Medicago USA

CP-PRO-AdjQVLP-020

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

14MAR2022

Statistical Analysis Plan

Version 5.0

Prepared by:

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Version	Detail of Change
Version 5.0 11MAR2022	• Updated relevant sections (Sections 2, 3, 8, 13) to reflect update to secondary immunogenicity objective (Protocol Version 5.0, dated 23 FEB2022): clarification that the MN assay will be performed on Day 0 and Day 28 only, and not on Day 182 and Day 365. • Update to 9.2 Solicited Adverse events: Clarification on which data to use in the event that both an e-diary and a paper diary were completed by the subject for the same solicited AE and the same timepoint. • Clarification of the H1 and H3 data set to be used for the primary immunogenicity analysis (section 8.1).
Version 4.0 15JUN2021	• 10. Interim Analysis: Interim analysis after Day 28 assessments will include all tables. • 11. Changes to Planned Analysis: Interim analysis after Day 28 assessments will include all tables.
Version 3.9 05MAY2021	• 1. Introduction: Reference to interim analysis at Day 28 with 120 subjects (30%) removed. • 10. Interim Analysis: Interim analysis at Day 28 with 120 subjects (30%) removed and new tables added to second interim analysis. • 11. Changes to Planned Analysis: Removal of interim analysis at Day 28 with 120 subjects (30%).
Version 3.8 12APR2021	• 3.1 Overall Study Design and Plan: Removal of the 2:1 age ratio for randomization. • 4.2.1 Randomization and Stratification: Removal of the 2:1 age ratio for randomization. • 9.2 Solicited Adverse Events: Oral Temperature presentation removed.
Version 3.7 23MAR2021	• 6.4 Prior and Concomitant Therapy added from protocol version 4.0. • 6.5 Prohibited Therapy added from protocol version 4.0. • 9.3.4 Adverse Events of Special Interest: Additional detail added to categories.
Version 3.6 15MAR2021	• Change to be consistent with protocol version 4.0. • 9.3 Unsolicited Adverse Event: Narcolepsy added as new AESI.
Version 3.5 18FEB2021	• 10. Interim Analysis: Added details about first interim analysis
Version 3.4 17FEB2021	• 1. Introduction: Precision added about who is responsible for different interim analyses. • 10. Interim Analysis: Added details about first interim analysis
Version 3.3 16FEB2021	• 10. Interim Analysis: Added details for a newly defined first interim analysis based on Day 28 HI data available as of the Feb. 12, 2021 data transfer to inform a business decision to confirm the vaccine formulation for a Phase 2/3 study for AdjQVLP and will include immunogenicity analyses for HI Antibody Response against Homologous Influenza Strains (GMT, GMFR and SC and SP rate analyses).

	• 11. Changes to Planned Analysis: Described the newly added first interim analysis herein as it is not planned per effective Protocol v3.0
Version 3.2 08FEB2021	• Section 6.1 updated. • Section 9.1 updated.
Version 3.1 2FEB2021	• 'CSR' included in the List of Abbreviations. • 'Severe' replaced by 'Grade 3 or higher' in Section 3.5. • Section 4.2.1 updated. • All Screened Set added and All Enrolled Set removed in Section 4.4 • Inclusion and Exclusion criteria added in Section 6.3. • Section 9.1 updated. • Section 9.3.2 updated.
Version 3.0 20JAN2021	• 'pIMDs' included in the List of Abbreviations. • "Unadjusted GMFR results will also be presented" removed from GMFR analyses. • 11. Changes in the Planned Analysis: Details added about Fisher's exact test. • SAS code added for immunogenicity analyses in appendix. • pIMDs list updated and added in appendix. • Other updates following Protocol Amendment.
Version 2.0 27OCT2020	• 10. Interim Analysis: Added details for a newly defined interim analysis after 120 subjects (30%) have completed Day 28 assessments and in line with it, issued changes to the following sections: o List of Abbreviations updated to include CBER o 1. Introduction: Clarified responsibilities and quality validation for the newly added interim analysis o 5. Subject Disposition: updated wording for interim analyses o 11. Changes to Planned Analysis: described the newly added interim analysis herein as it is not planned per effective Protocol v1.0 • List of Abbreviations updated to include QVLP • 4.4.3 Per Protocol (PP) Sets: Corrected a typo (from Day 183 to Day 182)
Version 1.0 19OCT2020	(Initial version)

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List of Abbreviations

AE	adverse event
AESI	adverse events of special interest
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATC3	Anatomical Therapeutic Chemical Code Level 3
BMI	body mass index
BP	blood pressure
CBER	Center for Biologics Evaluation and Research (FDA)
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
CSR	Clinical Study Report
DBL	Database lock
eCRF	electronic case report form
GMFR	geometric mean fold rise or seroconversion factor
GMT	geometric mean titer
HI	hemagglutination inhibition
HR	heart rate
IDMC	Independent Data Monitoring Committee
IM	intramuscular
ITT	intention-to-treat
LLOQ	Lower Limit of Quantification
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MN	microneutralization
NOCD	new onset of chronic disease
OT	oral temperature
pIMDs	potential immune-mediated diseases
PP	per protocol
PT	preferred term
QVLP	quadrivalent virus-like particle
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SAS®	Statistical Analysis System®
SC	seroconversion
SD	standard deviation
SP	seroprotection
SOC	system organ class
TLF	Tables, Listings, Figures
VLP	virus-like particle
WHO	World Health Organization

1. Introduction

This statistical analysis plan (SAP) describes the analyses and data presentations for Medicago's protocol CP-PRO-AdjQVLP-020 "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" which was issued and finalized as version 4.0 on 08-Mar-2021. The vaccine containing QVLP, which is intended for active immunization for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses, may be able to address several limitations of the currently licensed vaccines. The results of conducted preclinical and clinical studies show that QVLP was well-tolerated and able to induce a substantial antibody response in healthy adult (18 to 64 years) and elderly (65 years of age and older) populations. 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 conducts this Phase 1/2 clinical trial to study the possible advantage of administering QVLP with an adjuvant used in licensed vaccine products (AS03) by assessing the safety, tolerability, and immunogenicity of adjuvanted recombinant QVLP in healthy adults 65 years of age and older.

The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data. All statistical analyses detailed in this SAP will be conducted using SAS® 9.4 or higher (SAS Institute Inc., Cary, North Carolina). The SAP will be finalized and signed prior to the clinical database lock (DBL) for the final analysis.

CCI is responsible for developing randomization instructions, the SAP, TLF shells, CDISC datasets (SDTM & ADaM) including specifications and eCRT packages, development of validated TLFs for the first, second and third interim analyses and the final analysis and, reviewing the statistical part of the Clinical Study Report (CSR). Medicago is responsible for reviewing all aforementioned statistical deliverables. Assignment of subjects to individual PP sets based on PDs will be performed by Medicago (see details in Section 4.4.4).

Quality validation of all statistical deliverables pertinent to analyses described within this document which are within CCI scope will be performed according to CCI SOPs, including CDISC datasets (SDTM & ADaM) and TLFs (based on raw data or CDISC) for the first, second and third interim analyses, the final analysis, and including dry and final runs.

2. Objectives

2.1. Primary Objective

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 hemagglutination inhibition (HI) assay against homologous influenza strains.

