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Sponsor Name:	MEDICAGO
Protocol Number:	CP-PRO-QVLP-011
Protocol Title:	A Randomized, Observer-blind, Multicenter, Phase 3 Study to Evaluate the Lot Consistency, Immunogenicity, and Safety of a Plant-Derived Quadrivalent VLP Influenza Vaccine in Healthy Adults 18-49 Years of Age
Protocol Version and Date:	Final Version 1.3, 08AUG2017
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Statistical Analysis Plan

Version: Final version 1.0 **Version Date:** 24JAN2018

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

APPROVALS	
CCI	
PPD	13-Feb-2018 Date (dd-Mmm-yyyy)
	13Feb2018 Date (dd-Mmm-yyyy)
MEDICAGO	
PPD	13 Feb 2018 Date (dd-Mmm-yyyy)

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Statistical Analysis Plan

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BPM	Beats Per Minute
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
CRF	Case Report Form
CS	Clinically Significant
CV	Coefficient of Variation
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMT	Geometric Mean Titer
GMFR	Geometric Mean Folder Rise
ICF	Informed Consent Form
ICH	International Conference on Harmonization
HIV	Human Immunodeficiency Virus
MA	Memory Aid
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
NOCD	New Onset of Chronic Disease
N/A	Not Applicable

Statistical Analysis Plan

Abbreviation	Description
NCS	Not Clinically Significant
PP	Per Protocol
PT	Preferred Term
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SAS®	Statistical Analysis System®
SC	Seroconversion
SD	Standard Deviation
SE	Standard Error
SI	Standard International System of Units
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
SP	Seroprotection
TEAE	Treatment Emergent Adverse Event
TLF	Table, Listing and Figure
WHO	World Health Organization
WI	Work Instruction

2. PURPOSE

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures that will be produced and the statistical methodologies that will be used are complete and appropriate to allow valid conclusions regarding the study objectives described under MEDICAGO Protocol CP-PRO-QVLP-011 titled "A Randomized, Observer-blind, Multicenter, Phase 3 Study to Evaluate the Lot Consistency, Immunogenicity, and Safety of a Plant-Derived Quadrivalent VLP Influenza Vaccine in Healthy Adults 18-49 Years of Age" Final Protocol version 1.3 dated 08AUG2017.

2.1 RESPONSIBILITIES

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

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

2.2 TIMINGS OF ANALYSES

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

3. STUDY OBJECTIVES

3.1 PRIMARY OBJECTIVE

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

3.2 SECONDARY OBJECTIVES

Safety:

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

Immunogenicity:

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

3.3 BRIEF DESCRIPTION

This is a randomized, observer-blind, multicenter, Phase 3 study to evaluate the lot consistency, immunogenicity, and safety of a plant-derived Quadrivalent VLP influenza vaccine in healthy adults 18-49 years of age.

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

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

3.4 SUBJECT SELECTION

Healthy male and female subjects 18 to 49 years of age and with no clinically significant disease at the time of vaccination are to be included in this study. The subjects must

understand and agree to comply with study procedures and be available throughout the study. Subjects must not have received any influenza vaccine in the last 24 months.

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

3.4.1 Inclusion Criteria

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

1. Subjects must be able to read, understand, and sign the informed consent form (ICF); complete study-related procedures; and communicate with the study staff at visits and by phone;
2. Subjects must be considered by the Investigator to be reliable and likely to cooperate with the assessment procedures and be available for the duration of the study;
3. Male and female subjects must be 18 to 49 years of age, inclusive, at the Screening/Vaccination visit (Visit 1);
4. Subjects have a body mass index (BMI) ≤ 40.0 kg/m^2 on Day 0 pre-vaccination;
5. Subjects must be in good general health prior to study participation with no clinically relevant abnormalities that could jeopardize subject safety or interfere with study assessments as assessed by the Principal Investigator or sub-Investigator (thereafter referred as Investigator) and determined by medical history, physical examination, and vital signs;

