Hemisphere. The compositions of the active comparators are also based on the 2020-2021 recommended WHO strains for vaccination in the Northern Hemisphere.

Overall, approximately 120 healthy male and female subjects 65 years of age and older will be enrolled evenly into one of three parallel treatment groups, as presented in Table 4. A dose level of 30 µg/strain QVLP will be tested with the adjuvant AS03. The 30 µg/strain is the full dose of QVLP, used in previous clinical studies.

Table 4 Study Treatment Groups

Treatment Group	Treatments	Dose Level	No. of Subjects
1	QVLP adjuvanted with AS03	30 µg/strain	40
2	QVLP unadjuvanted	30 µg/strain	40
3	Fluzone HD Quad	60 µg/strain	40

The first 3 subjects per treatment group enrolled in the study will receive an IM injection of one of the three treatments listed in Table 4. The vaccinations for the first three subjects in each

treatment group will be staggered so that each vaccination must be performed at least 30 minutes apart. The seven-day safety data will be collected from these subjects and reviewed by the IDMC, prior to permitting the vaccination of the remaining subjects in these three treatment groups.

Subjects will be screened up to seven days in advance of the vaccine administration and will demonstrate a satisfactory baseline medical assessment by medical history, general physical examination, urinalysis, haematological and blood biochemistry analyses, and serum screening for HIV, Hepatitis B and Hepatitis C markers. On Day 0, vaccine administration will occur. Phone contacts will be made one day and eight days after the vaccine administration, specifically for review of the subject's safety and concomitant medication data. Visits to the Investigator site will occur 3 days after the vaccine administration (Day 3) for key safety assessments and 28 days after the vaccine administration (Day 28) for key safety and immunogenicity assessments. Subjects will have monthly telephone calls after Day 28 up to the end of the study. Subjects will return to the Investigator site on Day 182 for immunogenicity and safety assessments (6-month follow-up) and on Day 365 for final immunogenicity and safety assessments (12-month follow-up).

Subjects enrolled and vaccinated in the QVLP (15 µg/strain and 45 µg/strain) adjuvanted with AS03 adjuvant (full dose or half dose) and the QVLP (30 µg/strain) adjuvanted with AS03 adjuvant (half dose) treatment groups will complete study procedures as outlined above and will be followed for safety and immunogenicity assessments up to Day 365.

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.

Subjects will be randomized according to prior influenza vaccination status defined as enrolled subjects who have received a standard influenza vaccine during the 12 months prior to study vaccination.

4.2.2 Blinding

A partially-blinded treatment trial design consisting of both observer-blind and open-label elements will be utilized in this study. Observer-blinded treatment trial design elements will be used to reduce potential bias during data collection and evaluation of the study endpoints. Details of who will remain blinded during the study are presented in Section 6.2.

Open-label trial design elements will be used to allow a small number of Medicago personnel to remain unblinded throughout the study (see Section 6.2) to make informed design decisions of

the subsequent studies based on the Day 28 and Day 182 data analyses (see Section 12.3) results, without having to wait until after the end of the follow-up period for study completion.

4.2.3 Dose Selection and Dosage Regimen

In this study, three dose levels (15 µg/strain, 30 µg/strain, and 45 µg/strain) of QVLP will be tested in combination with two dose levels of AS03 adjuvant (full and half dose) in a single-dose regimen to select a dose level of QVLP and adjuvant dose level-combination that is safe and effective for further development. The 30 µg/strain dose is the full dose of QVLP, used in previous clinical studies, and the 15 µg/strain dose has been included to assess a possible dose-sparing effect in combination with the adjuvant AS03. A higher dose of 45 µg/strain will also be assessed since higher doses of 45-60 µg/strain are used by two commercially available vaccines [Flublok 2020, Fluzone High-Dose 2019] that target the elderly population.

The dosage and administration of the active comparator unadjuvanted QVLP is based on data from previous studies as dose used to establish non-inferior efficacy to another approved influenza vaccine in the elderly population. In addition, it is also the dose most comparable with commonly used licensed vaccines [Flublok 2020, Fluzone High-Dose 2019] in the elderly.

The dosage and administration of the active comparator Fluzone HD Quad is in accordance with the approved prescribing information for this vaccine.

4.2.4 Route of Administration

The route of administration used for adjuvanted QVLP and comparators is the intramuscular route, specifically in the deltoid muscle of the arm, since it is a more viable route of administration (compared to an oral route), has better absorption compared to the subcutaneous route, and is the same route of administration for the active comparators.

4.2.5 Active Comparators Selection

The active comparator unadjuvanted QVLP was selected since the safety, immunogenicity, and efficacy profile of this vaccine has been established in persons 65 years of age and older in previous studies. The same formulation of unadjuvanted QVLP will be used in combination with AS03 adjuvant.

The active comparator Fluzone HD Quad was selected on the basis that this product is an approved quadrivalent influenza vaccine for persons 65 years of age and older in the US. In addition, this product has been well-studied and has well-established immunogenicity, efficacy, and safety profiles for this population.

4.2.6 Study Duration

The duration of this study will be approximately 17 months.

5 STUDY POPULATION

5.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria at the Screening visit (Visit 1) and/or Vaccination visit (Visit 2) to be eligible for participation in this study; no protocol waivers are allowed. All Investigator assessment-based judgements must be carefully and fully documented in the source documents:

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

   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 that must be documented in the source documents, the condition is unlikely to confound the results of the study or pose additional risk to the subject by participating in the study. Stable disease is generally defined as no new onset or exacerbation of pre-existing chronic disease three months prior to vaccination. Based on the Investigator's judgment and documented in source documentation, a subject with more recent stabilization of a disease could also be eligible.

5.2 Exclusion Criteria

Subjects who meet any of the following criteria at the Screening visit (Visit 1) and/or Vaccination visit (Visit 2) will not be eligible for participation in this study; no protocol waivers are allowed. All Investigator assessment-based judgements must be thoroughly documented in the source documents:

1. According to the Investigator's opinion, significant acute or chronic, uncontrolled medical or neuropsychiatric illness. Acute disease is defined as presence of any moderate or severe acute illness with or without a fever within 48 hours prior to the Vaccination visit (Visit 2). 'Uncontrolled' is defined as:

- Requiring a new medical or surgical treatment during the three months prior to study vaccine administration;
- 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 and documented by the Investigator.

Investigator discretion is permitted with this exclusion criterion and must be carefully and fully documented in the source documents.

2. Any confirmed or suspected current immunosuppressive condition or immunodeficiency, including cancer, human immunodeficiency virus, hepatitis B or C infection (subjects with a history of cured hepatitis B or C infection without any signs of immunodeficiency at present time are allowed). Investigator discretion is permitted with this exclusion criterion;
3. Current autoimmune disease requiring systemic treatment (such as rheumatoid arthritis, systemic lupus erythematosus, or multiple sclerosis). Investigator discretion is permitted with this exclusion criterion, and subjects may be eligible to participate with appropriate written justification in the source document (i.e. subjects with a history of autoimmune disease who are disease-free without treatment for three years or more, or on stable thyroid replacement therapy, mild psoriasis [i.e. a small number of minor plaques requiring no systemic treatment], etc.);
4. Administration of any non-influenza vaccine within 30 days prior to the Vaccination visit (Visit 2); planned administration of any vaccine up to Day 28 of the study. Immunization on an emergency basis during the study will be evaluated on case-by-case basis by the Investigator.

   Note: Administration of an authorized COVID-19 vaccine prior to or during the study is acceptable;
5. Administration of influenza vaccine within six months prior to the Vaccination visit (Visit 2);
6. Administration of any adjuvanted or investigational influenza vaccine within one year prior to randomization or planned administration prior to the completion of the study;
7. Use of any investigational or non-registered product within 30 days or five half-lives, whichever is longer, prior to the Vaccination visit (Visit 2) or planned use during the study period. Subjects who are in a prolonged post-administration observation period of another investigational or marketed drug clinical study, for which there is no ongoing exposure to the investigational or marketed product and all scheduled on-site visits are completed, will be allowed to take part in this study, if all other eligibility criteria are met;
8. Administration of any medication or treatment that may alter the vaccine immune responses, such as:
   - Systemic glucocorticoids at a dose exceeding 10 mg of prednisone (or equivalent) per day for more than seven consecutive days or for 10 or more days in total, within one month prior to the Vaccination visit (Visit 2). Inhaled, nasal, intraarticular, ophthalmic, dermatological, and other topical glucocorticoids are permitted;

- Cytotoxic, antineoplastic or immunosuppressant drugs - within 36 months prior to the Vaccination visit (Visit 2);
- Any immunoglobulin preparations or blood products, blood transfusion – within 6 months prior to the Vaccination visit (Visit 2);

9. Use of any prescription antiviral drugs with the intention of COVID-19 prophylaxis, including those that are thought to be effective for prevention of COVID-19 but have not been licensed for this indication, within one month prior to the Vaccination visit (Visit 2);
10. Subjects at high risk of contracting SARS-CoV-2/COVID-19 infection, including, but not limited to, individuals with known close contact with:
    - anyone residing in, visiting, or working at a health care or long-term care institution (i.e. long-term care facilities, acute care hospitals, rehabilitation hospitals, mental health hospitals, emergency departments);
    - anyone with laboratory-confirmed SARS-CoV-2/COVID-19 infection within 2 weeks prior to vaccine administration;
    - anyone who traveled outside the country for any duration within 30 days before the study vaccination;
11. History of allergy to any of the constituents of QVLP, any components of Fluzone HD Quad, the adjuvant AS03, egg, or tobacco;
12. History of anaphylactic allergic reactions to plants or plants components (including fruits and nuts);
13. Subjects with a history of Guillain-Barré Syndrome;
14. Personal or family (first-degree relatives) history of narcolepsy;
15. Use of prophylactic medications (e.g. antihistamines [H1 receptor antagonists], nonsteroidal anti-inflammatory drugs [NSAIDs], systemic and topical glucocorticoids, non-opioid and opioid analgesics) within 24 hours prior to the Vaccination visit (Visit 2) to prevent or pre-empt symptoms due to vaccination;
16. Have a rash, dermatological condition, tattoos, muscle mass, or any other abnormalities at the injection site that may interfere with injection site reaction rating. Investigator discretion will be permitted with this exclusion criterion;
17. 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 employees of Medicago.

5.3 Prior and Concomitant Therapy

New or changed medications reported by the subject post-vaccination and through to the end of the study will be recorded in the source documents as a concomitant medication as per the conditions outlined in the next paragraph. Since AEs may be secondary to new medications, the Investigator will explore the reasons for the change or for the new medication intake and document these AEs, if any.

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

- Within 30 days preceding vaccination: any treatments and/or medications specifically contraindicated (e.g. influenza vaccines, any immunoglobulins or other blood products, or any immune modifying drugs, etc.);
- From randomization to Day 28, inclusive: any medication (including, but not limited to, over-the-counter medicines such as aspirin or antacids), vitamins, and mineral supplements;
- From Day 29 to the end of the study, inclusive: any concomitant medication(s) administered to treat a NOCD (see Section 13.1.4 for definition of NOCD), SAE, or AE leading to withdrawal; any concomitant medication used to treat an AE that occurred before Day 28 and that is still being used afterwards (i.e. on-going use);
- Any concomitant medication used to treat conditions reported as medical history;
- Any investigational medication or vaccine; any vaccine not foreseen in the study protocol.

5.4 Prohibited Therapy

The following medications or therapies are prohibited during the conduct of this study:

1. Administration of any non-influenza vaccine (excluding authorized COVID-19 vaccines) up to blood sampling on Day 28 of the study. Immunization on an emergency basis during the study will be evaluated on case-by-case basis by the Investigator;
2. Administration of any adjuvanted or investigational influenza vaccine (other than the study vaccine) up to completion of the study;
3. Use of any investigational or non-registered product during the study period. Subjects may not participate in any other investigational or marketed drug study while participating in this study until after the study;
4. Administration of any medication or treatment that may alter the vaccine immune responses, such as:
   - Systemic glucocorticoids at a dose exceeding 10 mg of prednisone (or equivalent) per day for more than seven consecutive days or for 10 or more days in total;
   - Cytotoxic, antineoplastic, or immunosuppressant drugs;
   - Any immunoglobulin preparations or blood products, or blood transfusion;
5. Use of prophylactic medications (e.g. antihistamines [H1 receptor antagonists], nonsteroidal anti-inflammatory drugs [NSAIDs], systemic and topical glucocorticoids, non-opioid and opioid analgesics) for seven days post-vaccination to prevent or pre-empt symptoms due to vaccination;
6. Use of any prescription antiviral drugs with the intention of COVID-19 prophylaxis, including those that are thought to be effective for prevention of COVID-19 but have not been licensed for this indication, during the study.