2.2. Secondary Objective

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.

3. Investigational Plan

3.1. Overall Study Design and Plan

This randomized, partially-blinded, active comparator-controlled multi-center, Phase 1/2 study will be conducted at multiple sites to evaluate the safety, tolerability, and immunogenicity of an adjuvanted seasonal recombinant quadrivalent VLP influenza vaccine in adults 65 years of age and older. 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 and subjects will be stratified by age into two groups (65 to 74 years of age and 75 years of age and older) and by prior influenza vaccination status (defined as having received a standard influenza vaccine during the 12 months prior to study vaccination). Before protocol version 4.0 became effective:

- In protocol version 2.0, a different randomization was in place with 2 additional treatment groups (QVLP adjuvanted with AS03 (half dose) 15 µg/strain and QVLP adjuvanted with AS03 (half dose) 45 µg/strain) and without prior influenza vaccine status as randomization stratification factor. The enrollment of these two treatment groups was stopped per protocol version 3.0. The number of subjects randomized into these two treatment groups will be documented in the CSR. The six treatment groups included three dose levels of QVLP (15 µg/strain, 30 µg/strain, and 45 µg/strain) with the full dose or QVLP (30 µg/strain) with the half dose of adjuvant AS03, unadjuvanted full dose of QVLP (30 µg/strain), and the active comparator Fluzone HD Quad.
- In protocol version 3.0, there was 3 additional treatments groups (QVLP adjuvanted with AS03 15 µg/strain, QVLP adjuvanted with AS03 (half dose) 30 µg/strain and QVLP adjuvanted with AS03 45 µg/strain). The enrollment of these 3 treatment groups was stopped per protocol version 4.0. The number of subjects randomized into these three treatment groups will be documented in the CSR. Moreover, the planned number of subjects has been decreased 50 to 40 by treatment group.

The three remaining treatment groups include QVLP adjuvanted with AS03 (30 µg/strain), unadjuvanted QVLP (30 µg/strain), and the active comparator Fluzone HD Quad.

Table 1: Study Treatment Groups

Treatment Group	Treatments	Dose Level	Planned 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 five stopped treatment groups (QVLP adjuvanted with AS03 (half dose) 15 µg/strain, QVLP adjuvanted with AS03 (half dose) 45 µg/strain, QVLP adjuvanted with AS03 15

µg/strain, QVLP adjuvanted with AS03 (half dose) 30 µg/strain and QVLP adjuvanted with AS03 45 µg/strain) were also considered at time of the two IDMC meetings for decision making presented below:

A total of two Independent Data Monitoring Committees (IDMCs) will be held according to the study plan: the first 18 subjects (three subjects per treatment group) enrolled in the study will receive an an intramuscular (IM) injection of one of the six treatment groups (QVLP adjuvanted with AS03 15 µg/strain, QVLP adjuvanted with AS03 (half dose) 15 µg/strain, QVLP adjuvanted with AS03 30 µg/strain, QVLP adjuvanted with AS03 (half dose) 30 µg/strain, QVLP unadjuvanted 30 µg/strain and Fluzone HD Quad 60 µg/strain) and their seven-day safety data will be collected and reviewed by the 1st IDMC in this study, prior to permitting the vaccination of the remaining subjects in these six treatment groups (282 subjects) and escalating to vaccination of subjects with the highest dose level of QVLP. If the IDMC permits vaccination at the highest dose level of QVLP in the study (QVLP adjuvanted with AS03 45 µg/strain and QVLP adjuvanted with AS03 (half dose) 45 µg/strain), then the first three subjects enrolled in these two treatment groups will receive an IM injection of the respective treatment and their seven-day safety data will be collected and reviewed by the 2nd IDMC, prior to permitting the vaccination of the remaining subjects in these two treatment groups (94 subjects). The vaccinations for the first three subjects in these two treatment groups will be staggered so that each vaccination must be performed at least 30 minutes apart.

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). The schedule of events to be performed from screening visit to all post-vaccination visits/contacts is presented in Appendix 13.1.

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.

3.2. Study Endpoints

3.2.1. Primary Endpoints

Safety:

The primary safety endpoints are:

- Occurrences, intensity, and relationship to vaccination of immediate Adverse Events (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 serious adverse events (SAEs), AEs leading to discontinuation, adverse events of special interest (AESIs), medically attended adverse events (MAAEs), new onset of chronic disease (NOCDs), and deaths up to Day 28;
- Occurrences of SAEs, AEs leading to discontinuation, AESIs, MAAEs, NOCDs, and deaths from Day 29 up to Day 182;
- Occurrences of SAEs, AEs leading to discontinuation, 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).

3.2.2. 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 compared to Day 0).

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 discontinuation, 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 discontinuation, 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 discontinuation, 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.

3.3. Treatments

Per protocol version 4.0, subjects will be enrolled into one of the three treatment groups and receive one IM injection of their assigned treatment on Day 0 (refer to Table 1). The volume of injection will be 0.7 mL for all treatments.

The 30 µg/strain dose is the full dose of QVLP, used in previous clinical studies. The dosage (30 µg/strain) 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 and is also the dose most comparable with commonly used licensed vaccines in the elderly. The dosage (60 µg/strain) and administration of the active comparator Fluzone HD Quad is in accordance with the approved prescribing information for this vaccine.

3.4. Dose Adjustment/Modifications

No dose adjustment/modification is allowed under normal circumstances in this study as the study treatments will be prepared and administered in a single-dose regimen by trained unblinded site staff via IM injection to each subject at each Investigator site on Day 0.

3.5. Stopping Rules

Safety monitoring of safety signals will be performed throughout the study. Refer to protocol version 4.0 section 13.1.12 for more details about safety review. The following events may result in at least a transient halt to the study:

- 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. The analyses will be performed based on the available subject data collected during study period since that even though the IDMC review decides to stop further use of specific dose level, the subjects already administered this dose level of the vaccine will still be followed to the end of the study for all safety and immunogenicity outcomes, if subject permits.

4. General Statistical Considerations

Continuous data (absolute values and change from baseline values) will be described using descriptive statistics (i.e., n, mean, standard deviation (SD), median, minimum, and maximum). Categorical data will be described using frequency count and percentage in each category. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation/ standard error will be displayed to two levels of precision greater than the data collected.

For the summary statistics of categorical variables, all percentages will be rounded to one decimal place. Number and percentage values will be presented as xx (xx.x). If the percentage is 100, no decimal is required. If it is below 0.1, it will be reported as "<0.1". P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999."

All summary tables will have the population sample size in the column headers in form of N=XXX for each treatment group and all subjects, and the analyses of the immunogenicity and safety endpoints 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 five stopped treatment groups (QVLP adjuvanted with AS03 (half dose) 15 µg/strain, QVLP adjuvanted with AS03 (half dose) 45 µg/strain, QVLP adjuvanted with AS03 15 µg/strain, QVLP adjuvanted with AS03 (half dose) 30 µg/strain and QVLP adjuvanted with AS03 45 µg/strain) will also be included in analyses as other treatment groups. All enrolled subject data recorded on CRF and entered into the database will be provided in separate data listings showing individual subject values. Data will be displayed in all listings sorted by treatment group, subject number and visit (time point, if applicable).