   Note: Subjects with a pre-existing chronic disease will be allowed to participate if the disease is stable and, according to the Investigator's judgment, the condition is unlikely to confound the results of the study or pose additional risk to the subject by participating in the study. Stable disease is generally defined as no new onset or exacerbation of pre-existing chronic disease six months prior to vaccination. Based on the Investigator's judgment, a subject with a more recent stabilization of a disease could also be eligible.
6. Female subjects must have a negative urine pregnancy test result at the Screening/Vaccination visit (Visit 1);
7. Female subjects of childbearing potential must use an effective method of contraception for one month prior to vaccination and agree to continue employing adequate birth control measures for the duration of the study. Abstinent subjects should be asked what method(s) they would use, should their circumstances change,

and subjects without a well-defined plan should be excluded. The following relationship or methods of contraception are considered to be effective:

- Hormonal contraceptives (e.g. oral, injectable, topical [patch], or estrogenic vaginal ring);
- Intra-uterine device with or without hormonal release;
- Male partner using a condom plus spermicide or a sterilized partner (at least one year prior to vaccination);
- Credible self-reported history of heterosexual vaginal intercourse abstinence until at least the Day 21 visit;
- Female partner.

8. Non-childbearing females are defined as:
   - Surgically-sterile (defined as bilateral tubal ligation, hysterectomy, or bilateral oophorectomy performed more than one month prior to vaccination); or
   - Post-menopausal (absence of menses for 24 consecutive months and age consistent with natural cessation of ovulation).

3.4.2 Exclusion Criteria

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

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

provide informed consent or unable to provide valid safety observations and reporting;

3. Any autoimmune disease other than hypothyroidism with stable replacement therapy; or any confirmed or suspected immunosuppressive condition or immunodeficiency including known or suspected human immunodeficiency virus (HIV), hepatitis B or C infection, or the presence of lymphoproliferative disease;
4. Administration or planned administration of any non-influenza vaccine within 30 days prior to randomization and up to blood sampling on Day 21. Immunization on an emergency basis will be evaluated case-by-case by the Investigator;
5. Administration of any adjuvanted or investigational influenza vaccine within 24 months prior to randomization or planned administration prior to the completion of Day 21;
6. Administration of any "standard", non-adjuvanted influenza vaccine (e.g. live attenuated trivalent/quadrivalent inactivated influenza vaccine intranasal or split trivalent/quadrivalent inactivated influenza vaccine by either intradermal or IM route) within 24 months prior to randomization and up to completion of the Day 21 visit;
7. Use of any investigational or non-registered product within 30 days prior to randomization or planned use during the study period. Subjects may not participate in any other investigational or marketed drug study while participating in this study until the Day 21 visit. Participation in observational studies is permitted;
8. Treatment with systemic glucocorticoids at a dose exceeding 10 mg of prednisone (or the equivalent) per day for more than seven consecutive days or for ten or more days in total, within one month of study vaccine administration; or any other cytotoxic or immunosuppressant drug, or any immunoglobulin preparation within three months of vaccination and until the completion of the Day 21 visit. Low doses of nasal or inhaled glucocorticoids and topical steroids are permitted;
9. Any significant disorder of coagulation including, but not limited to, treatment with warfarin derivatives or heparin. Persons receiving prophylactic anti-platelet medications (e.g. low-dose aspirin [no more than 325 mg/day]) and without a clinically apparent bleeding tendency are eligible. Subjects treated with new generation drugs that do not increase the risk of IM bleeding (e.g. clopidogrel) are also eligible.
10. History of allergy to any of the constituents of the Quadrivalent VLP Influenza Vaccine or a tobacco allergy;
11. History of anaphylactic allergic reactions to plants or plants components;