If one of the first five criteria is met by a subject during the study (after vaccination), the subject may still remain in the study however the inclusion of the subject's data within the PP set, ITT set, or SAS may be impacted.

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

6 TREATMENT ALLOCATION AND BLINDING

6.1 Randomization

Potential study subjects will be screened and assigned a six-digit 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. If a subject is randomized in error (i.e. does not meet eligibility criteria) and has not been vaccinated, then another eligible subject can be randomized to replace this subject.

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

Randomization will be stratified by prior influenza vaccination status (defined as enrolled subjects who have received a standard influenza vaccine during the 12 months prior to study vaccination). Subjects will then be enrolled into 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 number and treatment will be recorded for each subject in the investigational product accountability log.

6.2 Blinding

This is a partially-blinded study: the subjects, the Investigator and all personnel involved in the clinical conduct of the study (except the staff involved in the preparation and administration of the study vaccine, the quality assurance auditor, and quality control reviewers), Medicago clinical and medical staff involved in safety evaluations (e.g. causality assessments), and all personnel involved in sample analysis at the central and testing (HI and MN assays) laboratories

will not have access to treatment allocation (i.e. randomization codes) for the entire duration of the study.

The IDMC and the independent statistician involved in the preparation of the safety data summary for the IDMC reviews will have access to or be aware of treatment allocation (i.e. be "unblinded"). The IDMC will review safety data and will make recommendations for the entire duration of the study.

In addition, select personnel of the third-party statistical team will have access to treatment allocation (i.e. be "unblinded") for the entire duration of the study since these personnel will be involved in the Day 28 and Day 182 data analyses (see Section 12.3).

A small number of Medicago personnel will have access to treatment allocation (i.e. be unblinded" to results and/or treatment allocation) and will be able to look at data throughout the study. The Medicago personnel will include senior personnel in Scientific and Medical Affairs, Biostatistics, Safety, Product Development, and Regulatory Affairs. The unblinded procedure will be strictly followed, and the process of unblinding and the selected individuals will be documented in writing.

Although there may be some visual differences in QVLP, the adjuvant, and the active comparator preparations (e.g. possibly physical appearance), the site staff involved in the preparation and administration of the treatments will not be involved in any activity that could introduce a bias, such as the evaluations of AEs, or reactogenicity of the subjects following vaccination.

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 Monitor as soon as possible after the unblinding to discuss the case. The treatment allocation should not be disclosed by the Investigator to the responsible Medical Monitor.

The third-party statistical team will perform data analyses after Day 28 (last subject) and Day 182 (last subject). The data analyses will involve select individuals from the third-party statistical team and Medicago who will be unblinded (as described above). The Day 28 and Day 182 data analyses will allow discussions of the clinical data to inform study design decisions of the subsequent study, without having to wait until after the end of the follow-up period for study completion.

Since the study is carried out over approximately 17 months and study design for the subsequent study needs will be determined in advance (this is also true for the batch(es) manufacturing for the subsequent study), a risk assessment will be performed to verify that 1) processes were maintained to ensure against operational bias; 2) data breach did not occur that could compromise the integrity of the trial and veracity of the data. Said risk assessment will be completed prior to initiating any unblinding process; moreover, in relation to the study protocol,

the assessment will evaluate relevant procedures, policies, SAP, data transfer and communication plans, IT system validation and its adequacy in functionally supporting Medicago's study.

7 DOSAGE AND ADMINISTRATION

On Day 0, subjects will receive one IM injection into the deltoid region of the non-dominant (if possible) arm, of their assigned treatment:

- 30 µg/strain of QVLP adjuvanted with AS03, or
- 30 µg/strain of QVLP unadjuvanted, or
- Fluzone HD Quad.

The volume of injection will be 0.7 mL for all treatments.

8 SPECIMENS AND CLINICAL SUPPLIES

8.1 Management of Samples

Blood samples for biochemistry, haematology, and serology (for HIV, Hepatitis B, and Hepatitis C) will be collected at screening and/or during the study as well as urine samples for urinalysis.

Blood samples for immunogenicity analysis will be collected during the study. Should a subject be discontinued from the study, a sample will be drawn at the time of the final safety visit and sent to Medicago for analysis. Analysis of the immunogenicity blood samples will be conducted at central laboratories.

Complete information on the handling, storage, and shipment of all laboratory samples will be described in the study-specific documentation.

8.2 Collection of Samples

Blood samples for biochemistry and haematology will be collected at screening and Days 3 and 28. Serology tests for HIV, Hepatitis B, and Hepatitis C will be conducted at screening. Sample collected during the screening visit should be performed under fasting conditions (approximately 12 hours) for cholesterol and triglyceride analysis. Note that cholesterol and triglyceride analysis will be performed only at screening. Urine samples for testing will be collected at screening and Days 3 and 28.

Blood samples will be collected from each subject immediately prior to study treatment administrations on Day 0 and on Days 28, 182, and 365 for serological (immunogenicity) assays.

8.3 Clinical Supplies

The study center will be provided with or be responsible for the provision of supplies for blood collection and shipment (e.g. aliquot tubes, aliquot labels, aliquot storage, shipping boxes, and accompanying manifests) as described in the study-specific documentation. Sites will be authorized to use their own materials if agreed to by Medicago (or its designee).

9 TREATMENT COMPLIANCE

Study treatments will be prepared and administered by trained unblinded site staff via IM injection to each subject at each Investigator site. In addition, the Investigator or designated study center personnel will maintain a log of all study treatments dispensed and administered to the subject. Investigational product inventory and accountability will be managed throughout the study by unblinded site staff (details will be provided in the study-specific documentation). If an eligible subject refuses vaccination post-randomization, the reason will be documented in the source and electronic case report form (eCRF).

10 STUDY EVALUATIONS

10.1 Study Procedures

10.1.1 Overview

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

All subjects will have blood sampled. Subjects will have blood volumes drawn of approximately 64 mL over a period of 365 days (Table 5).

Table 5 Estimated Blood Volume Drawn

Type of Sample	Volume per Sample (mL)	Number of Samples per Subject							Total Volume of Blood per Subject (mL)
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Total	
Biochemistry, haematology, and serology (HIV, Hepatitis B & C)*	8	1		1	1			3	24
Serology for immunogenicity	10		1		1	1	1	4	40
Total volume of blood per subject (mL)		8	10	8	18	10	10		64

*Serology tests for HIV, Hepatitis B and C will only be performed at Visit 1.

10.1.2 General COVID-19 Precautions at Clinical Sites

Sites participating in this study will have processes in place locally for following recommendations of the local Public Health authorities for the management of COVID-19. Subjects will be asked to follow good hygiene and safe physical distancing measures such as wearing a face mask on site, frequent hand hygiene, and maintaining a physical distance of 2 meters (or 6 feet) from others, except during procedures where staff must come into close proximity of subjects (e.g. vaccination, blood draws, collecting vital sign measurements).

Staff at the clinical sites will also follow the same good hygiene and safe physical distancing measures as the subjects at the site. In addition, the staff will be responsible for disinfecting materials and/or areas between each use by subjects and staff. All staff involved with on-site

procedures will have a back-up member who is qualified to perform the same duties / responsibilities in the event that a member of the staff is infected with SARS-CoV-2 or comes into contact with an individual known to have COVID-19 and is restricted to self-isolation and following the recommendations of the local Public Health authorities for the management of COVID-19.

Subjects will be asked to inform the clinical site if they have tested positive for COVID-19 and if they are following the recommended actions (e.g. quarantine, re-testing) by local Public Health authorities. Subjects will be asked to not visit the clinic site until after they have fully recovered (i.e. no more clinical symptoms) and completed all of the recommended actions (e.g. quarantine, re-testing) by local Public Health authorities. If the quarantine period for the subject overlaps with a post-vaccination clinical site visit and the visit window, then the procedures for that particular visit will be performed by trained medical staff, using reliable personal protective equipment and following good hygiene, at the subject's home (or place of quarantine).

10.1.3 Screening (Visit 1)

The following procedures will be performed at the initial screening visit (Visit 1):

- Review and proceed with the signature of the ICF. The Investigator or his/her designee, will fully inform the subject of the nature and scope of the study, potential risks and benefits of participation, and the study procedures involved and will answer all questions prior to requesting the subject's signature on the ICF. The subject's consent must be obtained prior to performing any study-related procedures; this must be clearly recorded and a copy of the signed ICF retained in the source documents. A copy of the ICF must be provided to the subject;
- 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 after review of all procedures and findings and prior to randomization;
- Collect and review demographics (gender, date of birth, age, race, and ethnicity) and body measurements (BMI, weight [kg or lbs], and height [cm or inches]) data. BMI is to be calculated as body weight (kg) divided by the square of height (m); the BMI result will be rounded to one decimal place using the standard convention. For the measurement of body weight, subjects will be lightly clothed, without shoes;
- Collect and review medical history, including the grade of any medical conditions (medical conditions are to be graded using the same scale as for AEs; see Section 13.1.2). The medical history should record significant problems active at the time of screening and present within the preceding six months. Problems that have been clinically inactive for more than six months preceding screening, but which might alter the subject's current or future medical management, should also be noted (e.g. cancer, autoimmune disease, 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), with the following exception (refer to exclusion criterion 8):

  - For subjects who have been administered the following medication or treatment, review and record current and previous medication use up to the time period specified for the medication or treatment:
    - cytotoxic, antineoplastic, or immunosuppressant drugs – within 36 months prior to vaccination;
    - any immunoglobulin preparations or blood products, blood transfusions – within 6 months prior to vaccination;
- 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 oral temperature (OT). OT will be collected in degrees Celsius or Fahrenheit using a digital thermometer. The OT measurement should not be collected immediately following consumption of a hot or cold beverage or after smoking. The BP will be taken after the subject has been in a seated position as per the site's standard procedure. The BP should be taken by cuff (manual or automated are both acceptable). BP and HR may be repeated once if judged necessary. All measurements (including any repeats) will be recorded in the source documents. Inclusion of subjects with an out-of-range BP or HR measurement will be based on the Investigator's judgment;
- Perform a history- or symptom-directed physical examination. The physical exam will be performed by the Investigator or sub-Investigator;
- Collect screening blood samples for biochemistry, haematology, and serology (HIV, Hepatitis B, and Hepatitis C) for analysis. Sample blood collection at the screening visit should be performed under fasting conditions (approximately 12 hours) for cholesterol and triglyceride analyses;
- Perform urinalysis on all subjects.

10.1.4 Vaccination (Day 0) (Visit 2)

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 (minimum of 30 minutes after vaccination) 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.

10.1.4.1 Prior to Vaccination

The following procedures will be performed on Day 0 (Visit 2) prior to vaccination:

- Record changes in medical history and medications and confirm that the subject continues to meet all inclusion and no exclusion criteria;

- Perform a vital signs measurement, including resting BP, HR, and OT. OT will be collected in degrees Celsius or Fahrenheit using a digital thermometer. The OT measurement should not be collected immediately following consumption of a hot or cold beverage or after smoking. The BP will be taken after the subject has been in a seated position as per the site's standard procedure. The BP should be taken by cuff (manual or automated are both acceptable). BP and HR may be repeated once if judged necessary. All measurements (including any repeats) will be recorded in the source documents. Inclusion of subjects with an out-of-range BP or HR measurement will be based on the Investigator's judgment;
- Measure the BMI; for this visit, only weight will be measured while the height will be obtained from that measured at the initial screening visit. 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;
- Perform a history- or symptom-directed physical examination. The physical exam will be performed by the Investigator or sub-Investigator;
- If the subject is judged eligible for the study and is still willing to participate in the study, randomize the subject into the study;
- After confirmation of eligibility, collect baseline blood samples for immunogenicity (serology) assessments and prepare and store these samples until shipment to the analytical laboratory.