All laboratory data will be reported using international system of units (SI).

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that clinical diagnosis category within the analysis set of interest, unless otherwise specified.

Baseline value is defined as the last non-missing data on or before the IM injection of the study vaccine, unless otherwise specified.

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

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

During the programming period, the table/listing/figure shell format and footnote might be edited. And this kind of change is not be considered as analysis changes or impact the analysis results.

4.1. Sample Size

No statistical sample size calculations were performed. The determined 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 sizable differences in rates of adverse events since 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.

4.2. Randomization, Stratification, and Blinding

4.2.1. Randomization and Stratification

The randomization numbers will be allocated to subjects within the appropriate treatment group by the randomization system once all screening procedures, including Day 0 pre-randomization procedures, have been completed and the study eligibility is confirmed by the Investigator. Randomization will be stratified by age group (65 to 74 years of age and 75 years of age and older). In addition, after the implementation of the new randomization strategy per protocol version 3.0, prior influenza vaccination status (defined as having received a standard influenza vaccine during the 12 months prior to study vaccination) was also added as a stratification factor (i.e., it was not in place for the randomization of any subjects enrolled prior to protocol version 3.0).

Considering the study design with two scheduled IDMCs, as per protocol version 1.0, the randomization schedule was to include subjects in treatment groups 1-6 and begin the enrolment in treatment groups 7 and 8 once 1st IDMC permits. However, as described previously, two treatment groups (QVLP adjuvanted with AS03 (half dose) 15 ug/strain and QVLP adjuvanted with AS03 (half dose) 45 ug/strain) in protocol version 3.0 and three treatment groups (QVLP adjuvanted with AS03 15 µg/strain, QVLP adjuvanted with AS03 (half dose) 30 µg/strain and QVLP adjuvanted with AS03 45 µg/strain) in protocol version 4.0 were stopped.

The randomization of the two stopped treatment groups in protocol version 3.0 was generated according to the randomization schema (with age group only as stratification factor) planned in the protocol version 1.0 (refer to Appendix 13.2). Some patients enrolled in the 3 treatments groups stopped in protocol version 4.0 were randomized according to the new randomization schema (with age and influenza history vaccine as stratification factor). Patients enrolled after the implementation of protocol version 4.0 will be randomized into the three remaining treatment groups. The randomization schedule will be generated by computer.

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 and the admission of subsequent eligible subjects will continue using the next unallocated number in the sequence.

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. Subjects who withdraw or are withdrawn from the study after vaccination will not be replaced.

4.2.2. Blinding

This is a partially-blinded study and the blinded/unblinded personnel is listed as below.

Blinded:

- Subjects;
- Investigator;
- 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),
    - all personnel involved in sample analysis at the central and testing (HI and MN assays) laboratories,
    - CCI blinded statistical team who will be responsible for development of statistical outputs and performance of the final analysis after DBL and unblinding.

Unblinded:

- Staff involved in the preparation and administration of the study vaccine, the quality assurance auditor, and quality control reviewers;
- The IDMC and the independent statistician involved in the preparation of the safety data summary for the IDMC reviews;
- CCI unblinded statistical team who will perform the unblinded run and delivery for interim analyses, and a small number of Medicago personnel (include senior personnel in Scientific and Medical Affairs, Biostatistics, Safety, Product Development, and Regulatory Affairs) will be able to look at data throughout the study.

The unblinded procedure should be strictly followed, and the process of unblinding and the selected individuals should be documented in writing. 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.

4.3. Imputation of Incomplete Data

Generally, missing values will not be substituted by estimated values but treated as missing in the statistical evaluation. All observed data from all subjects dosed in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate. Missing and incomplete date of adverse event, medical/vaccination history, prior and concomitant medication, concomitant procedure or non-drug therapy will be specifically imputed according to the following rules for analysis.

Adverse Event

Besides imputation of dates, below logic contains information on possible recategorization of events collected on the 'Adverse Event' eCRF as medical history.

- If only Day of AE start date is missing:
  - If the AE start year and month are the same as that for the first vaccination dose date, then:
    - If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date;
    - otherwise, impute the AE start day as 1.
  - Otherwise, impute the AE start day as 1.

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

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

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

- If Year of AE start date is missing:

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

Prior and Concomitant Medications/Concomitant Procedure or Non-drug Therapy

- Missing or partial concomitant medication start date:
  - If only DAY is missing, use the first day of the month.
  - If DAY and Month are both missing, use the first day of the year.
- Missing or partial concomitant medication stop date:
  - If only DAY is missing, use the last day of the month.
  - If DAY and Month are both missing, use the last day of the year.
  - If DAY, Month and year are all missing, assign 'continuing' status to stop date.

4.4. Analysis Set

All safety analysis will be performed using the Safety Analysis Set (SAS). The analyses of all immunogenicity endpoints will be performed using the Per-Protocol (PP) set and the Intention-To-Treat (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.

4.4.1. All Screened Set

The All Screened Set will consist of all subjects who were screened.

4.4.2. Safety Analysis Set (SAS)

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.

4.4.3. Intent-to-Treat (ITT) 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.

4.4.4. Per Protocol (PP) Sets

Four individual per protocol (PP) sets will be defined which will consist of a subset of subjects 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. Only protocol deviations up to the visit of interest will be observed for each PP set. In particular, immunogenicity assessments should be available on certain visits, as follows:

- Per Protocol Set 1: Day 0,
- Per Protocol Set 2: Day 0 and Day 28,

- Per Protocol Set 3: Day 0 and Day 182,
- Per Protocol Set 4: Day 0 and Day 365.

Subjects who had blood samples for immunogenicity taken outside of the time window for blood sample collection at Day 0 or the respective visit (Day 28 / Day 182 / Day 365) are to be excluded from the PP set for the specific visit. Major protocol deviations will be identified and documented by Medicago during a blinded data review prior to database lock and confirmed at the time of database lock. Assignment of subjects to each of the PP sets (yes/no) will be provided to CCI 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. For analyses using the Per Protocol set, subjects will be analyzed according to the vaccines actually received.

5. Subject Disposition

Subject disposition will be summarized for each treatment group and total for subjects in All Screened Set. Tables will indicate the number of subjects who were enrolled into the study, the number of subjects who are vaccinated, the number of subjects in each analysis set, the number of subjects who completed Day 28, Day 182 and the entire study, and the number of subjects who prematurely discontinued study for any of, but not limited to, the following reasons:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Protocol violation
- Screen failure
- Screen failure-enrollment closed
- Trial site terminated by sponsor
- Study terminated by sponsor
- Subject withdrew consent
- other

In addition, in case of the third interim analysis, the frequency and percentage of subjects who are ongoing at the data cut time will also be summarized.

Subject disposition data (including subject identifier, date of completion/early discontinuation and, for those who discontinued early, the specific reason(s) for discontinuation) will be presented in a listing. In listings, data for all screened subjects will be presented, including those who were not randomized (e.g., screening failures).

5.1. Protocol Deviations

All protocol deviations (significant or not) will be reviewed by the study team and sponsor prior to the database lock, to identify major protocol deviations that would potentially exclude a subject from the PP population. Major protocol deviations will be summarized for the SAS population.