12. Any history of serious asthma (e.g. status asthmaticus, hospitalization for asthma control) in the last three years;
13. Use of antihistamines 48 hours prior to study vaccination;
14. The use of prophylactic medications (e.g. acetaminophen/paracetamol, aspirin, naproxen, or ibuprofen) within 24 hours of randomization to prevent or pre-empt symptoms due to vaccination. Subjects discovered to have taken a prophylactic medication to prevent or pre-empt symptoms due to vaccination within the 24 hours prior to planned randomization must be delayed until at least the 24-hour period is met;
15. Subjects who have a dermatological condition at the injection site that may interfere with injection site reaction rating;
16. Subjects who have received a blood transfusion within 90 days prior to study vaccination;
17. Any female subject who has a positive or doubtful pregnancy test result prior to vaccination or who is lactating;
18. Presence of any febrile illness (including oral temperature [OT] ≥ 38.0 ˚C within 24 hours prior to vaccination). Such subjects may be re-evaluated for enrolment after resolution of illness;
19. Cancer or treatment for cancer within three years of study vaccine administration. Persons with a history of cancer who are disease-free without treatment for three years or more are eligible. Individuals with treated and uncomplicated basal cell carcinoma of the skin or with non-treated, non-disseminated local prostate cancer are eligible;
20. Subjects identified as an Investigator or employee of the Investigator or clinical site with direct involvement in the proposed study, or identified as an immediate family member (i.e. parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study or any employee of Medicago. Immediate family members of the Investigator or employees of a clinical site can participate in the study at another clinical site, as long as the Investigator or employees are not involved in the study at that site;
21. Subject with a history of Guillain-Barré syndrome.

3.5 DETERMINATION OF SAMPLE SIZE

Based on data from the CP-Q14VLP-009 study, a sample size of 400 subjects per lot (a

total of 1,200 subjects) will have a greater than 90 % power to test the consistency criterion between the lots (i.e. to test that the pairwise comparisons of the two-sided 95 % confidence interval (CI) for adjusted geometric mean titer (GMT) ratios of the three lots being tested [lot 1/lot 2, lot 1/lot 3, lot 2/lot 3] fall within the equivalence range of 0.67 to 1.5 for all four vaccine strains).

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

3.6 TREATMENT ASSIGNMENT & BLINDING

3.6.1 Treatment Assignment

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

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

Once a randomization number has been assigned, it will not be re-used for any reason. No subjects will be randomized into the study more than once. If a randomization number is allocated incorrectly, no attempt will be made to remedy the error once the study vaccine has been dispensed: the subject will continue on the study with the assigned randomization number and associated treatment. The study staff will notify the Sponsor Contact as soon as the error is discovered. Admission of subsequent eligible subjects will continue using the next unallocated number in the sequence.

3.6.2 Blinding

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

The site staff involved in the preparation and administration of the treatments will not be involved in any activity that could introduce a bias, such as the evaluations of AEs or reactogenicity of the subjects following vaccination.

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

3.7 ADMINISTRATION OF STUDY MEDICATION

On Day 0, subjects will receive one IM injection, into the deltoid region of the non-dominant arm (if possible), of their assigned treatment (one of three lots of 30 µg/strain of Quadrivalent VLP Influenza Vaccine). The volume of injection will be 0.5 mL for all treatments.

3.8 STUDY PROCEDURES AND FLOWCHART

Table 1 Time and Events Schedule

Visit Type	**Screening/ Vaccination**	**Post-vaccination Visits/Contacts**		
Study Day	**Day 0**	**Day 1 (+ 1)**	**Day 8 (- 1/+ 1)**	**Day 21 (- 2/+ 3)**
Visit Number	**1**	**Phone**	**Phone**	**2**
Informed consent	X			
Demographics	X			
Medical history/prior medication	X			
Vaccination history[1]	X			
Inclusion/exclusion criteria	X			
Randomization	X			
Vaccine administration	X			
Immediate surveillance (15 min)	X			
Serology for HI titers	X			X
Vital Signs (blood pressure [BP], heart rate [HR], oral temperature [OT])	X			
Height, weight, and body mass index (BMI)	X			
History/symptom-directed physical examination	X			X[2]
Urine (dipstick) pregnancy test	X			X
Memory aid (MA)[3] and digital thermometer instructions	X			
Collection of solicited local/ systemic	X	X	X	

Visit Type	**Screening/ Vaccination**	**Post-vaccination Visits/Contacts**		
Study Day	**Day 0**	**Day 1 (+ 1)**	**Day 8 (- 1/+ 1)**	**Day 21 (- 2/+ 3)**
Visit Number	**1**	**Phone**	**Phone**	**2**
reactions				
Concomitant medications	At any time during the study period			
AEs, SAEs, and NOCDs	X	X	X	X

[1] Information on past influenza vaccinations for two years prior to study entry; subjects who received an influenza vaccine within 24 months prior to study start are to be excluded from the study.
[2] History/symptom-directed physical examinations will be performed on Day 21 if deemed necessary by the Investigator. If a subject complains of arm and/or shoulder pain of the vaccinated arm or neck pain on the day of the visit, a direct examination of the lymph nodes for swelling (neck and axilla) will be performed by the Investigator.
[3] The MA must be verified with the subject for completeness. All corrections must be made by the subjects before leaving the clinic.