10.1.4.2 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, as described in the Investigational Product Management Manual. In order to prevent possible confounding of vaccination site reactions, whenever possible, blood samples will not be collected from the same arm as the one used for vaccination. The arms used, both for blood collection and vaccination, will be documented in the source documents. For subjects with BMI < 30 kg/m^2, a 23 gauge needle of at least one inch or 2.5 cm in length can be used for vaccination. For subjects with BMI ≥ 30 kg/m^2, a needle of at least 1.5 inches or 3.5 cm in length must be used to ensure intramuscular delivery.

10.1.4.3 Thirty Minutes Post-vaccination

The post-vaccination observations will be performed by a blinded site staff member. 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 30 minutes post-vaccination for observation. The observation period will include an assessment of immediate solicited local and systemic AEs. Solicited local and systemic AEs occurring within 30 minutes post-vaccination will be recorded in the subject diary (manual or electronic) and corresponding eCRF. All unsolicited AEs occurring within 30 minutes post-vaccination will be recorded

in the subject source and AE eCRF. Any unusual signs or symptoms reported during the initial 30 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 30 minutes after vaccination (the reason will be recorded in the source documents). All data (including the assessment of solicited local and systemic AEs) will be recorded in the source documents during and after the observation period. Refer to Section 10.2.1 for details regarding the assessment of AEs and/or solicited local and systemic AEs;

- During the observation period, subjects will be provided with a measurement device template (Section 19.1) for measuring (in mm) solicited local AEs of erythema (redness) and swelling and an oral digital thermometer for recording daily temperature (in degrees Celsius or Fahrenheit). Subjects will also be provided with a diary (manual or electronic; Section 19.2) and will be shown how to enter their data in the diary. Each subject will be provided with the following instructions on the measurements they are to make:
  - How to collect his/her OT in degrees Celsius or Fahrenheit with the provided digital thermometer:
    - From the evening of Day 0 to the evening of Day 7, the subject will measure his/her OT at approximately the same time each evening and will record the results;
    - The OT should not be collected immediately following consumption of a hot or cold beverage or after smoking.
    - The subject is to also take his/her OT if he/she feels feverish and to record the highest temperature of the day. In the event that a temperature ≥ 38.0 °C or ≥ 100.4 °F is obtained, the subject will be allowed to take over-the-counter antipyretics (e.g. acetaminophen/paracetamol, aspirin, naproxen, or ibuprofen) and will be advised to increase the frequency of OT measurements to approximately every four hours, until he/she is no longer febrile (fever is defined as a temperature of ≥ 38.0 ºC or ≥ 100.4 °F). The subject is to document medication intake, which will be reviewed by the site personnel;
  - How to measure any solicited local AEs, 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 AEs will be assessed every day starting in the evening of Day 0 and up to the evening of Day 7 and the results will be recorded. The severity of solicited local AEs will be graded according to the Food and Drug Administration (FDA) Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [FDA 2007], as presented in Table 6.
  - How to grade, on a daily basis from the evening of Day 0 through to the evening of Day 7, each of the solicited systemic AEs and their severity (as per the same guidance used for solicited local AEs; see Table 6) [FDA 2007] and to record the worst grade of the day for each of these solicited systemic AE. The instructions will include how to examine and grade swelling in the neck and axilla and to record any unusual feeling and/or swelling;

- Subjects will be advised that they will be asked about the occurrence of any symptoms or events requiring medical attention and the use of any concomitant medication during the 28-day post-vaccination period and until the end of the study. Subjects will also be provided with a memory aid (manual or electronic; Section 19.3) to record unsolicited AEs and any concomitant medication use and will be shown how to enter their data in the memory aid;
- Subjects will be instructed to contact the clinical site for any unsolicited AEs and/or solicited local and systemic AEs 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 30-minute observation period (allowed window of + 15 minutes) is completed, measure vital signs (BP, HR, and OT) as described in Section 10.2.1.4. Any out-of-range measurements will be assessed by the Investigator (or his/her designee) and any further action will be determined upon his/her medical decision;
- Instruct the subjects to perform measurements of local and systemic AEs at approximately the same time each day from Day 0 to Day 7 (preferably in the evening);
- Advise subjects to report to the clinical site if they have tested positive for COVID-19;
- Provide appointments (date and time) for the next planned visit to the clinical site (Day 3) 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.

10.1.5 Day 1 and Day 8 (Telephone Contact)

The post-vaccination phone contacts will be performed by blinded site staff members. The following procedures will be performed during the phone contact (acceptable interval of + 1 day for Day 1 and + 1 day for Day 8):

- Ask the subjects about any difficulties in recording their data, any change in health, any visits to health care facilities and/or medical practitioners, and any use of concomitant medications. Record the information in the source documents;
- For any unsolicited AEs and/or solicited local and systemic AEs 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;
- Instruct the subjects to contact the clinical site immediately in case they were tested positive for COVID-19;
- Remind the subjects how to measure and record any solicited local and systemic AEs. Subjects should also be reminded to record any changes in health, including changes in AEs and changes in medications;
- Remind subjects of their next appointment (date and time) for the clinical visit and/or the next phone contact. Subjects will also be reminded to record their data in their diary and memory aid in a timely manner.

In the event that a subject cannot be reached via phone, he/she may be contacted by text message or via email (if these contacts are available). However, the phone should be the initial and preferred means of communication. At least three attempts within allowed time window should be made in order to reach the subject.

10.1.6 Day 3 Follow-up (Visit 3)

The post-vaccination follow-up visit procedures will be performed by blinded site staff members at the clinical site. For subjects in quarantine, these procedures will be performed by blinded trained medical staff at the subject's home (or place of quarantine). The following procedures will be performed during the Day 3 visit (± 1 day):

- Perform a vital signs measurement, including resting BP, HR, and OT;
- Perform a history- or symptom-directed physical examination. The physical exam will be performed by the Investigator or sub-Investigator;
- Collect blood samples for biochemistry and haematology;
- Perform urinalysis on all subjects;
- Review the diary and memory aid 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;
- Review the subject's safety data and ensure all updates on concomitant medication usage and any changes in the subject's health (AEs, SAEs, AESIs, MAAEs, or NOCDs) are recorded appropriately;
- Advise the subjects to immediately contact the Investigator or his/her designee, in the event of any AE that requires a visit to an emergency room and/or hospitalization;
- Instruct the subjects to contact the clinical site immediately in case they were tested positive for COVID-19;
- Remind the subjects of their next phone contact (date and time).

10.1.7 Day 28 (Visit 4)

The post-vaccination follow-up visit procedures will be performed by blinded site staff members at the clinical site. For subjects in quarantine, these procedures will be performed by blinded trained medical staff at the subject's home (or place of quarantine). For all subjects a safety follow-up will be performed on or shortly after Day 28 (± 2 days):

- Perform a vital signs measurement, including resting BP, HR, and OT;
- Perform urinalysis on all subjects;
- Collect blood samples for biochemistry and haematology;
- Collect blood samples for immunogenicity (serology) assessments and prepare and store these samples until shipment to the analytical laboratories.
- Review the diary and memory aid 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. Collect manual diary and memory aid and provide subjects with just a memory aid for the collection of safety data from Day 29 to Day 182;
- Review the subject's safety data and ensure all updates on concomitant medication usage and any changes in the subject's health (AEs, SAEs, AESIs, MAAEs, or NOCDs) are recorded appropriately;
- Advise the subjects to immediately contact the Investigator or his/her designee, in the event of any AE that requires a visit to an emergency room and/or hospitalization;
- Provide appointments (date and time) for the next telephone contacts and the next planned visit to the clinical site (Day 182).

10.1.8 Monthly Calls Thereafter (Telephone Contact)

Subjects should be contacted by telephone once every month (every 30 days ± 14 days; Day 28 visit date as starting reference). The post-vaccination monthly phone contacts will be performed by blinded site staff members. The following procedures will be performed during the phone contacts:

- Ask the subjects about any change in health (AEs ongoing from Day 28, SAEs, AESIs, MAAEs, or NOCDs), any visits to health care facilities, and/or medical practitioners and use of any concomitant medications. Record the information in the source documents;
- Advise the subjects to immediately contact the Investigator (or his/her designee), in the event of any AE which require a visit to the emergency and/or hospitalization;
- Instruct the subjects to contact the clinical site immediately in case they were tested positive for COVID-19;
- Remind the subjects of their next appointment (date and time) for the next telephone contact and/or the next planned visit to the clinical site (Day 182 or Day 365);
- Inform the subjects that during the subsequent visit to the clinical site, they will be questioned regarding any events that may have occurred since the last contact.

In the event that a subject cannot be reached via telephone, he/she may be contacted by text message or via email (if these contacts are available). However, the telephone should be the initial and preferred means of communication. At least three attempts within allowed time window should be made in order to reach the subject.

10.1.9 Day 182 (Visit 5)

For some subjects, the Day 182 visit may occur during the time the subject may want to receive the 2021-2022 seasonal influenza vaccine. Hence, the tests/procedures (including immunogenicity sample collection) originally planned for the Day 182 visit will be collected at the Day 182 timepoint or immediately prior to administration of the 2021-2022 seasonal influenza vaccine (whichever comes first).

The post-vaccination visit procedures will be performed by blinded site staff members at the clinical site. For subjects in quarantine, these procedures will be performed by blinded trained medical staff at the subject's home (or place of quarantine). The following procedures will be performed during the Day 182 visit (± 14 days):

- Review the memory aid 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. Collect manual memory aid and provide subjects with another memory aid for the collection of safety data from Day 183 to Day 365;
- Review the subject's safety data and ensure all updates on concomitant medication usage and any changes in the subject's health (AEs ongoing from Day 28, SAEs, AESIs, MAAEs, or NOCDs) are recorded appropriately;
- Confirm that the subject has continued to comply with protocol requirements (e.g. no use of prohibited concomitant medications);
- Perform a vital signs measurement, including resting BP, HR, and OT;
- Collect blood samples for immunogenicity (serology) assessments and prepare and store these samples until shipment to the analytical laboratories.

10.1.10 Final Visit – Day 365 (Visit 6)

The post-vaccination final visit procedures will be performed by blinded site staff members at the clinical site. For subjects in quarantine, these procedures will be performed by blinded trained medical staff at the subject's home (or place of quarantine). The following procedures will be performed during the Day 365 visit (± 14 days):

- Review the subject's safety data and ensure all updates on concomitant medication usage and any changes in the subject's health (AEs ongoing from Day 28, SAEs, AESIs, MAAEs, or NOCDs) are recorded appropriately. Collect the subject's memory aid;
- Confirm that the subject has continued to comply with protocol requirements (e.g. no use of prohibited concomitant medications);
- Perform a vital signs measurement, including resting BP, HR, and OT;

- Collect blood samples for immunogenicity (serology) assessments and prepare and store these samples until shipment to the analytical laboratories.

Any subject who withdraws consent from the study will be asked to undergo Day 365 visit (Visit 6) procedures within two weeks of withdrawal, if the subject agrees.

10.2 Safety

10.2.1 Evaluations

Safety and tolerability will be evaluated by solicited local and systemic AEs (immediate AEs within 30 minutes post-vaccination and solicited AEs up to seven days post-vaccination), unsolicited AEs up to 28 days post-vaccination (including immediate unsolicited AEs within 30 minutes post-vaccination), and SAEs, AESIs, MAAEs, NOCDs, and AEs leading to withdrawal up to the end of the study. In addition, events will be monitored for a possible hypersensitivity component and potential immune-mediated diseases from all reported events during the study (collected AEs, SAEs, AESIs, NOCDs, and AEs leading to withdrawal). Clinical safety methods will include repeated urine, blood chemistry and haematology testing.

10.2.1.1 Solicited Local and Systemic AEs

Subjects will be monitored for both solicited local AEs (erythema, swelling, and pain at the injection site) and solicited systemic AEs (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 (at least 30 minutes), staff will monitor them for local and systemic AEs; after release from the clinic facility, from the evening of Day 0 to the evening of Day 7, subjects will measure and record their local and systemic AEs in their diary.

The intensity of the solicited local and systemic AEs will be assessed by the subject, documented in the diary, and graded as: mild (1), moderate (2), severe (3) or potentially life threatening (4) (please refer to Table 6). The causal relationship of all solicited local and systemic AEs will be considered related.