A listing of protocol deviations in all subjects will be provided.

6. Demographics and Baseline Characteristics

6.1. Demographics

All baseline subject characteristics of demographics data will be presented for the SAS, ITT Set, Per Protocol Set 1, and overall for the population as well as by prior influenza vaccine status strata. Demographic characteristics will be collected at Screening.

The following variables will be summarized:

1. Continuous baseline demographic variables:

- Age (years)
- Height (cm)
- Weight (kg)
- BMI (kg/m2)

2. Categorical baseline demographic variables:

- Age stratification and prior influenza vaccine status (65-74, Received standard influenza vaccine during 12 months prior to study vaccination; 65-74, Has not received standard influenza vaccine during 12 months prior to study vaccination; ≥75, Received standard influenza vaccine during 12 months prior to study vaccination; ≥75, Has not received standard influenza vaccine during 12 months prior to study vaccination)
- Sex (male, female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other, Multiple)
- Immunization history (Both Influenza and Non-Influenza, Only Influenza, Only Non-Influenza, None)

Subject demographics will be presented in a listing.

6.2. Medical History

6.2.1. General Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 or higher and actual version number will be denoted in the outputs. The number and percentage of subjects with any medical history at Baseline will be summarized overall and for each system organ class (SOC) and preferred term (PT). Percentages will be calculated based on number of subjects in the SAS population. Incomplete dates will be imputed following rules in Section 4.3.

Subject medical history data including specific details will be presented in a listing.

6.2.2. Influenza and Non-Influenza Vaccination History

All vaccination history data including specific details will be presented in a listing.

6.3. Inclusion and Exclusion 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/m2 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.

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 preempt 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.

Inclusion criteria not met and exclusion criteria met number will be listed for subjects that did not respect inclusion/exclusion criteria.

6.4. 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 protocol version 4.0 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.

6.5. 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.).

7. Treatments and Medications

Information on prior and concomitant medications/procedures or non-drug therapy taken by subjects are recorded in the electronic Case Report Form (eCRF). Incomplete dates will be imputed following rules in Section 4.3. All data will be listed.

7.1. Prior and Concomitant Medications

If a medication ended before IM injection, then it will be categorized as prior medication; if a medication started or kept using on or after IM injection then it will be categorized as concomitant medication. All medications will be mapped to preferred terms according to the World Health Organization (WHO) drug dictionary September 2020 or later. The number and percentage of all subjects in the SAS population having prior medications or concomitant medications will be tabulated by Anatomical Therapeutic Chemical Code Level 3 (ATC3) classification system and WHO drug preferred term (PT). At each level of summarization, a subject is counted only once if she/he reported one or more medication. All prior and concomitant medications will be presented in listings.

7.2. Concomitant Procedures or Non-Drug Therapy

All concomitant procedures or non-drug therapy data will be presented in listings.

7.3. Study Treatments

Exposure to study treatments will be summarized for all subjects in the SAS population. Number and percentage of subjects who received vaccine administration and the volume

administered will be summarized using descriptive statistics. All vaccine administration information recorded in eCRF will be presented in a listing.

7.4. Randomization

The randomization number and relevant information will be presented in a listing.

8. Immunogenicity Analysis

All the primary and secondary immunogenicity evaluations will be analyzed by treatment group and strain based on the PP populations (the one belonging to the particular visit) and will include each treatment group as a whole. Sensitivity analyses will be performed using the ITT population and all collected data will be listed. Reverse Cumulative Distribution Curves (RCDC) will be presented for each post-baseline visit, as follows: homologous & heterologous strains measured by HI, based on PP sets; homologous strains measured by HI, based on ITT set; homologous strains measured by MN, based on PP sets.

8.1. Primary Immunogenicity Analysis

The primary immunogenicity analysis endpoint is to evaluate the 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, analyzed as follows:

- GMT at Day 0 and Day 28;
- SC rate at Day 28: 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 at Day 28: 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 (Day 28/Day 0): the geometric mean of the ratio of GMTs (Day 28/Day 0).

For the H1 and H3 analysis, results from the assay using VLP reagents will be used. Any antibody titer that is below the LLOQ of assay will be imputed with a value equal to half of the LLOQ of assay of the antigen specific antibody titer.

GMT will be calculated as anti-logarithm of (∑(log-transformed titer)/number of subjects with titer information). The 95% CI for GMT will be calculated as the anti-log transformation of upper and lower limits for a 2-sided CI of the mean of the log-transformed titers. The log-transformed GMT will be compared among treatment groups by using the analysis of variance (ANOVA) model on log-transformed titer values and the Tukey's test will also be performed for the pairwise comparisons between treatment groups within the frame of the same model.

The point estimates and the corresponding two-sided 95 % Clopper-Pearson CI [Clopper, 1934] for subjects achieving SC and SP will be calculated and compared among treatment groups using Fisher's exact test.

GMFR will be calculated as anti-logarithm of ∑ [log-transformed titer ratio of Yi/Bi)/number of subjects with titer information], where Yi is the post-vaccination titer and Bi is the pre-vaccination (baseline) titer for subject i. The 95% CI for GMFR will be calculated as the anti-log transformation of upper and lower limits for a 2-sided CI of the mean of the log-transformed titers fold rise from pre-vaccination. The log-transformed

GMFRs will be compared among treatment groups by using analysis of covariance (ANCOVA) with treatment group as main effect and baseline as covariate on log-transformed titer values fold rise from pre-vaccination. Tukey's test will be performed for pairwise comparisons between treatment groups within the frame of the same model.

SAS code is presented in Appendix 13.3.

8.2. Secondary Immunogenicity Analysis

The secondary immunogenicity analysis endpoints include the following evaluations:

- 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, which will be analyzed as follows:
    - GMT at Days 0 and Day 28;
    - SC rate at Day 28: 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 (Day 28/Day 0): the geometric mean of the ratio of GMTs.

  These analyses will be repeated but 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.
- 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. The same summaries will be provided as primary analysis.
    - GMT at Day 0 and Day 28;
    - SC rate at Day 28;
    - SP rate at Day 28;
    - GMFR (Day 28/Day 0).

  These analyses will be repeated but 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.
- 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 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 same summaries will be provided as primary analysis.
    - GMT at Day 0 and Day 28;
    - SC rate at Day 28;
    - SP rate at Day 28;
    - GMFR (Day 28/Day 0).

- Durability of antibody responses 6 months (Day 182) and 12 months (Day 365) post-vaccination determined by HI antibody responses.
    - HI antibody titers will be analyzed as follows:
        - GMT at Day 182 and Day 365;
        - SC rate at Day 182 and Day 365;
        - SP rate at Day 182 and Day 365;
        - GMFR (Day 182/Day 0 and Day 365/Day 0).

The statistical analysis method of secondary immunogenicity endpoints is the same as the primary endpoint analysis for the relevant parameters, including GMT, SC rate, SP rate and GMFR.

SAS code is presented in Appendix 13.3.

9. Safety Analysis

Safety analyses will be performed using SAS population defined in Section 4.4. For each of the safety parameters, a summary statistic will be provided overall and by treatment group. All safety summaries will be descriptive and no statistical significance tests will be performed.