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4. ENDPOINTS

4.1 PRIMARY IMMUNOGENICITY ENDPOINT

GMTs of the three vaccine lots (21 days after vaccination) for all four vaccine strains:

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

4.2 SECONDARY IMMUNOGENICITY ENDPOINTS

HI antibody response induced by the Quadrivalent VLP Influenza Vaccine (pooled data from the three lots) against the homologous influenza strains on Days 0 and 21; HI antibody titers will be analyzed as follows:

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

The immunogenicity endpoints for all four homologous influenza antigens will be evaluated according to the Center for Biologics Evaluation and Research (CBER) criteria for SC rate and SP rate.

4.3 SAFETY ENDPOINTS

The following safety and tolerability endpoints will be evaluated:

- Percentage, intensity, and relationship to vaccination of immediate complaints (15 minutes post-vaccination)
- Percentage, intensity, and relationship to vaccination of solicited local and systemic signs and symptoms (for seven days following study vaccine administration)
- Percentage, intensity, and relationship of treatment-emergent adverse events (TEAEs) for 21 days following study vaccine administration

- Occurrences of deaths, serious adverse events (SAEs), adverse events (AEs) leading to withdrawal, and new onset of chronic diseases (NOCDs) up to Day 21

5. ANALYSIS SETS

The definitions of the analysis sets of subjects may be updated before or during the data review prior to database lock. Assignment of subjects to the analysis sets will be completed before data base lock and unblinding the study.

5.1 SAFETY ANALYSIS SET

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

5.2 FULL ANALYSIS SET

The Full Analysis Set (FAS) will consist of the subset of subjects in the SAS with Day 0 and Day 21 immunogenicity assessments.

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

5.3 PER PROTOCOL SET

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

6. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

6.1 SUMMARY STATISTICS

The standard summary statistics that will be calculated for quantitative and qualitative variables are:

- Quantitative: number of subjects (N), mean, standard deviation (SD), median, minimum and maximum of the raw data
- Qualitative: number of subjects (n), absolute and relative frequencies (%) per category

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

6.2 REPORTING PRECISION

Summary statistics will be presented to the following degree of precision:

Table 2 Reporting Precision

Statistics	**Degree of Precision**
Mean (of all kinds), Median, Quartiles, Confidence limit boundaries	One more decimal place than the raw data
Standard deviation, Standard error	Two more decimal places than the raw data
Minimum, Maximum	The same number of decimal places as the raw data
P-value	Rounded to 3 decimal places and formatted as 0.xxx; P-values smaller than 0.001 as '<0.001'
Percent, Coefficient of variation	One decimal place

All fractional numeric values will be presented with a zero to the left of the decimal point (for example, 0.12 - 0.30, not .12 - .30).

All analyses and summaries will be produced using Statistical Analysis System® (SAS®) version 9.3 (or higher).

6.3 KEY DEFINITIONS AND LABELS

6.3.1 Baseline Values

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

6.3.2 Study Day

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

6.3.3 Onset day

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

6.4 MISSING DATA

Subjects who withdraw from the study will have all data listed and, wherever relevant, included in any subject summaries. No imputation of values for missing data will be performed.

Adverse events and concomitant medications with missing assessment times will have imputed times for the purposes of calculation of relativity to study vaccine or duration. However, the assessment times (start date, stop date) without imputation will be presented in the listings.

For the start of a concomitant medication or adverse event:

- Only the year is reported: If the subject received the study vaccine in the year reported, then the date of the first injection of study vaccine will be used as the start date; otherwise January 1 of the year reported will be used as the start date.

- The month and year are reported: If the subject received study vaccine in the month and year reported, then the date of the first injection of study vaccine will be used as the start date; otherwise the first day of the month and year will be used as the start date.
- The time is missing: If the start date, either actual or estimated, is the same as the date the subject started receiving study vaccine or experienced the adverse event, then the time of the first injection of study vaccine will be used as the start time; otherwise 00:00 will be used as the start time.