The Investigator should assess solicited AEs and determine if any meet the criteria for SAE. Any solicited local or systemic AEs that meet the criteria for SAE should be reported to the Sponsor within 24 hours (Section 13.1.6) and entered as an SAE in the eCRF.

Table 6 Severity Grades for Solicited Local and Systemic AEs

Symptoms	Severity				
	None	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially life-threatening)
Injection Site AEs (Local AEs)					
Erythema (redness)	< 25 mm	25 - 50 mm	51 - 100 mm	> 100 mm	Necrosis or exfoliative dermatitis
Swelling	< 25 mm	25 - 50 mm and does not interfere with activity	51 – 100 mm or interferes with activity	> 100 mm or prevents daily activity	Necrosis
Pain	None	Does not interfere with activity	Repeated use of non-narcotic pain reliever for more than 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Results in a visit to emergency room (ER) or hospitalization
Solicited Systemic AEs					
Fever (ºC or ºF)	< 38.0 ºC < 100.4 ºF	38.0 - 38.4 ºC 100.4 - 101.1 ºF	38.5 - 38.9 ºC 101.2 - 102.0 ºF	39.0 - 40.0 ºC 102.1 - 104.0 ºF	> 40.0 ºC > 104.0 ºF
Headache	None	No interference with activity	Repeated use of non-narcotic pain reliever for more than 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	Results in a visit to emergency room (ER) or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Results in a visit to emergency room (ER) or hospitalization
Muscle aches	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Results in a visit to emergency room (ER) or hospitalization
Joint aches, chills, feeling of general discomfort or uneasiness (malaise), swelling in the axilla, swelling in the neck	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Results in a visit to emergency room (ER) or hospitalization

10.2.1.2 Adverse Events

All spontaneous unsolicited AEs occurring within 28 days after vaccination will be reported in the "Adverse Event" screen in the subject's eCRF, irrespective of intensity or whether or not they are considered to be vaccination-related. Thereafter, from Day 29 to the end of the study, SAEs, AEs leading to withdrawal, AESIs, and NOCDs will be monitored and reported in the eCRF.

The intensity of unsolicited 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.

The Investigator should assess unsolicited AEs and determine if any meet the criteria for SAE. Any unsolicited AEs that meet the criteria for SAE should be reported to the Sponsor within 24 hours (Section 13.1.6) and entered as an SAE in the eCRF.

10.2.1.3 Clinical Laboratory Tests

Blood samples for biochemistry and haematology, HIV, Hepatitis B and Hepatitis C markers in serum, and urine samples for urinalysis will be collected according to the Time and Events Schedule (see Table 1). Any laboratory result outside of the testing laboratory's normal range will be classified as 'clinically significant' (CS) or 'not clinically significant' (NCS) by the site Investigator, with appropriate documentation. Any laboratory test performed at screening with a value outside the normal range may be repeated (prior to vaccination) at the discretion of the Investigator. Repeated tests will be considered the Baseline results.

The Investigator must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the study in the source documents. The tests to be performed by the laboratory are presented in Table 7.

Table 7 Clinical Laboratory Tests

Biochemistry (serum):	
Sodium	Alkaline phosphatase
Potassium	Alanine transferase (ALT)
Urea	Aspartate transferase (AST)
Creatinine	Gamma glutamyltransferase (GGT)
Glucose	Cholesterol (total, HDL, LDL)
Bilirubin (total)	Triglyceride
Albumin	Chloride
Total protein	Calcium
	Phosphorus
Haematology:	
Haemoglobin	Mean cell haemoglobin (MCH)
Hematocrit	Mean cell concentration (MCHC)
Red blood cells	Mean cell volume (MCV)
Platelets	Lymphocytes
Mean platelet volume (MPV)	Monocytes
White cell count (total, WBC)	Eosinophils
Neutrophils	Basophils

Serology:	
HIV Hepatitis C	Hepatitis B
Urinalysis:	
Macroscopic examination (color, aspect) pH Specific gravity	Glucose Protein Blood

All protocol required safety laboratory parameters are defined in study-specific documentation.

10.2.1.4 Vital Signs

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

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

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

10.2.1.5 Physical Examinations

A limited physical examination will be performed by the Investigator (or sub-Investigator) as part of screening procedures and on Day 0 (prior to eligibility assessment) and Day 3. History/symptom-directed physical examinations may be performed at any other study visits if 1) new complaints or concerns are raised by either the study subject or study staff and 2) deemed to be necessary by the Investigator.

10.2.2 Safety Endpoints

10.2.2.1 Primary Endpoints

- Occurrences, intensity, and relationship to vaccination of immediate AEs (30 minutes post-vaccination);
- Occurrences and intensity of solicited local and systemic AEs (for seven days following study vaccine administration);
- Occurrences, intensity, and relationship of unsolicited AEs for 28 days following study vaccine administration;
- Number and percentage of subjects with normal and abnormal, clinically significant urine, haematological and blood biochemistry values, and urinalysis at Days 0, 3, and 28;

- Occurrences of SAEs, AEs leading to withdrawal, AESIs, MAAEs, NOCDs, and deaths up to Day 28;
- Occurrences of SAEs, AEs leading to withdrawal, AESIs, MAAEs, NOCDs, and deaths from Day 29 up to Day 182;
- Occurrences of SAEs, AEs leading to withdrawal, AESIs, MAAEs, NOCDs, and deaths from Day 183 up to the end of the study (Day 365).

10.2.2.2 Secondary Endpoints

- Occurrences, intensity, and relationship to vaccination of immediate AEs (30 minutes post-vaccination), stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination;
- Occurrences and intensity of solicited local and systemic AEs (for seven days following study vaccine administration), stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination;
- Occurrences, intensity, and relationship of unsolicited AEs for 28 days following study vaccine administration, stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination;
- Number and percentage of subjects with normal and abnormal, clinically significant urine, haematological and blood biochemistry values, and urinalysis at Days 0, 3, and 28, stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination;
- Occurrences of SAEs, AEs leading to withdrawal, AESIs, MAAEs, NOCDs, and deaths up to Day 28, stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination;
- Occurrences of SAEs, AEs leading to withdrawal, AESIs, MAAEs, NOCDs, and deaths from Day 29 up to Day 182, stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination;
- Occurrences of SAEs, AEs leading to withdrawal, AESIs, MAAEs, NOCDs, and deaths from Day 183 up to the end of the study (Day 365), stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination.

10.3 Immunogenicity

10.3.1 Immunogenicity Evaluations

Immunogenicity will be evaluated by the humoral immune response induced in subjects, using the HI assay on Days 0, 28, 182, and 365 and using the MN assay on Days 0 and 28.

The blood samples for immunogenicity will be analyzed in one or more central laboratories; information on processing and the central laboratories will be provided in the study-specific documentation.

10.3.2 Immunogenicity Endpoints

Unless otherwise mentioned, point estimates and 95 % CI will be calculated for all immunogenicity endpoints and responses in the adjuvanted QVLP recipients will be compared with the active comparator groups using descriptive statistics.

10.3.2.1 Primary Endpoint

- HI antibody response induced by adjuvanted and unadjuvanted QVLP and Fluzone HD Quad against the homologous influenza strains on Day 28, compared to Day 0 values, will be analyzed as follows:
  - GMTs of HI antibody on Days 0 and 28;
  - SC rate: the proportion of subjects in a given treatment group with either a ≥ 4-fold increase in reciprocal HI titers between Day 0 and Day 28 or a rise of undetectable HI titer (i.e. < 10) pre-vaccination (Day 0) to an HI titer of ≥ 40 on Day 28;
  - SP rate: the proportion of subjects in a given treatment group attaining a reciprocal HI titer of ≥ 40 on Day 28 (the percentage of vaccine recipients with a serum HI titer of at least 1:40 following vaccination);
  - GMFR: the geometric mean of the ratio of GMTs (Day 28/Day 0).

10.3.2.2 Secondary Endpoints

- MN antibody response induced by adjuvanted and unadjuvanted QVLP and Fluzone HD Quad against the homologous influenza strains on Day 28, compared to Day 0 values, will be analyzed as follows:
  - GMTs of MN antibody on Days 0 and 28;
  - SC rate: the proportion of subjects in a given treatment group with either a ≥ 4-fold increase in reciprocal MN titers between Day 0 and Day 28 or a rise of undetectable MN titer (i.e. 7.1) pre-vaccination (Day 0) to an MN titer of ≥ 28.3 at Day 28 post-vaccination;
  - GMFR: the geometric mean of the ratio of GMTs (Day 28/Day 0).

- HI antibody response induced by adjuvanted and unadjuvanted QVLP and Fluzone HD Quad against the heterologous influenza strains on Day 28, compared to Day 0 values. HI antibody titers will be analyzed as follows:
  - GMTs of HI antibody on Days 0 and 28;
  - SC rate: the proportion of subjects in a given treatment group with either a ≥ 4-fold increase in reciprocal HI titers between Day 0 and Day 28 or a rise of undetectable HI titer (i.e. < 10) pre-vaccination (Day 0) to an HI titer of ≥ 40 on Day 28;
  - SP rate: the proportion of subjects in a given treatment group attaining a reciprocal HI titer of ≥ 40 on Day 28 (the percentage of vaccine recipients with a serum HI titer of at least 1:40 following vaccination);
  - GMFR: the geometric mean of the ratio of GMTs (Day 28/Day 0).
- HI antibody response (against homologous and heterologous influenza strains) and MN antibody response (against homologous influenza strains) induced by adjuvanted and unadjuvanted QVLP and Fluzone HD Quad on Day 28, compared to Day 0 values, stratified by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination;
- Durability of antibody responses 6 months post-vaccination, as determined by HI antibody responses induced by adjuvanted and unadjuvanted QVLP and Fluzone HD Quad against the homologous influenza strains on Day 182, compared to Day 0 values.
  - HI antibody titers will be analyzed as follows:
    - GMTs of HI antibody on Day 182;
    - SC rate: the proportion of subjects in a given treatment group with either a ≥ 4-fold increase in reciprocal HI titers between Day 0 and Day 182 or a rise of undetectable HI titer (i.e. < 10) pre-vaccination (Day 0) to an HI titer of ≥ 40 on Day 182;
    - SP rate: the proportion of subjects in a given treatment group attaining a reciprocal HI titer of ≥ 40 on Day 182 (the percentage of vaccine recipients with a serum HI titer of at least 1:40 following vaccination);
    - GMFR: the geometric mean of the ratio of GMTs (Day 182/Day 0).
- Durability of antibody responses 12 months post-vaccination, as determined by HI antibody responses induced by adjuvanted and unadjuvanted QVLP and Fluzone HD Quad against the homologous influenza strains on Day 365, compared to Day 0 values.
  - HI antibody titers will be analyzed as follows:
    - GMTs of HI antibody on Day 365;
    - SC rate: the proportion of subjects in a given treatment group with either a ≥ 4-fold increase in reciprocal HI titers between Day 0 and Day 365 or a rise of undetectable HI titer (i.e. < 10) pre-vaccination (Day 0) to an HI titer of ≥ 40 on Day 365;
    - SP rate: the proportion of subjects in a given treatment group attaining a reciprocal HI titer of ≥ 40 on Day 365 (the percentage of vaccine recipients with a serum HI titer of at least 1:40 following vaccination);

- GMFR: the geometric mean of the ratio of GMTs (Day 365/Day 0);

11 SUBJECT COMPLETION/WITHDRAWAL

11.1 Temporary Contraindications

An exclusion criterion that renders subjects ineligible for the study may be temporary in nature:

- Acute disease defined as presence of any moderate or severe acute illness with or without a fever within 48 hours prior to vaccination.

If, on Day 0, a subject is considered ineligible due to one of these "temporary contraindications", the subject should be considered as a screening failure. Following the resolution of such conditions, a subject may be rescreened (including the informed consent process) under a new number and, if considered eligible by the Investigator, be enrolled in the study.

11.2 Screening Failures

Screening failures are subjects who have signed the study-specific ICF but are not eligible for enrollment (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.

Recording of screening failures will be documented in the study records maintained at the participating clinical sites and recorded in the IRT system. Screen failures will not receive a safety follow-up. Any subjects who are considered as a screening failure should be indicated as such. A screening failure subject can be rescreened (under a new number). If the subject is rescreened (including the informed consent process), a new subject number will be allocated.