Safety and tolerability will be evaluated by all AEs, immediate AEs (30 minutes post-vaccination), solicited local and systemic AEs up to seven days post-vaccination, unsolicited AEs up to 28 days post-vaccination, SAEs, AESIs, MAAEs, NOCDs, AEs leading to discontinuation up to the end of the study, and deaths. In summary tables, only Treatment-Emergent AEs (TEAEs) will be counted. The clinical laboratory (haematology, chemistry, urinalysis), vital signs, and symptom-directed physical examination abnormalities will also be part of safety evaluation.

These tables will also be presented 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 assess the secondary safety endpoints.

All safety data will be listed by subject.

9.1. Incidence of Adverse Events

An overall summary of the number and percentage of subjects will be presented for following categories:

- Immediate solicited and unsolicited AEs
- Immediate solicited AEs
- Immediate unsolicited AEs
- Solicited AEs:
    - Grade 3 or higher solicited AEs
    - Solicited local AEs
    - Solicited Systemic AEs

- Unsolicited AEs:
  - Related unsolicited AEs
  - Grade 3 or higher unsolicited AEs
  - Grade 3 or higher related unsolicited AEs
- Any SAE
- Any related SAE
- Any related Hypersensitivity reactions
- Any Potential Immune-Mediated Diseases (pIMDs) and other AESI
- Any related pIMDs and other AESI
- Any MAAE
- Any related MAAE
- Any NOCD
- Any related NOCD
- Any AE leading to discontinuation
- Any related AE leading to discontinuation
- Any AE leading to deaths
- Any related AE leading to deaths
- Any clinically significant lab data

9.2. Solicited Adverse Events

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 post dose. The causal relationship of all solicited local and systemic AEs will be considered related.

Table 2: Intensity Grades for Solicited Local and Systemic AEs

Symptoms	**Intensity**				
	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

Symptoms	Intensity				
	None	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Potentially life-threatening)
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

For following timepoints, the number and percentage of subjects will be summarized for each solicited AE, intensity grade, and treatment group as a whole:

- 30 min post-dose;
- Up to 7th day post-dose.

E-diary is considered to be the principal system to be used to collected solicited adverse events. Paper diary could be used as back-up. In the event that both an e-diary and a paper diary were completed by the subject for the same solicited AE and the same timepoint, the record with the PI assessment will be used for analysis; otherwise, the higher grade will be used in the analysis.

Immediate solicited AE and all solicited AE up to 7 days information will specifically be presented by gender (Both, Male and Female), race (All, Caucasian or White; Black or

African American; Asian) and prior vaccine status (Both, Yes and No), if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination, for the overall population (65 years of age and older).

Solicited local and systemic AE data including specific details will be presented in listings.

9.3. Unsolicited Adverse Events

An adverse event (AE) 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.

For the purpose of inclusion in AE tables, incomplete data will be imputed based on section 4.3. Subsequently, AEs might be reclassified as medical history based on the rules described in the same section.

All AEs will be classified by System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA**,** version 23.1 or later).

Summaries of the number and percentage of subjects with AEs will be provided by SOC (in internationally agreed order) and PT (in alphabetical order) separately. At each level of subject summarization, a subject is counted once if the subject reported 1 or more events.

Percentages will be calculated out of the number of subjects in the SAS population.

Subjects with at least 1 AE will be summarized by treatment group as a whole.

For the following categories, AE information will specifically be presented by gender (Both, Male and Female), race (All, Caucasian or White; Black or African American; Asian) and prior vaccine status (Both, Yes and No), if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination, for the overall population (65 years of age and older):

- Unsolicited AEs for 28 days following study vaccine administration;
- Immediate unsolicited AEs up to 30 minutes after vaccination;
- SAEs;
- Related Hypersensitivity Reactions (AESI);
- Narcolepsy
- pIMDs and Other AESI;
- MAAEs;
- NOCD;
- AEs leading to study discontinuation;
- AEs leading to death;
- Most frequent (defined as ≥ 1.0 % of subjects in one of AdjQVLP treatment groups) unsolicited AEs within 28 days after vaccination.

Subject AE data including specific details will be presented in listings.

9.3.1. Relationship of Adverse Events to Study Vaccine

A related AE is an event where the investigator determined that the relationship to study vaccine was "Possibly Related", "Probably Related" or "Definitely Related".

Related AEs will be summarized for pIMDs and Other AESI.

If a subject reports multiple occurrences of the same AE, only the most closely related occurrence will be presented.

9.3.2. Intensity of Adverse Event

Summaries of the number and percentage of subjects with at least one unsolicited AE up to 28 days post-vaccination, one related unsolicited AE up to 28 days post-vaccination, and one related immediate unsolicited AE will be provided by intensity (grade 1 to grade 4). Each SOC (in internationally agreed order) and PT (in alphabetical order) separately will also be presented by intensity.

In the AE intensity tables, if a subject reported multiple occurrences of the same AE, only the most severe will be presented.

9.3.3. Serious Adverse Events

An SAE is any untoward medical occurrence (whether considered to be related to the study vaccine or not) 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 ($\geq$ 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.

In addition to being presented by gender (Both, Male and Female), race (All, Caucasian or White; Black or African American; Asian) and prior vaccine status (Both, Yes and No), if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination, for the overall population (65 years of age and older) as indicated in section 9.1, summaries of the number and percentage of subjects with at least one SAE will be presented by SOC and PT for following time period separately (based on AE analysis start date):

- from Day 1 up to Day 28;

- from Day 29 up to Day 182;
- from Day 183 up to the end of study (Day 365).

At each level of subject summarization, a subject is counted once if the subject reported 1 or more events.

All SAEs will be presented in a listing separately. If there are no SAEs at the end of the study, the tables or listings will state that there are no SAEs in the study.

9.3.4. Adverse Events of Special Interest

AESI includes following categories, which will be presented in separate tables:

- Related Hypersensitivity Reactions identified using both narrow and broad standardized MedDRA® queries;
- Narcolepsy identified using MedDRA PT Narcolepsy;
- pIMDs and Other AESI (refer to Appendix 13.4).

In addition to being presented by gender (Both, Male and Female), race (All, Caucasian or White; Black or African American; Asian) and prior vaccine status (Both, Yes and No), if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination, for the overall population (65 years of age and older) as indicated in section 9.1, summaries of the number and percentage of subjects with at least one of these AESIs will be presented by SOC and PT for following time period separately (based on AE analysis start date):

- from Day 1 up to Day 28;
- from Day 29 up to Day 182;
- from Day 183 up to the end of study (Day 365).

Also, subjects with at least one related pIMDs and Other AESI and with at least one related Narcolepsy will be summarized in the same way.

At each level of subject summarization, a subject is counted once if the subject reported 1 or more events.

All AESIs will be presented in a listing separately.

9.3.5. Medically Attended Adverse Events

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

In addition to being presented by gender (Both, Male and Female), race (All, Caucasian or White; Black or African American; Asian) and prior vaccine status (Both, Yes and No), if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination, for the overall population (65 years of age and older) as indicated in section 9.1, summaries of the number and percentage of subjects with at least

one MAAE will be presented by SOC and PT for following time period separately (based on AE analysis start date):

- from Day 1 up to Day 28;
- from Day 29 up to Day 182;
- from Day 183 up to the end of study (Day 365).