For the end of a concomitant medication or adverse event:

- If the adverse event or concurrent medication continues after the last study contact date, then no stop date or time will be estimated.
- Only the year is reported: The earlier of December 31 of the year reported and the date of the last study contact with the subject will be used as the stop date.
- The month and year are reported: The earlier of the last date of the month and year reported and the date of the final contact with the subject will be used as the stop date.
- The time is missing: 23:59 will be used as the stop time

6.5 VISIT WINDOWS

In general, all safety data will be summarized by scheduled visits based on the scheduled events indicated in Table 1. The visits indicated on the eCRF (i.e. eCRF visit) will be used as the analysis visits for analysis of most safety parameters. The following rules will apply unless other handling is specified for a particular analysis.

- For repeatable safety assessments collected at scheduled time points pre-vaccination, the last usable value will be used in by-time point analyses but all values will be included in the listings.
- For repeatable safety assessments collected at scheduled time points post-vaccination and at follow-up, the first usable value for the time point will be used in by-time point analyses but all values will be included in the listings
- If a patient has no record in an analysis window, the patient will be considered missing at that time point.

6.6 POOLING OF CENTERS

No center pooling will be employed.

7. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

7.1 SUBJECT DISPOSITION AND WITHDRAWALS

The following frequencies (number and percent) will be displayed based on the vaccinated subjects:

- Screened Subjects (numbers only)
- Screen Failures (numbers only) and reason for screen failure
- Randomized Subjects (numbers only)
- Vaccinated Subjects
- Subjects in the Safety Analysis Set
- Subjects in the Full Analysis Set
- Subjects in the Per Protocol Set
- Subjects who completed the study (Day 21)
- Subjects who withdrew early from study (Day 21) and reason for withdrawal

The denominators for the percent calculations will be the number of subjects vaccinated, whether or not they are included in any of the analyses.

Subjects' completion/discontinuation status will be listed, including subject identifier, date of completion/early discontinuation and, for those who discontinued early, the specific reason(s) for discontinuation.

Inclusion/exclusion criteria definitions and deviations will be listed. If no inclusion/exclusion criteria are reported, this will be noted in place of the listing.

A listing of subjects excluded from the analysis sets will also be produced.

7.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data will be displayed in listings and summarized by vaccine lot (treatment group). Continuous variables including age, weight, height and BMI will be summarized with N, Mean (SD), Median, Min and Max. Count and percentage of subjects will be presented for categorical variables such as sex, race, and ethnicity.

7.3 PROTOCOL DEVIATIONS

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

All protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment will be listed and assessed during the course of the study. The list of protocol deviations will be finalized before database lock.

The protocol deviations will be grouped into different categories which may include, but are not limited to:

- Eligibility criteria
- Visit window
- Informed consent procedure
- Prohibited medication
- Administration/dispensing of vaccine
- Failure to report SAE or Pregnancy within specified timelines
- Biological sample procedures
- Assessments procedures
- Other

A summary table of protocol deviations by vaccine lot and category will be provided.

7.4 MEDICAL HISTORY AND CONCOMITANT DISEASES

Medical histories will include grade of medical condition, if they are ongoing. Medical history abnormalities will be coded to Medical Dictionary for Regulatory Activities (MedDRA®) terms, using version 20.0. All findings on medical history will be evaluated by the investigator for clinical significance.

Medical history findings will be summarized by system organ class (SOC) using internationally agreed order and listed by subject.

7.5 PRIOR AND CONCOMITANT MEDICATIONS

Any new or changed medications reported by the subject post-vaccination and through to the end of the study will be recorded in the electronic case report form (eCRF) as a concomitant medication. Any AEs associated with the new or changed medication use must also be documented.

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

- Within 30 days preceding vaccination: any treatments and/or medications specifically contraindicated (e.g. influenza vaccines, any immunoglobulins or other blood products, or any immune modifying drugs, etc.);
- From randomization to Day 21, inclusive: any medication (including, but not limited to, over-the-counter medicines such as aspirin or antacids), vitamins, and mineral supplements;
- Any concomitant medication use to treat conditions reported as medical history;
- Any investigational medication or vaccine; any vaccine not foreseen in the study protocol.