11.3 Removal of Subjects from Treatment or Assessment

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

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

- The subject withdraws consent;
- The subject is lost to follow-up;
- The subject is incarcerated or incapacitated during the conduct of the clinical study;
- The subject has moved away from the study area and can no longer fulfill the terms of their participation in the clinical study;
- The subject displays non-compliance to the terms of their participation in the clinical study (based on Investigator's or Medicago's [or its designee's] opinion);

- The Investigator has lost confidence in the subject's ability to adhere to the terms of their participation in the clinical study (based on Investigator's opinion);
- Safety reasons as judged by the Investigator and/or Medicago (or its designee);
- Medicago or the regulatory authority(ies) terminates the clinical study.

Withdrawal subjects will be those who leave the study before Day 365, for whatever reason; withdrawal subjects will not be replaced. Any subject who withdraws consent from the study will be asked to visit the clinical site within two weeks of withdrawal, if the subject agrees. The procedures performed for the final assessment will comprise of those for the Day 365 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 and in the appropriate section of the eCRF. The eCRF must be completed up to and including the time of the drop-out/final assessment.

11.3.1 Follow-up of Discontinuations

All subjects who receive a study vaccine will be followed for safety until the end of the study, 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. In addition, the IDMC may interrupt or halt the study for safety reasons (refer to Section 13.1.12). The Investigator will immediately, on discontinuance of the clinical study at the clinical site, inform both the study subjects and the Institutional Review Board (IRB) responsible for the study of the discontinuance, provide them with reasons for the discontinuance and advise them in writing of any potential health risks to the subjects themselves or to other persons. It is Medicago's (or its designee's) responsibility to report discontinuance of the study to the local regulatory agencies within the appropriate timeframe, providing them with the reasons for the discontinuance and advising them in writing of any potential health risks to the study subjects or to other persons. Medicago (or its designee) must then inform the Investigator that the appropriate notifications were done.

12 STATISTICAL METHODS

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

All descriptive and inferential statistical analyses will be performed using Statistical Analysis System® (SAS®) software (version 9.4 or higher).

12.1 Analysis Populations

12.1.1 Safety Analysis Set

The SAS is defined as all subjects who received either the adjuvanted QVLP or the active comparators. All safety analysis will be performed using the SAS, according to the treatment the subjects actually received.

12.1.2 Intention-To-Treat Set

The ITT set will consist of all subjects who were randomized in the study. Subjects who received the wrong treatment will be analyzed as randomized.

12.1.3 Per Protocol Set

The per protocol (PP) set will consist of a subset of subjects with a Day 0 and any post-vaccination immunogenicity assessment who completed the study with no major protocol deviations related to subject eligibility, the ability to develop a valid immune response, prohibited medication use, or the immunogenicity analyses; and who received QVLP or the active comparators. For the Day 28 analysis, this should include the subjects who received the vaccine dose and had Day 0 and Day 28 immunogenicity sample collections. For the Day 182 analysis, this should include the subjects who received the vaccine dose and had Day 0 and Day 182 immunogenicity sample collections. For the Day 365 analysis, this should include the subjects who received the vaccine dose and had Day 0 and Day 365 immunogenicity sample collections. Subjects who had blood samples for immunogenicity taken outside of the time window for blood sample collection are to be excluded from the PP set for the specific visit. Major protocol deviations will be identified and documented during a blinded data review prior to database lock and confirmed at the time of database lock. Subjects who received the wrong treatment, but for whom the treatment received can be unequivocally confirmed, will be analyzed as treated, provided they have no other deviations that compromise their data.

The analyses of all immunogenicity endpoints will be performed using the PP set and the ITT set. The analysis in the PP set will be considered the primary analysis for these objectives in order to collect information regarding the immunogenicity responses that most closely reflect the scientific model underlying the protocol. The ITT set will be used as sensitivity analysis.

12.2 Sample Size Determination

The sample size up to approximately 120 subjects with 40 subjects in each treatment group will make it possible to perform the initial evaluation of vaccine immunogenicity and detect gross differences in rates of adverse events. The sample size is not large enough to detect all types of adverse reactions, including less frequent or rare events. The objective of this study is to quantify the type, percentage, intensity, duration, and relationship of common post-vaccination safety events to determine if they differ clinically among the treatment groups.

12.3 Day 28 and Day 182 Data Analyses

Data analyses will be performed after the last subject has completed Day 28 assessments and Day 182 assessments; selected tables, listings and figures (as applicable) will be generated according to the SAP, by the third-party statistical team (see Section 6.2). The results of the interim analysis will be confidential and strictly limited to the authorized staff members (see Section 6.2). Moreover, these results will allow discussions of the clinical data to inform study design decisions of the subsequent study, without having to wait until after the end of the follow-up period for study completion.

12.4 Baseline and Subject Disposition

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

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

12.5 Safety Analyses

The safety endpoints are defined in Section 10.2.2.

12.5.1 Analysis of Primary Endpoints

The primary safety endpoints are defined in Section 10.2.2.1.

The original terms used in the eCRFs by Investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). All eCRF reported AEs with onset post-vaccination will be included in the safety analyses.

Safety and tolerability endpoints (immediate AEs [30 minutes post-vaccination], solicited local and systemic AEs, unsolicited AEs, SAEs, AEs leading to subject withdrawal, AESIs, MAAEs, NOCDs, and deaths) will be summarized by treatment using descriptive statistics.

Laboratory (biochemical, haematological, and urine) data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory test at Baseline and at each scheduled timepoint (Day 3 and Day 28). Changes from Baseline results will be presented in pre- versus post-treatment cross tabulations (with classes for below, within, and above normal ranges).

Special attention will be given to those subjects who die, who discontinue from the study due to an AE, who experience an SAE (e.g. summaries, listings, and narrative preparation may be provided, as appropriate), or who experience an AESI (see Section 13.1.3).

Analyses of primary safety endpoints will include each group as a whole. For the following categories, AE information will also be presented by gender (male and female) and race (Caucasian or White; Black or African American; Asian) for the overall population (65 years of age and older):

- Immediate solicited and unsolicited AEs up to 30 minutes after vaccination;
- Solicited local and systemic AEs within Days 0 to 7;
- Most frequent unsolicited AEs within 28 days after vaccination;
- AESIs;
- MAAEs;
- SAEs;
- AEs leading to death;
- AEs leading to withdrawal.

12.5.2 Analysis of Secondary Endpoints

The secondary safety endpoints are defined in Section 10.2.2.2.

The analysis of the secondary safety endpoints will be identical to the analysis of the primary safety endpoints (refer to Section 12.5.1) with the exception that the analysis will only include comparisons by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination. For the following categories, AE information will also be presented by gender (male and female) and race (Caucasian or White; Black or African American; Asian) according to prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination:

- Immediate solicited and unsolicited AEs up to 30 minutes after vaccination;
- Solicited local and systemic AEs within Days 0 to 7;
- Most frequent unsolicited AEs within 28 days after vaccination;
- AESIs;
- MAAEs;

- SAEs;
- AEs leading to death;
- AEs leading to withdrawal.

12.6 Immunogenicity Analyses

12.6.1 Analysis of Primary Endpoint

The primary immunogenicity endpoint is defined in Section 10.3.2.1.

The following analyses for the HI assay (homologous strains) will be performed on the PP set:

- GMT (Day 0 and Day 28): The point estimates and the corresponding two-sided 95 % CI by treatment group and strain will be calculated as the antilog of the mean and 95 % CI of log transformed titer values;
- SC rate (Day 28): The point estimates and the corresponding two-sided 95 % CI for subjects achieving SC by treatment group and strain will be calculated and reported;
- SP rate (Day 0 and Day 28): The point estimates and the corresponding two-sided 95 % CI for subjects achieving SP by treatment group and strain will be calculated and reported;
- GMFR: the geometric mean of the ratio of GMTs (Day 28/Day 0).

The GMFR will be derived by using ANCOVA to model the difference in the log of the titer values between Day 28 and Day 0, with treatment group as main effect and baseline titer as covariate.

GMT for HI will be compared between treatment groups using the analysis of variance (ANOVA) model. GMFR for HI will be compared using the ANCOVA model. For SC rate and SP rate, Fisher's exact tests or chi square tests will be used to compare between the treatment groups.

Analyses of primary immunogenicity endpoint will include each group as a whole.

The analyses of the primary immunogenicity endpoints will also be performed using the ITT set.

12.6.2 Analysis of Secondary Endpoints

The secondary immunogenicity endpoints are defined in Section 10.3.2.2.

The following analyses for the MN assay (homologous strains) will be performed on the PP set:

- GMT (Day 0 and Day 28): The point estimates and the corresponding two-sided 95 % CI by treatment group and strain will be calculated as the antilog of the mean and 95 % CI of log transformed titer values;
- SC rate (Day 28): The point estimates and the corresponding two-sided 95 % CI for subjects achieving SC by treatment group and strain will be calculated and reported;
- GMFR: the geometric mean of the ratio of GMTs (Day 28/Day 0).

The following analyses for the HI assay (heterologous strains) will be performed on the PP set:

- GMT (Day 0 and Day 28): The point estimates and the corresponding two-sided 95 % CI by treatment group and strain will be calculated as the antilog of the mean and 95 % CI of log transformed titer values;
- SC rate (Day 28): The point estimates and the corresponding two-sided 95 % CI for subjects achieving SC by treatment group and strain will be calculated and reported;
- SP rate (Day 0 and Day 28): The point estimates and the corresponding two-sided 95 % CI for subjects achieving SP by treatment group and strain will be calculated and reported;
- GMFR: the geometric mean of the ratio of GMTs (Day 28/Day 0).

The GMFR will be derived by using ANCOVA to model the difference in the log of the titer values between Day 28 and Day 0, with treatment group as main effect and baseline titer as covariate.

The durability of the HI antibody responses will be evaluated up to 6 months post-vaccination. The following analyses for the HI assay will be performed on the PP set:

- GMT (Day 182): The point estimates and the corresponding two-sided 95 % CI by treatment group and strain will be calculated as the antilog of the mean and 95 % CI of log transformed titer values;
- SC rate (Day 182): The point estimates and the corresponding two-sided 95 % CI for subjects achieving SC by treatment group and strain will be calculated and reported;
- SP rate (Day 182): The point estimates and the corresponding two-sided 95 % CI for subjects achieving SP by treatment group and strain will be calculated and reported;
- GMFR: the geometric mean of the ratio of GMTs (Day 182/Day 0).

The GMFR will be derived by using ANCOVA to model the difference in the log of the titer values between Day 182 and Day 0, with treatment group as main effect and baseline titer as covariate.

The durability of the HI antibody responses will be evaluated up to 12 months post-vaccination. The following analyses for the HI assay will be performed on the PP set:

- GMT (Day 365): The point estimates and the corresponding two-sided 95 % CI by treatment group and strain will be calculated as the antilog of the mean and 95 % CI of log transformed titer values;
- SC rate (Day 365): The point estimates and the corresponding two-sided 95 % CI for subjects achieving SC by treatment group and strain will be calculated and reported;
- SP rate (Day 365): The point estimates and the corresponding two-sided 95 % CI for subjects achieving SP by treatment group and strain will be calculated and reported;
- GMFR: the geometric mean of the ratio of GMTs (Day 365/Day 0).

The GMFR will be derived by using ANCOVA to model the difference in the log of the titer values between Day 365 and Day 0, with treatment group as main effect and baseline titer as covariate.

GMTs for HI and MN (at Days 0 and 28 only) will be compared between treatment groups using the ANOVA model. GMFRs for HI and MN (at Days 0 and 28 only) will be compared using the ANCOVA model. For SC rate (HI and MN [at Day 28 only]) and SP rate (HI only), Fisher's exact tests or chi square tests will be used to compare between the treatment groups.

The analyses for the HI assay (homologous strains) will include comparisons by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination.

The analyses for the HI assay (heterologous strains) and the MN assay (homologous strains, at Days 0 and 28 only) will include each group as a whole as well as comparisons by prior influenza vaccination status, if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination.

The analyses of the secondary immunogenicity endpoints will also be performed using the ITT set.

13 ADVERSE EVENT REPORTING

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

13.1 Definitions

13.1.1 Serious Adverse Events

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

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

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

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

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

13.1.2 Adverse Events

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

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

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

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.