At each level of subject summarization, a subject is counted once if the subject reported 1 or more events.

All MAAEs will be presented in a listing separately.

9.3.6. 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 addition to being presented by gender (Both, Male and Female), race (All, Caucasian or White; Black or African American; Asian) and prior vaccine status (Both, Yes and No), if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination, for the overall population (65 years of age and older) as indicated in section 9.1, summaries of the number and percentage of subjects with at least one NOCD will be presented by SOC and PT for following time period separately (based on AE analysis start date):

- from Day 1 up to Day 28;
- from Day 29 up to Day 182;
- from Day 183 up to the end of study (Day 365).

At each level of subject summarization, a subject is counted once if the subject reported 1 or more events.

All NOCDs will be presented in a listing separately.

9.3.7. Adverse Events Leading to Discontinuation

In addition to being presented by gender (Both, Male and Female), race (All, Caucasian or White; Black or African American; Asian) and prior vaccine status (Both, Yes and No), if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination, for the overall population (65 years of age and older) as indicated in section 9.1, summaries of the number and percentage of subjects with AE leading to discontinuation will be presented by SOC and PT for following time period separately (based on AE analysis start date):

- from Day 1 up to Day 28;

- from Day 29 up to Day 182;
- from Day 183 up to the end of study (Day 365).

At each level of subject summarization, a subject is counted once if the subject reported 1 or more events.

All AEs leading to discontinuation will be presented in a listing separately.

9.3.8. Adverse Events Leading to Death

In addition to being presented by gender (Both, Male and Female), race (All, Caucasian or White; Black or African American; Asian) and prior vaccine status (Both, Yes and No), if >25% of the enrolled subjects have received a standard influenza vaccine during the 12 months prior to study vaccination, for the overall population (65 years of age and older) as indicated in section 9.1, summaries of the number and percentage of subjects with AE leading to death will be presented by SOC and PT for following time period separately (based on AE analysis start date):

- from Day 1 up to Day 28;
- from Day 29 up to Day 182;
- from Day 183 up to the end of study (Day 365).

Listings will be provided for deaths in details.

9.4. Clinical Laboratory Evaluations

Laboratory (biochemical, haematological, and urinalysis) data will be summarized by type of laboratory test. Summary tabulations (i.e., n, mean, SD, median, minimum, and maximum) for the observed values and changes from Baseline will be presented for clinical laboratory evaluations with numeric values for subjects in the SAS population. Observed results at each scheduled timepoint and changes from Baseline for each scheduled post-Baseline timepoint (Day 3 and Day 28) will be presented.

Out of range (abnormal) values should be assessed by the Investigator for clinical significance relevant to the subject population. For this protocol, assessments will be defined as not clinically significant (NCS) or clinically significant (CS). Number and percentage of subjects with normal and abnormal, clinically significant biochemical, haematological, and urinalysis values at Days 0, 3, and 28 will be summarized by treatment 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.

All relevant clinical laboratory tests will be classified as Low (below normal ranges), Normal (within normal ranges), and High (Above normal ranges). This categorical data will be summarized in shift tables based on normal range comparing the results at post-Baseline timepoints (Day 3 and Day 28) and the worst post-Baseline value (minimum or maximum value of any post-Baseline visit) with those at Baseline.

Summaries by scheduled timepoint will include data from scheduled assessments only, and all data will be reported according to the nominal study date for which it was recorded (i.e., no visit windows will be applied). Unscheduled data will be included in the shift table summaries, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment.

All individual laboratory values will be listed by visit.

9.5. Vital Sign Measurements

Measurement of vital signs will include assessment of blood pressure (BP), heart rate (HR), and oral temperature (OT).

Summary tabulations (i.e., n, mean, SD, median, minimum, and maximum) for the observed values at each scheduled timepoint and changes from Baseline for each scheduled post-Baseline timepoint will be presented for vital sign data for subjects in the SAS population.

All vital sign data by subject will be presented in a listing.

9.6. Symptom-directed Physical Examination

All symptom-directed physical examination findings will be listed.

10. Interim Analysis

Interim analyses will be performed (i) after Day 28 HI data available as of the Feb. 12, 2021 data transfer, (ii) after the last subject has completed Day 28 assessments and (iii) after the last subject has completed Day 182 assessments.

The first interim analysis based on Day 28 HI data available as of the Feb. 12, 2021 data transfer will inform a business decision to confirm the vaccine formulation for a Phase 2/3 study for AdjQVLP and will include immunogenicity analyses for HI Antibody Response against Homologous Influenza Strains (GMT, GMFR and SC and SP rate analyses).

The second interim analysis will include all tables.

The third interim analyses at Day 182 will be a full interim analysis with all tables/listings/figures planned for the final analysis.

The results of the interim analyses will be confidential and strictly limited to the authorized staff members and 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. No adjustments to the final analyses as a result of these interim analyses were therefore deemed necessary.

11. Changes in the Planned Analysis

- The second interim analysis at Day 28 with 120 subjects (30%) described in Section 10 is added as an ad-hoc analysis upon agreement with FDA. The purpose is to

mitigate the risk of administration of an investigational vaccine during influenza season to an elderly population.

- Initially, Fisher's exact test or Chi Square test were planned to compare number of subjects achieving SC and SP. However, only Fisher's exact test will be used.
- An interim analysis based on Day 28 HI data available as of the Feb. 12, 2021 data transfer was added in Section 10 to inform a business decision to confirm the vaccine formulation for a Phase 2/3 study for AdjQVLP.
- The interim analysis at Day 28 with 120 subjects (30%) is removed after confirmation from CBER. Full Day 28 interim analysis will be shared with FDA instead.
- Full Day 28 interim analysis will include all tables instead of demographic tables, tables relating to all immunogenicity analyses, AE overview, immediate solicited AEs, solicited AEs up to Day 7, related unsolicited AE by intensity, SAEs and AESIs.

12. References

- Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of binomial. Biometrika. 1934; 26: 404-413.
- Medicago CP-PRO-AdjQVLP-020 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

13. Appendices

13.1. Schedule of Study Procedures

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[10] (± 14)**	**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.

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[10] (± 14)	Day 365 (± 14)
Visit Number	1	2	Phone	3	Phone	4	Phone	5	6

[2] A limited physical examination will occur at screening, Day 0, and Day 3. History/symptom-directed physical examinations may be performed 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 discontinuation, 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 discontinuation, 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 discontinuation, 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.

[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.

13.2. Overview of Randomization Strategy

The description below reflects the randomization strategy before protocol version 3.0.

Note: the five stopped treatment groups (QVLP adjuvanted with AS03 (half dose) 15 µg/strain, QVLP adjuvanted with AS03 (half dose) 45 µg/strain, QVLP adjuvanted with AS03 15 µg/strain, QVLP adjuvanted with AS03 (half dose) 30 µg/strain and QVLP adjuvanted with AS03 45 µg/strain) were also considered at time of the two IDMC meetings for decision making.