Note: According to the FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials [FDA 2007]: "*Nonetheless, we believe that categorization or grading of data as outlined in this document is supplementary to and should not replace full and complete data analysis. These guidelines for toxicity grading scales are primarily intended for healthy adult and adolescent volunteers*." and "*Toxicity grading scales for laboratory abnormalities should consider the local laboratory reference values when the parameter limit values are defined. The characterization of laboratory parameters among some populations of healthy adults and adolescents may require the exercise of clinical judgment, for example, consideration of the potential for ethnic differences in white blood cell (WBC) counts or gender differences in creatine phosphokinase (CPK) values*."

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 AEs persist beyond Day 7, these will also be recorded as unsolicited 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 unsolicited AEs occurring within 28 days after vaccination must be reported in the "Adverse Event" screen in the subject's eCRF, irrespective of intensity or whether or not they are considered to be vaccination-related. Thereafter, from Day 29 through to Day 365, SAEs, AEs leading to withdrawal, AESIs, MAAEs, and NOCDs (see Section 13.1.4 for definition) will be monitored and reported in the eCRF. Additional details on eCRF entries can be found in the eCRF completion guidelines.

13.1.2.1 Medically Attended Adverse Events

Medically attended adverse events are defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider.

13.1.3 Adverse Events of Special Interest

13.1.3.1 Adverse Events of Special Interest for QVLP

13.1.3.1.1 Hypersensitivity Reactions

In the eight studies completed to date, all reported events were monitored for a possible hypersensitivity component (events were searched using both narrow and broad standardized MedDRA® queries). Based on the data available so far, there is no definitive evidence of anaphylaxis associated with use of QVLP in humans. However, one subject who received QVLP experienced a possible, truncated anaphylactic reaction assessed as possibly related to the vaccine by the Investigator. Also, a small number of subjects had potential hypersensitivity reactions judged to be related to vaccine administration (no more than 0.5 % of subjects in any given VLP treatment group experienced one of these events) and these events were distributed fairly evenly among treatment groups, including the placebo and the active comparator groups. However, since severe reactions are considered to be an important potential risk (based on the theoretical risk that using plants for the production of biotherapeutics may induce hypersensitivity) the Sponsor will continue to require that appropriate medical treatment and supervision are available to manage any possible anaphylactic reactions. Further, to collect

additional data on these events, Medicago will closely monitor and assess anaphylaxis and severe allergic reactions (grade 3 and above) assessed as related to the Investigational product as AESIs.

13.1.3.2 Adverse Events of Special Interest for AS03

13.1.3.2.1 Narcolepsy

An increased risk of narcolepsy (a lifelong disease causing an overwhelming daytime drowsiness and sudden attacks of sleep) was observed in some individuals after vaccination with a flu vaccine containing AS03 (called Pandemrix™) during the H1N1 pandemic in 2009-2010. This study vaccine contains AS03. A similar risk of narcolepsy was not identified with other vaccines containing AS03. Currently available data suggest that the cases of narcolepsy seen immediately following the 2009-2010 pandemic in some people were most likely triggered by a reaction in those people to a protein from the flu virus itself which was used to manufacture the Pandemrix™ vaccine. Research is continuing to assess whether either of the main components of the 2009-2010 flu pandemic vaccine (e.g., the viral proteins in the form used in the vaccine or the AS03 adjuvant) may have contributed to the reaction.

Safety signal of narcolepsy after exposure to QVLP with adjuvant AS03 will be closely monitored by retrieving data for this AESI using MedDRA PT Narcolepsy and analyzing available data via Medicago's safety governance process for any potential signal.

13.1.3.2.2 Potential Immune-Mediated Diseases and Other AESI as Listed in Section 19.5

These important potential risks remain "theoretical" as they were for other vaccines containing adjuvants and hence will be collected as AESIs. Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology. Adverse events that need to be recorded and reported as pIMDs include those listed in Section 19.5.

However, the Investigator will exercise their medical and scientific judgement in deciding whether other diseases have an autoimmune origin (that is pathophysiology involving systemic or organ-specific pathogenic autoantibodies) and should also be recorded as a pIMD.

When there is enough evidence to make any of the diagnoses mentioned in Section 19.5, the AE must be reported as a pIMD. Symptoms, signs or conditions which might (or might not) represent the above diagnoses, should be recorded and reported as AEs but not as pIMDs until the final or definitive diagnosis has been determined, and alternative diagnoses have been eliminated or shown to be less likely.

In order to facilitate the documentation of pIMDs in the eCRF, a pIMD standard questionnaire and a list of preferred terms (PTs) and PT codes corresponding to the above diagnoses will be available to Investigators at study start.

Once a pIMD is diagnosed (serious or non-serious) in a study subject, the Investigator (or designate) must complete, date and sign an Adverse Events Report Form.

13.1.4 New Onset of Chronic Disease

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

NOCDs will be collected from vaccination on Day 0 to Day 365 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

Details on safety reporting are defined in study-specific documentation, including SAE processing, country-specific reporting requirements, regulatory unblinding, roles and responsibilities of different stake holders, and contact details of personnel responsible for safety reporting. A brief summary of salient information is presented below.

All post-vaccination SAEs and AESIs will be reported from the time of receiving the study vaccine on Day 0 through to the end of the study (final scheduled visit). The Investigator (or designee) must report, by e-mail, all SAEs and AESIs, whether considered related to the study vaccine or not to Medicago (or its designee) within 24 hours of the Investigator learning of the event. The Investigator must also complete the electronic SAE/AESI form in the electronic data capture (EDC) database within 24 hours of awareness of the event following the Electronic Case Report Form Completion Guidelines (eCCG). An automatic email notification will be sent to the Medicago Clinical Safety mailbox after the Investigator submits the electronic SAE/AESI form. If the EDC database is not available, the Investigator must complete, sign, and date the paper SAE/AESI report form, and send, via e-mail, a copy to the Medicago safety e-mail address (listed below) and the appropriate regional e-mail address, as required, within 24 hours of awareness of event. If the SAE/AESI paper reporting process is followed, the Investigator will need to enter the SAE/AESI information in the EDC system once available.

Medicago Safety e-mail address: Medicago-ClinicalSafety@medicago.com

Sponsor Safety Contact: PPD

Serious AEs will be reported to the local (or contract) IRB by the Investigator according to the IRB's policy and procedures.

13.1.7 Follow-up Reporting by the Investigator

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

13.1.8 Reporting of SAEs Occurring after Surveillance Period or Study Termination

All SAEs occurring during the safety follow-up period will be followed until resolution or for a period of 30 days from the final subject's visit (whichever occurs first), regardless of conclusion of the study. However, all related SAEs occurring during the safety follow-up period will be followed until resolution or stabilization.

A post-study AE/SAE is defined as any event that occurs outside of the AE/SAE detection period (post-Day 365). Active follow-up for AEs or SAEs will continue until Day 365 for all subjects. However, after Day 365, 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. These related SAEs will be followed until resolution or stabilization.

13.1.9 Causal Relationship

The Investigator must make the determination of relationship to the study vaccine for each unsolicited AE. The causal relationship of all solicited local and systemic AEs will be considered related. 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.

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

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

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

13.1.11 Independent Data Monitoring Committee

The IDMC will consist of a multidisciplinary group of three clinicians and/or physicians and one biostatistician who will, collectively, have extensive experience in the use of vaccines for patient treatment and in the conduct and safety monitoring of randomized clinical trials.

The IDMC will monitor the study conduct and review safety data at pre-defined times during the study for the purpose of providing recommendations to the Sponsor about whether:

- subject vaccination at a dose level will continue;
- subject vaccination at the next higher dose level will proceed;
- the study will continue in the event of a pre-defined safety signal.

The IDMC review will ensure the ongoing safety of the subjects in the study and the scientific integrity of the study.

The IDMC will participate in 2 planned review meetings, as described in Section 13.1.12 and will be provided with an unblinded seven-day safety data summary (refer to Section 19.4 and further defined in the IDMC charter) for each review meeting. Additional review meetings may be scheduled with the IDMC, if deemed necessary by the IDMC or the Sponsor.

13.1.12 Safety Review and Stopping Rules

A review of seven-day safety data will be carried out after the vaccination of the first three subjects in each of the treatment groups to ensure ongoing safety of study subjects as well as maintaining study scientific integrity. The review will include safety data from the first three subjects in treatment groups 1 to 3 (as presented in Table 4) and will determine whether vaccination of the remaining subjects in these three treatment groups. IDMC reviews will detect any early negative trends in the subjects and may necessitate a decision to not administer the study vaccine to the remaining subjects. The vaccinations for the first three subjects in each treatment group will be staggered so that each vaccination must be performed at least 30 minutes apart. A phone call reminding study subjects to complete the diary will be made at Day 1 and Day 8 post-vaccination and the subjects will be asked to visit the clinical site on Day 3 for safety assessments. Early accumulated safety outcome data which will include all self-reported solicited local and systemic symptoms, any adverse and/or serious adverse events occurring following administration of the injection will be collected and tabulated.

The IDMC will be provided the following unblinded seven-day solicited local and systemic AEs for the first three subjects enrolled in each of the three treatment groups:

- Occurrences of erythema, swelling and pain at the injection site;
- Occurrences of fever, headache, muscle aches, joint aches, fatigue, chills, and feelings of general discomfort or uneasiness;
- Swelling in the axilla or neck;
- Occurrence of any adverse or serious adverse events;
- Concomitant medications, doctor or emergency room or hospital visits associated with an adverse event or serious adverse event.

If the seven-day safety data summary (refer to Section 19.4) for the first three subjects in treatment groups 1 to 3 reviewed by the IDMC shows the safety of the vaccine (see Stopping rules below), the remaining subjects in treatment groups 1 to 3 will receive their vaccination. If the data does not show safety of the vaccine (see Stopping Rules below) for a particular treatment and the decision from the IDMC review is to stop further use of this treatment, then the following will apply:

- Subjects administered this treatment will be followed to the end of the study for all safety and immunogenicity outcomes, if subject permits;

- Subjects originally planned to be administered this treatment will not be redistributed to the other treatment groups (i.e. the planned sample size for each treatment group will not change);
- The study will continue in accordance with the protocol for the treatments deemed safe by the IDMC.

Stopping Rules

Safety monitoring of safety signals will be performed throughout the study. Stopping rules or conditions for stopping this clinical trial would occur if there was clear evidence of harm or harmful effects such as SAEs related to the treatment (study vaccine). An SAE which was thought to be unrelated to the study vaccine would not warrant stopping the trial.

The following event(s) may result in a halt to the study, for further review and assessment of the event(s):

- Any vaccine-related SAE in a subject for which causality cannot be attributed to another cause;
- If 2 or more subjects in a single treatment group experience the same or similar event(s) that cannot be clearly attributed to another cause:
  - a Grade 3 or higher vaccine-related AE during the study;
  - a Grade 3 or higher vaccine-related vital sign(s) abnormality;
  - a Grade 3 or higher vaccine-related clinical laboratory abnormality.

In the case that a pre-defined safety signal is met in any treatment group, subsequent dosing will result in at least a transient halt in the study to permit a complete evaluation of the reported event(s) and to consult an IDMC. A decision as to whether the study can progress as planned must be made and documented in the event of any safety signal.

14 INVESTIGATIONAL PRODUCT INFORMATION

14.1 Identity of Investigational Product

The study vaccine QVLP is composed of recombinant H1, H3, and two B proteins (hemagglutinin) expressed as VLPs and will be administered with the adjuvant AS03.

14.1.1 Study Vaccine Composition

QVLP is a sterile transparent to opalescent colorless to slightly yellowish liquid suspension consisting of a mix of VLPs from four strains, each bearing the hemagglutinin of one of the recommended virus strains, in a phosphate buffered saline (PBS) solution (100 mM $NaKPO_4$, 150 mM NaCl) and 0.01 % polysorbate 80 at pH 7.4).

AS03 is an established effective adjuvant that has been used in a licensed monovalent vaccine in the USA targeting H5N1 (Influenza A [H5N1] Virus Monovalent Vaccine, Adjuvanted). The adjuvant is a whitish to yellowish homogeneous milky liquid emulsion and it will be provided in

the original sterile vial container received from the manufacturer (GlaxoSmithKline). A 0.25 mL dose of AS03 represents one human dose.

14.1.2 Active Comparators

One of the two active comparators will be unadjuvanted QVLP (30 µg/strain), which was shown to be non-inferior to another licensed influenza vaccine. This quadrivalent influenza vaccine is a non-infectious, plant-derived influenza vaccine that will contain four types of purified VLP, each bearing trimeric, recombinant HA proteins of one of the targeted strains and is formulated to match the influenza virus strains as per the WHO recommendations for the 2020-2021 influenza season in the Northern Hemisphere.

The other active comparator will be an approved influenza vaccine, Fluzone HD Quad. This quadrivalent influenza vaccine will contain four split-virion, inactivated influenza virus strains propagated in embryonated chicken eggs, based on the influenza strains recommended by WHO for the 2020-2021 influenza season. Each 0.7 mL dose of vaccine contains 60 µg of hemagglutinin of each of the four influenza virus strains.

14.1.3 Preparation and Administration of Study Vaccine

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

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

The products 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 adjuvanted QVLP at a volume of 0.7 mL, the site will use a single dose vial of QVLP, a vial of AS03, and diluent (for use with half dose of AS03) that require mixing prior to vaccination;
- For the administration of the unadjuvanted QVLP at a volume of 0.7 mL, the site will use a single dose vial of QVLP and diluent that require mixing prior to vaccination;
- For the administration of Fluzone HD Quad at a volume of 0.7 mL, the site will prepare and administer the vaccine as per the manufacturer's information.

All study treatments will be administered on study Day 0 as an IM injection. For subjects with BMI < 30 kg/m^2, a 23 gauge needle of at least one inch or 2.5 cm in length can be used for vaccination. For subjects with BMI ≥ 30 kg/m^2, a needle of at least 1.5 inches or 3.5 cm in length must be used to ensure intramuscular delivery. According to randomization scheme, subjects will receive either adjuvanted or unadjuvanted QVLP or Fluzone HD Quad in the deltoid muscle of (preferably) the non-dominant arm. Whenever possible, the injection will be given in the

opposite arm from which blood samples are drawn, when applicable.

The product administered will be recorded in study-specific documentation (refer to Investigational Product Management Manual) by the clinical site, which will be separate from the study medication record for drug preparation. After drug accountability monitoring and reconciliation has been completed by the site and unblinded monitor, all study treatments (used and unused vials) will be destroyed locally upon Medicago's approval or returned to Medicago (or its designee) in accordance with instructions provided in the Investigational Product Management Manual.

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

14.1.4 Preparation, Handling, Storage, and Precautions for Use

The study treatment (including QVLP, the adjuvant, and Fluzone HD Quad) should be stored in an access-restricted area between 2 ºC and 8 ºC and protected from light; the vaccine should, however, be at room temperature before administration (i.e. the vaccine should not be administered cold and should be taken out of the refrigerator at least five minutes prior to administration). 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 QVLP and the adjuvant AS03 must NEVER be vigorously 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

Adjuvanted QVLP will be presented as a single dose vial of QVLP and a vial of the adjuvant AS03 and packaged in separate boxes. The active comparator, unadjuvanted QVLP, will be packaged in boxes containing single dose vials. The other active comparator, Fluzone HD Quad, will be provided as packaged by the manufacturer.

14.3 Labeling

The vials will have a product and study-specific label containing information that meets the applicable regulatory requirements.

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

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 study-specific documentation.

The study treatments or drugs must be handled in strict accordance with the Investigational Product Management Manual and the vial and syringe labels and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions. All unused study drugs must be available for verification by Medicago's (or its designee's) unblinded site monitor during on-site monitoring visits. The return of all unused study drugs to Medicago (or its designee) for destruction will be documented on study-specific documentation. 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), who remains blinded as to which treatment is administered. 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;
- 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.

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

16.2 Regulatory Ethics Compliance

16.2.1 Investigator Responsibilities

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

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

16.2.2 Independent Ethics Committee or Institutional Review Board

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

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

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

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

- Protocol amendments;

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

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

16.2.3 Informed Consent

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

16.2.4 Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to support the development, registration, and future marketing of the investigational product. The data must be collected and processed with adequate

precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be in place. Medicago (or its designee) personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential.

17 ADMINISTRATIVE REQUIREMENTS

17.1 Protocol Amendments

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

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

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

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

17.2 Regulatory Documentation

17.2.1 Regulatory Approval/Notification

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

17.3 Source Documentation

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

- Subject identification, eligibility, and study identification;
- ICF discussion and date of informed consent;
- Dates of visits;
- Results of safety and study procedures as required by the protocol;
- Record of all reactions, AEs, and associated follow-ups;
- Concomitant medication;
- Drug receipt, dispensing, and return records;
- Study drug preparation and 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. If Investigator judgement was used in the determination of eligibility, an explanation for inclusion of the subject in the study must be provided in the source documents. 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).

17.3.1 Diary and Memory Aid

Subjects will be provided with a diary (manual or electronic) in which to record AEs and other safety information. Subject diaries are considered source documents; the manual diary will be returned by the subject to the site at the Day 28 visit and kept with each subject's study chart. In the event the manual diary 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. The electronic diary will capture information directly in the electronic data capture system.

Corrections to data entered by the subject in the diary should only be performed by the subject him/herself, when possible. Clarifications can be made in the comment section of the manual diary by the study personnel if the subject is not present onsite to make the correction him/herself.

Subjects will be provided with memory aids (manual or electronic) to record information on unsolicited AEs, SAEs, AESIs, MAAEs, NOCDs, AEs leading to withdrawal, and reportable concomitant medications from the Day 0 to Day 28, Day 29 to Day 182, and Day 183 to the end of the study (Day 365). These memory aids will be collected by the site and are intended to be used by the subject to help them in reporting this information to site staff during phone contacts and clinical site visits. The electronic memory aids will capture information directly in the electronic data capture system.

17.4 Case Report Form Completion

An eCRF will be provided for each subject who is randomized and receives a dose of study vaccine. Screening failures will also be entered in an eCRF; 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.

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

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 qualified person who will accept the responsibility and is approved by Medicago. 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 (or new custodian) must permit access to such reports in a timely manner.

17.8 Study Completion/Termination

17.8.1 Study Completion

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

17.8.2 Study Termination

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

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

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

sufficient notice is given in advance of the intended closure.

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

17.9 Registration of Clinical Studies and Disclosure of Results

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

17.10 Publication Policy

The data derived from this study are the property of Medicago and cannot be published without prior authorization from Medicago. Any publication activities (i.e. preparation and submission of abstracts and manuscripts) will be at the discretion of Medicago.

Any proposed publication regarding this study, not prepared by Medicago personnel, must be provided to Medicago for comments and review at least 45 days prior to its intended publication. The proposed publication shall not include any confidential information or protected information to preserve Intellectual Property rights; any such information must be removed from the proposed publication.

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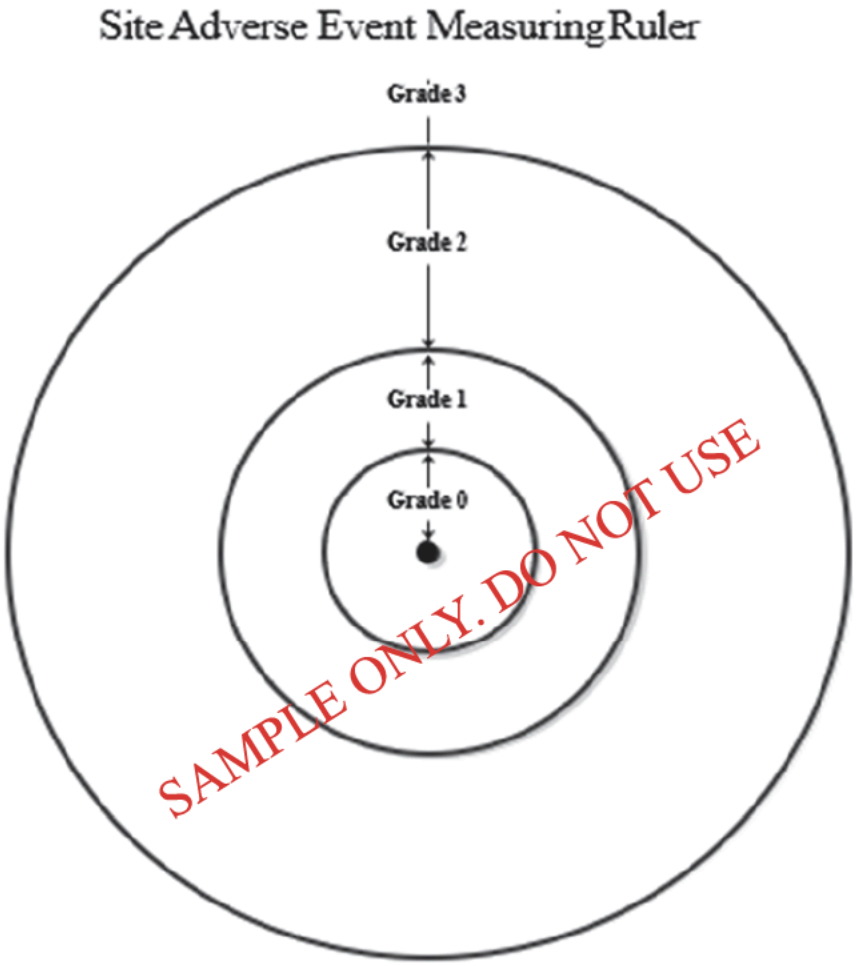
19 APPENDICES

The clinical documents included in the appendices are meant as examples only; the actual documents used during the trial may differ slightly.

19.1 Appendix 1 – Sample Ruler to Measure Local Adverse Events



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

19.2 Appendix 2 – Subject Diary Sample Pages

DIARY (DAY 0 to DAY 7)	
Study Name	A Randomized, Partially-Blinded, Active Comparator-Controlled, Dose-Ranging, Safety, Tolerability, and Immunogenicity Phase 1/2 Study of an Adjuvanted Seasonal Recombinant Quadrivalent VLP Influenza Vaccine in Adults 65 Years of Age and Older
Protocol Number	CP-PRO-AdjQVLP-020
Sponsor	Medicago USA Inc. 7 Triangle Drive Durham (NC), United States 27713
Clinical site Address	
Principal Investigator Name	
Clinical Research Coordinator	
24-hour Emergency Number	

DIARY (DAY 0 to DAY 7) INSTRUCTIONS

- You should fill in your Diary at approximately the same time, preferably in the evening.
- You will need to refer to this Diary during the Telephone Calls (on Day 1 and Day 8).
- You need to bring this Diary with you at the Day 3 and Day 28 visits.

- Fill in the Day 0 to Day 7 tables EVERY DAY for the first 7 days after you receive your vaccine dose.
- Fill in each day's column by entering the WORST grade for each symptom that you had during the period.
- Grayed out sections are to be left blank and will be completed by the site personnel.
- To complete this document, use blue or black ink. No pencil or liquid paper is allowed.
- If you made a mistake, cross out the incorrect information, initial and date, and write the correct answer beside.
- Date should be recorded with 2 digits for day, 3 letters for month and 4 digits for year

January	JAN	April	APR	July	JUL	October	OCT
February	FEB	May	MAY	August	AUG	November	NOV
March	MAR	June	JUN	September	SEP	December	DEC

TEMPERATURE:

- To record the temperature, use the thermometer you were given at the clinic. Do not drink, eat food or smoke prior to taking your temperature.
- You should take your temperature for the first 7 days following vaccination at approximately the same time each evening and at any other time if you feel feverish.
- You will need to record the highest temperature of the day on page 4.
- If your temperature is 38°C or 100.4°F or higher, you are allowed to take over-the-counter antipyretics (e.g., acetaminophen/paracetamol, aspirin, naproxen, or ibuprofen) and you should increase the frequency of temperature measurements to approximately every 4 hours, until you don't have a fever anymore.
- Medication intake needs to be documented on the Memory Aid and will be reviewed by the site personnel.