Below list details steps of decision making in chronological order which are to be followed throughout the duration of the study:

1. Schedule 1 open: 18 records (3 subjects per treatment groups 1-6)
2. Schedule 1 closed
3. 1st IDMC
    - If IDMC1 doesn't permit group 7-8 then open schedule 1 (47 subjects per treatment groups 1-6) and study complete
    - If IDMC1 permits group 7-8 then continue as below:
4. Schedule 2 open: 6 records (3 subjects per treatment groups 7-8)
5. Schedule 2 closed
6. Schedule 1 open 282 records (47 subjects per treatment groups 1-6)
7. 2nd IDMC
    - If IDMC2 doesn't permit group 7-8 then continuing open schedule 1 (47 subjects per treatment groups 1-6) and study complete
    - If IDMC2 permits group 7-8 then
        - If group 1-6 is fully enrolled, close Schedule 1 and open Schedule 2 (94 subjects per treatment groups 7-8)> study complete
        - If group 1-6 is not fully enrolled, continuing open schedule 1 till fully enrollment is reached, close Schedule 1 and open Schedule 2 (94 subjects per treatment groups 7-8)> study complete

Numbering of treatment groups in above description is as follows:

QVLP adjuvanted with AS03 15 µg/strain**	1
QVLP adjuvanted with AS03 (half dose) 15 µg/strain*	2
QVLP adjuvanted with AS03 30 µg/strain	3
QVLP adjuvanted with AS03 (half dose) 30 µg/strain**	4
QVLP unadjuvanted 30 µg/strain	5
Fluzone HD Quad 60 µg/strain	6

QVLP adjuvanted with AS03 45 µg/strain**	7
QVLP adjuvanted with AS03 (half dose) 45 µg/strain*	8

**Enrollment into these 2 treatment groups was stopped as per protocol version 3.0.*

***Enrollment into these 3 treatment groups was stopped as per protocol version 4.0.*

13.3. SAS code for Immunogenicity Analyses

To calculate adjusted GMT and do the ANOVA:

```
PROC MIXED data=tab(where=(avisitn = Day <0, 28, 182, 365>));
BY STRAIN;
CLASS TRT;
MODEL var = TRT;
LSMEANS TRT / DIFF=ALL CL ALPHA=0.05 ADJUST=tukey;
RUN;
```

** to be repeated for each relevant timepoints

** where var=LOG10(Analysis value)

To calculate adjusted GMFR and do the ANCOVA:

```
PROC MIXED data=tab(where=(avisitn = Day <0, 28, 182, 365>));
BY STRAIN;
CLASS TRT;
MODEL var = TRT BASE;
LSMEANS TRT / DIFF=ALL CL ALPHA=0.05 ADJUST=tukey;
RUN;
```

** to be repeated for each relevant timepoints

** where var=LOG10(Analysis value/Baseline value) and BASE is LOG10(Baseline value)

Analysis of SC/SP

- 95% CI

```
PROC FREQ data=tab;
BY STRAIN TRT;
TABLE var / binomial (exact);
RUN;
```

** where var=Subject achieving SC or SP

- Fisher's Exact Test:

```
PROC FREQ data=tab;
BY STRAIN;
TABLE var*TRT/ fisher;
RUN;
```

** where var=Subject achieving SC or SP

Note: The MN assay will be performed on Day 0 and Day 28 only, and not on Day 182 and Day 365.