DIARY (DAY 0 to DAY 7) INSTRUCTIONS

SYMPTOMS:

- Complete the table referring to the following periods:
  - For the 1st column: the period between the vaccination and the 30 minutes post-vaccination;
  - For the 2nd column: the period between the last evaluation (30 minutes post-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.
- Evaluate the grade of all other symptoms according to the definitions:
  - **0= No symptom**
  - **1= Does not interfere with activity**
  - **2= Repeated use of non-narcotic pain reliever (e.g. Advil, Tylenol) >24 hours or interferes with activity but does not require medical intervention**
  - **3= Any use of narcotic pain reliever (e.g. codeine, morphine) or prevents daily activity and require medical intervention**
  - **4= Visit to Emergency room or hospitalization**
- List any other problems (not listed on pages 4 to 6) on the Memory Aid (Day 0 to Day 28) page "side effects (symptoms)".
- Symptoms listed on pages 4 to 6 which persist longer than 7 days after study vaccine administration must also be listed on the Memory Aid (Day 0 to Day 28) page "side effects (symptoms)".

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

Initial and date: |_|_|_|_|_|_|_|_|_| (dd mmm yyyy)

DIARY (DAY 0 to DAY 7)										
Day 0 to Day 7		**30 min, Post-dose**	**Evening, day of dose**	**1st Day after dose**	**2nd Day after dose**	**3rd Day after dose**	**4th Day after dose**	**5th Day after dose**	**6th Day after dose**	**7th Day after dose**
Date (dd-mmm-yyyy)										
Oral Temperature	°C / °F									
	Causality									
Redness where the injection was given	Grade									
	Causality									
	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									
	Causality									
	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									
	Causality									
	0= No symptom; **1**= Does not interfere with activity; **2**= Repeated use of non-narcotic pain reliever >24 hours or interferes with activity; **3**= Any use of narcotic pain reliever or prevents daily activity; **4**= Visit to Emergency room or hospitalization.									
Comments:										
MD signature and date:		dd mmm yyyy								

DIARY (DAY 0 to DAY 7)										
Day 0 to Day 7		**30 min, Post-dose**	**Evening, day of dose**	**1st Day after dose**	**2nd Day after dose**	**3rd Day after dose**	**4th Day after dose**	**5th Day after dose**	**6th Day after dose**	**7th Day after dose**
Headache	Grade									
	Causality									
GRADES	**0**= No symptom; **1**= Does not interfere with activity; **2**= Repeated use of non-narcotic pain reliever >24 hours or interferes with activity; **3**= Any use of narcotic pain reliever or prevents daily activity; **4**= Visit to Emergency room or hospitalization.									
Muscle aches	Grade									
	Causality									
GRADES	**0**= No symptom; **1**= Does not interfere with activity; **2**= Interferes with activity; **3**= Prevents daily activity; **4**= Visit to Emergency room or hospitalization.									
Fatigue	Grade									
	Causality									
GRADES	**0**= No symptom; **1**= Does not interfere with activity; **2**= Interferes with activity; **3**= Prevents daily activity; **4**= Visit to Emergency room or hospitalization.									
Joint aches	Grade									
	Causality									
GRADES	**0**= No symptom; **1**= Does not interfere with activity; **2**= Interferes with activity but does not require medical intervention; **3**= Prevents daily activity and requires medical intervention; **4**= Visit to Emergency room or hospitalization.									

Comments:

MD signature and date: dd mmm yyyy

DIARY (DAY 0 to DAY 7)										
Day 0 to Day 7		**30 min, Post-dose**	**Evening, day of dose**	**1st Day after dose**	**2nd Day after dose**	**3rd Day after dose**	**4th Day after dose**	**5th Day after dose**	**6th Day after dose**	**7th 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 (armpit)	Grade									
	Causality									

GRADES **0**= No symptom; **1**= Does not interfere with activity; **2**= Interferes with activity but does not require medical intervention; **3**= Prevents daily activity and requires medical intervention; **4**= Visit to Emergency room or hospitalization.

Comments:

I confirm I have reviewed the 3 pages of solicited symptoms and evaluated the causalities when needed. I confirm I have reviewed all entries in the Comments section on this page.

MD signature and date: _____ dd mmm yyyy

19.3 Appendix 3 – Subject Memory Aid Sample Pages

MEMORY AID (DAY 0 to DAY 28)	
Study Name	A Randomized, Partially-Blinded, Active Comparator-Controlled, Dose-Ranging, Safety, Tolerability, and Immunogenicity Phase 1/2 Study of an Adjuvanted Seasonal Recombinant Quadrivalent VLP Influenza Vaccine in Adults 65 Years of Age and Older
Protocol Number	CP-PRO-AdjQVLP-020
Sponsor	Medicago USA Inc. 7 Triangle Drive Durham (NC), United States 27713
Clinical site Address	
Principal Investigator Name	
Clinical Research Coordinator	
24-hour Emergency Number	

MEMORY AID (DAY 0 to DAY 28) INSTRUCTIONS

- You should fill in your Memory aid at approximately the same time, preferably in the evening.
- You will need to refer to this Memory Aid during the Telephone Calls (on Day 1 and Day 8).
- You need to bring this Memory Aid with you at the Day 3 and Day 28 visits.

- Grayed out sections are to be left blank and will be completed by the site personnel.
- To complete this document, use blue or black ink. No pencil or liquid paper is allowed.
- If you made a mistake, cross out the incorrect information, initial and date, and write the correct answer beside.
- Date should be recorded with 2 digits for day, 3 letters for month and 4 digits for year

January	JAN	April	APR	July	JUL	October	OCT
February	FEB	May	MAY	August	AUG	November	NOV
March	MAR	June	JUN	September	SEP	December	DEC

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 are taking. Examples may include prescription drugs (including vaccines), over-the-counter drugs, herbal supplements and/or vitamins. Indicate each intake of medication you are usually taking as needed.
- 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 an 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 28 visit, you will be required to tick the ongoing checkbox.
- Please contact the study site if you experience any severe effects or if you have any concerns at any time by using the emergency contact number provided on the first page of this Memory Aid.

You received your study vaccine on: dd mmm yyyy at: hh : mm **Initial and date:** dd mmm yyyy

MEMORY AID (DAY 0 to DAY 28)

Day 0 to Day 28 ❑ 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 28	❑ Yes ❑ No	❑ Initial and date: dd mmm yyyy
			dd mmm yyyy hh : mm	dd mmm yyyy hh : mm ❑ Ongoing at Day 28	❑ Yes ❑ No	❑ Initial and date: dd mmm yyyy

GRADES **0**= No symptom; **1**= Does not interfere with activity; **2**= Repeated use of non-narcotic pain reliever >24 hours or interferes with activity but does not require medical intervention; **3**= Any use of narcotic pain reliever or prevents daily activity and does require medical intervention; **4**= Visit to Emergency room or hospitalization.

Comments:

MD signature and date: dd mmm yyyy

MEMORY AID (DAY 0 to DAY 28)

Day 0 to Day 28 ❑ Nothing to report

#	**Medication** (Name, Dose, Route and Frequency)	**Start date**	**Stop date**	**Reason(s) why you are taking this medication?**	**Validated with subject**
		dd mmm yyyy	dd mmm yyyy ❑ Ongoing at Day 28		❑ Initial and date: dd mmm yyyy
		dd mmm yyyy	dd mmm yyyy ❑ Ongoing at Day 28		❑ Initial and date: dd mmm yyyy

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

Comments:

MD signature and date: dd mmm yyyy

19.4 Appendix 4 – Seven-Day Safety Summary (Sample)

1. Study Description
    a. Brief statement of the purpose of trial.
2. Recruitment Status
    a. Listings of enrollment status by site – (# screened, # enrolled, # vaccinated, # withdrawn or dropped out).
3. Safety Data Listings – present data by subject
    a. Severity (including hospitalization), duration, and relationship of any AEs;
    b. Vital signs abnormalities;
    c. Safety lab abnormalities;
    d. Concomitant medication;
    e. Physical examination abnormalities.
4. Safety Data – present data by treatment groups
    a. Safety data overview (number of subjects experiencing AEs, SAEs, solicited AEs, unsolicited AEs, related AEs, lab abnormalities, vital signs abnormalities, physical examination abnormalities);
    b. Present solicited AEs and solicited Grade 3-4 AEs;
    c. Present related-solicited AEs and related-solicited Grade 3-4 AEs;
    d. Present unsolicited non-serious AEs and unsolicited non-serious Grade 3-4 AEs;
    e. Present related-unsolicited non-serious AEs and related-unsolicited none-serious Grade 3-4 AEs;
    f. Present SAEs and related-SAEs by SOC/PT.

19.5 Appendix 5 – List of Potential Immune-Mediated Diseases

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve neuropathy, including paralysis and paresis (eg, Bell's palsy). • Optic neuritis. • Multiple sclerosis. • Transverse myelitis. • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants. • Acute disseminated encephalomyelitis, including site specific variants, eg, noninfectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis. • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome. • Demyelinating peripheral neuropathies and plexopathies including: - Chronic inflammatory demyelinating polyneuropathy. - Multifocal motor neuropathy. - Polyneuropathies associated with monoclonal gammopathy. • Narcolepsy. • Tolosa Hunt syndrome.	• Systemic lupus erythematosus and associated conditions. • Systemic scleroderma (systemic sclerosis), including: - Diffuse scleroderma. - CREST syndrome. • Idiopathic inflammatory myopathies, including: - Dermatomyositis. - Polymyositis. • Anti-synthetase syndrome. • Rheumatoid arthritis and associated conditions including: - Juvenile idiopathic arthritis. - Still's disease. • Polymyalgia rheumatica. • Spondyloarthropathies, including: - Ankylosing spondylitis. - Reactive arthritis (Reiter's syndrome). - Undifferentiated spondyloarthritis. - Psoriatic arthritis. - Enteropathic arthritis. • Relapsing polychondritis. • Mixed connective tissue disorder. • Gout.	• Psoriasis. • Vitiligo. • Erythema nodosum. • Autoimmune bullous skin diseases (including pemphigus, pemphigoid, and dermatitis herpetiformis). • Lichen planus. • Sweet's syndrome. • Localized scleroderma (morphea). • Cutaneous lupus erythematosus. • Rosacea.
Vasculitis	**Blood disorders**	**Others**
• Large vessels vasculitis including: - Giant cell arteritis (temporal arteritis). - Takayasu's arteritis. • Medium sized and/or small vessels vasculitis including: - Polyarteritis nodosa. - Kawasaki's disease. - Microscopic polyangiitis. - Wegener's granulomatosis (granulomatosis with polyangiitis).	• Autoimmune hemolytic anemia. • Autoimmune thrombocytopenia. • Antiphospholipid syndrome. • Pernicious anemia. • Autoimmune aplastic anemia. • Autoimmune neutropenia. • Autoimmune pancytopenia.	• Autoimmune glomerulonephritis including: - IgA nephropathy. - Glomerulonephritis rapidly progressive. - Membranous glomerulonephritis. - Membranoproliferative glomerulonephritis. - Mesangioproliferative glomerulonephritis. - Tubulointerstitial nephritis and uveitis syndrome.

Vasculitis (continued)	Blood disorders (continued)	Others (continued)

- Churg–Strauss syndrome (allergic granulomatous angiitis or eosinophilic granulomatosis with polyangiitis).
- Buerger's disease (thromboangiitis obliterans).
- Necrotizing vasculitis (cutaneous or systemic).
- Antineutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified).
- Henoch-Schonlein purpura (IgA vasculitis).
- Behcet's syndrome.
- Leukocytoclastic vasculitis.
		• Ocular autoimmune diseases including:
		  - Autoimmune uveitis.
		  - Autoimmune retinitis.
		• Autoimmune myocarditis/cardiomyopathy.
		• Sarcoidosis.
		• Stevens-Johnson syndrome.
		• Sjögren's syndrome.
		• Alopecia areata.
		• Idiopathic pulmonary fibrosis.
		• Goodpasture syndrome.
		• Raynaud's phenomenon.

Liver disorders	**Gastrointestinal disorders**	**Endocrine disorders**

• Autoimmune hepatitis.
• Primary biliary cirrhosis.
• Primary sclerosing cholangitis.
• Autoimmune cholangitis.
	• Inflammatory bowel disease, including:
	  - Crohn's disease.
	  - Ulcerative colitis.
	  - Microscopic colitis.
	  - Ulcerative proctitis.
	• Celiac disease.
	• Autoimmune pancreatitis.
		• Autoimmune thyroiditis (including Hashimoto thyroiditis).
		• Grave's or Basedow's disease.
		• Diabetes mellitus type 1.
		• Addison's disease.
		• Polyglandular autoimmune syndrome.
		• Autoimmune hypophysitis.