13.4. List of Potential Immune-Mediated Diseases

Acoustic neuritis

Acute cutaneous lupus erythematosus

Acute disseminated encephalomyelitis

Acute febrile neutrophilic dermatosis

Acute flaccid myelitis

Acute haemorrhagic leukoencephalitis

Acute haemorrhagic oedema of infancy

Acute macular outer retinopathy

Acute motor axonal neuropathy

Acute motor-sensory axonal neuropathy

Addison's disease

Administration site vasculitis

Alopecia areata

Ankylosing spondylitis

Anosmia

Anti-glomerular basement membrane disease

Anti-myelin-associated glycoprotein associated polyneuropathy

Anti-neutrophil cytoplasmic antibody positive vasculitis

Antiphospholipid syndrome

Anti-RNA polymerase III antibody increased

Anti-RNA polymerase III antibody positive

Antisynthetase syndrome

Aortitis

Application site vasculitis

Arteritis

Arteritis coronary

Arthritis enteropathic

Arthritis reactive

Atrophic thyroiditis

Autoimmune anaemia

Autoimmune aplastic anaemia

Autoimmune arthritis

Autoimmune blistering disease

Autoimmune cholangitis

Autoimmune colitis

Autoimmune demyelinating disease

Autoimmune dermatitis

Autoimmune encephalopathy

Autoimmune endocrine disorder

Autoimmune enteropathy

Autoimmune eye disorder

Autoimmune haemolytic anaemia

Autoimmune heparin-induced thrombocytopenia

Autoimmune hepatitis

Autoimmune hypothyroidism

Autoimmune lung disease

Autoimmune myocarditis

Autoimmune myositis

Autoimmune nephritis

Autoimmune neuropathy

Autoimmune neutropenia

Autoimmune pancreatitis

Autoimmune pancytopenia

Autoimmune pericarditis

Autoimmune retinopathy

Autoimmune thyroid disorder

Autoimmune thyroiditis

Autoimmune uveitis

Basedow's disease

Behcet's syndrome

Bickerstaff's encephalitis

Brachial plexopathy

Bulbar palsy

C1q nephropathy

Capillaritis

Cardiomyopathy

Caplan's syndrome

Central nervous system lupus

Central nervous system vasculitis

Cerebral arteritis

Cervical neuritis

Cholangitis sclerosing

Chronic autoimmune glomerulonephritis

Chronic cutaneous lupus erythematosus

Chronic inflammatory demyelinating polyradiculoneuropathy

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids

Chronic pigmented purpura

Clinically isolated syndrome

Coeliac disease

Cogan's syndrome

Cold type haemolytic anaemia

Colitis microscopic

Colitis ulcerative

Concentric sclerosis

Coombs positive haemolytic anaemia

Cranial nerve disorder

Cranial nerve palsies multiple

Cranial nerve paralysis

CREST syndrome

Crohn's disease

Cutaneous lupus erythematosus

Cutaneous sarcoidosis

Cutaneous vasculitis

Demyelinating polyneuropathy

Demyelination

Dermatitis bullous

Dermatitis herpetiformis

Dermatomyositis

Diffuse vasculitis

Encephalitis allergic

Encephalitis autoimmune

Encephalitis brain stem

Encephalitis haemorrhagic

Encephalitis periaxialis diffusa

Encephalitis post immunisation

Encephalitis toxic

Encephalomyelitis

Enteropathic spondylitis

Eosinophilic granulomatosis with polyangiitis

Erythema induratum

Erythema multiforme

Erythema nodosum

Evans syndrome

Expanded disability status scale score decreased

Expanded disability status scale score increased

Facial paralysis

Facial paresis

Felty's syndrome

Fulminant type 1 diabetes mellitus

Giant cell myocarditis

Glomerulonephritis membranoproliferative

Glomerulonephritis membranous

Glomerulonephritis rapidly progressive

Glossopharyngeal nerve paralysis

Goodpasture's syndrome

Gout

Gouty arthritis

Gouty tophus

Granulomatosis with polyangiitis

Guillain-Barre syndrome

Haemorrhagic vasculitis

Hashimoto's encephalopathy

Hashitoxicosis

Henoch-Schonlein purpura

Henoch-Schonlein purpura nephritis

Hypersensitivity vasculitis

Hypoglossal nerve paralysis

Hypoglossal nerve paresis

Idiopathic interstitial pneumonia

Idiopathic pulmonary fibrosis

IgA nephropathy

IgM nephropathy

IIIrd nerve paralysis

IIIrd nerve paresis

Immune-mediated arthritis

Immune-mediated cholangitis

Immune-mediated dermatitis

Immune-mediated encephalitis

Immune-mediated endocrinopathy

Immune-mediated enterocolitis

Immune-mediated hepatic disorder

Immune-mediated hepatitis

Immune-mediated hyperthyroidism

Immune-mediated hypothyroidism

Immune-mediated myocarditis

Immune-mediated myositis

Immune-mediated nephritis

Immune-mediated neuropathy

Immune-mediated pancreatitis

Immune-mediated pancytopenia

Immune-mediated pneumonitis

Immune-mediated renal disorder

Immune-mediated thyroiditis

Immune-mediated uveitis

Immune thrombocytopenia

Inflammatory bowel disease

Injection site vasculitis

Interstitial lung disease

Intramyelinic oedema

IVth nerve paralysis

IVth nerve paresis

Juvenile idiopathic arthritis

Juvenile polymyositis

Juvenile psoriatic arthritis

Juvenile spondyloarthritis

Kawasaki's disease

Langerhans' cell histiocytosis

Laryngeal rheumatoid arthritis

Leukoencephalomyelitis

Leukoencephalopathy

Lewis-Sumner syndrome

Lichen planopilaris

Lichen planus

Limbic encephalitis

Liver sarcoidosis

Lupus cystitis

Lupus encephalitis

Lupus endocarditis

Lupus enteritis

Lupus hepatitis

Lupus-like syndrome

Lupus myocarditis

Lupus myositis

Lupus nephritis

Lupus pancreatitis

Lupus pleurisy

Lupus pneumonitis

Lupus vasculitis

Lymphocytic hypophysitis

MAGIC syndrome

Marburg's variant multiple sclerosis

Marine Lenhart syndrome

Membranous-like glomerulopathy with masked IgG-kappa deposits

Mesangioproliferative glomerulonephritis

Microscopic polyangiitis

Miller Fisher syndrome

Mixed connective tissue disease

Mononeuritis

Mononeuropathy multiplex

Morphoea

Multifocal motor neuropathy

Multiple sclerosis

Multiple sclerosis relapse

Multiple sclerosis relapse prophylaxis

Muscular sarcoidosis

Myasthenia gravis

Myasthenia gravis crisis

Myasthenic syndrome

Myelitis

Myelitis transverse

Myopathy

Narcolepsy

Neuralgic amyotrophy

Neuritis

Neuritis cranial

Neuromyelitis optica pseudo relapse

Neuromyelitis optica spectrum disorder

Neuropsychiatric lupus

Neurosarcoidosis

Nodular vasculitis

Noninfectious myelitis

Noninfective encephalitis

Noninfective encephalomyelitis

Ocular myasthenia

Ocular pemphigoid

Ocular sarcoidosis

Ocular vasculitis

Oculofacial paralysis

Optic ischaemic neuropathy

Optic neuritis

Optic neuropathy

Overlap syndrome

Palindromic rheumatism

Panencephalitis

Paresis cranial nerve

Pemphigoid

Pemphigus

Pericarditis lupus

Peritonitis lupus

Pernicious anaemia

Polyarteritis nodosa

Polychondritis

Polyglandular autoimmune syndrome type I

Polyglandular autoimmune syndrome type II

Polyglandular autoimmune syndrome type III

Polymyalgia rheumatica

Polymyositis

Polyneuropathy idiopathic progressive

Primary biliary cholangitis

Primary progressive multiple sclerosis

Proctitis ulcerative

Progressive multiple sclerosis

Progressive relapsing multiple sclerosis

Psoriasis

Psoriatic arthropathy

Pulmonary fibrosis

Pulmonary sarcoidosis

Pulmonary vasculitis

Radiculitis brachial

Radiologically isolated syndrome

Rasmussen encephalitis

Raynaud's phenomenon

Relapsing multiple sclerosis

Relapsing-remitting multiple sclerosis

Renal arteritis

Renal vasculitis

Retinal vasculitis

Reynold's syndrome

Rheumatic brain disease

Rheumatoid arthritis

Rheumatoid lung

Rheumatoid neutrophilic dermatosis

Rheumatoid nodule

Rheumatoid scleritis

Rheumatoid vasculitis

Sarcoidosis

Scleroderma

Scleroderma associated digital ulcer

Scleroderma renal crisis

Secondary progressive multiple sclerosis

Segmented hyalinising vasculitis

Silent thyroiditis

Sjogren's syndrome

SJS-TEN overlap

SLE arthritis

Spondylitis

Spondyloarthropathy

Stevens-Johnson syndrome

Still's disease

Subacute cutaneous lupus erythematosus

Subacute inflammatory demyelinating polyneuropathy

Systemic lupus erythematosus

Systemic lupus erythematosus disease activity index abnormal

Systemic lupus erythematosus disease activity index decreased

Systemic lupus erythematosus disease activity index increased

Systemic lupus erythematosus rash

Systemic scleroderma

Systemic sclerosis pulmonary

Takayasu's arteritis

Temporal arteritis

Terminal ileitis

Thromboangiitis obliterans

Thrombocytopenic purpura

Thrombotic thrombocytopenic purpura

Tongue paralysis

Toxic epidermal necrolysis

Trigeminal nerve paresis

Trigeminal palsy

Tubulointerstitial nephritis and uveitis syndrome

Tumefactive multiple sclerosis

Type 1 diabetes mellitus

Urticarial vasculitis

Uveitis

Vaccination site vasculitis

Vagus nerve paralysis

Vascular purpura

Vasculitic rash

Vasculitic ulcer

Vasculitis

Vasculitis gastrointestinal

Vasculitis necrotising

VIth nerve paralysis

VIth nerve paresis

Vitiligo

Vocal cord paralysis

Vocal cord paresis

Vogt-Koyanagi-Harada disease

Warm type haemolytic anaemia

XIth nerve paralysis

Radiculopathy

CCI

CCI Biostatistics and Programming

Statistical Analysis Plan (SAP) Client Approval Form

Client:	**Medicago**
Protocol Number:	**CP-PRO-AdjQVLP-020**

Document Description:	Final Statistical Analysis Plan
SAP 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
SAP Version Number:	4.0
Effective Date:	15 June 2021

Author(s):

For CCI PPD

Approved by:

PPD

Medicago

PPD

2021-06-17 | 9:39 AM EDT

Date *(DD-MMM-YYYY)*

CCI

CCI **Biostatistics and Programming**

Statistical Analysis Plan (SAP) Client Approval Form

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Protocol Number:	**CP-PRO-AdjQVLP-020**

Document Description:	Final Statistical Analysis Plan
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SAP Version Number:	5.0
Effective Date:	16 March 2022

Author(s):

Fo CCI PPD

Approved by:

PPD

022-03-17 | 3:26 PM EDT

Date *(DD-MMM-YYYY)*