The use of prophylactic medications to prevent or pre-empt symptoms due to vaccination is specifically prohibited up to Day 7.

The original verbatim terms (entered in the case report form (CRF) for prior and concomitant medications) will be coded using the World Health Organization Drug Dictionary (WHO DD), March 2017, into drug class (up to anatomical therapeutic chemical (ATC) level 4) and preferred term.

Prior and concomitant medication data will be summarized by ATC level 1 and level 3, and listed chronologically by subject including all data collected in the eCRF (eCRF), along with coded variables (ATC and Preferred Term) and other related variables (e.g., start/stop date, dose). If no prior or concomitant medications are reported, this will be noted in place of the listing.

7.6 TREATMENT EXPOSURE

Vaccine administration data will be shown in listing.

8. IMMUNOGENICITY ANALYSIS

8.1 PRIMARY IMMUNOGENICITY ENDPOINT AND ANALYSIS

8.1.1 Datasets analyzed

Immunogenicity analysis (GMTs and GMT Ratios) will be based on the PP set, and repeated using the FAS as the sensitivity analysis.

8.1.2 Measurements

Immunogenicity will be evaluated by measuring the serum antibody response induced in subjects, using the HI test against the homologous vaccine strains. HI antibody response will be measured using titer values.

The homologous influenza strains are as below:

1. A/California/7/2009 (H1N1)
2. A/Hong Kong/4801/2014 (H3N2)
3. B/Brisbane/60/2008 (B/Brisbane)
4. B/Phuket/3073/2013 (B/Phuket)

8.1.3 Scheduled Collection

Immunogenicity data will be collected on Days 0 and 21.

8.1.4 Derived and Imputed Data

- For the purpose of endpoints calculation, all HI antibody responses below the lower limit of quantitation (BLQ, <10) will be attributed a value of 5.
- GMT and 95% confidence intervals for the vaccine lots are calculated as the antilog of the mean and 95% confidence limits of log (base 10) transformed total titer values.
- GMT Ratios and 95% confidence intervals for the pairwise comparisons of the lots are calculated as the antilog of the differences of the means and 95% confidence limits of log (base 10) transformed total titer values.

8.1.5 Data Summarization

The adjusted Day 21 GMTs and the lot-to-lot adjusted Day 21 GMT ratios will be summarized by the vaccine lots and by homologous influenza strains. Mean and 95% CIs

will be calculated for the adjusted Day 21 GMTs and GMT ratios. Reverse cumulative distribution curves of HI titers will be plotted.

8.1.6 Model Fitting

Analysis of log (base 10) transformed titer will be performed using Analysis of Covariance (ANCOVA) with vaccine lot as main effect and baseline titer as covariate. Pairwise comparisons between each vaccine lot will be performed using two-sided, 95% CIs on the vaccine lot differences in GMTs, based on the least-squares mean differences from the ANCOVA model.

The model is shown below:

```
Proc mixed data=ADZ (with the appropriate pooled subset);
  class trtpn;
  model aval= trtpn Base;
  Lsmeans trtpn/ diff cl alpha=0.05;
Ods output LSMEANS-=_outmix DIFFS =_outdiff;
run;
Quit;
Data   outdiff;
Set   outdiff;
GMTR = 10**(Estimate); *GMTR: GMT Ratio;
GMTR  LCL = 10**(Lower); *GMTR  LCL: GMT Ratio 95%CI lower limit;
GMTR_UCL = 10**(Upper); *GMTR_LCL: GMT Ratio 95%CI upper limit;
Run;
```

where aval is the $\log_{10}$ transformed titer values.

8.1.7 Primary Analysis

The following analyses for primary endpoints will be performed for three vaccine lots for all four vaccine strains.

- The adjusted GMT ratios (Day 21) and the corresponding two sided 95 % CI for each pairwise comparison of the lots will be calculated using ANCOVA models to assess if the two-sided 95 % CI limit falls between 0.67 and 1.5 for all four strains.

Hypotheses:

H0 : The lower bound of the 95 % CI is less than or equal to 0.67, or the upper bound of the 95 % CI is greater than or equal to 1.5.

H1 : The lower bound of the 95 % CI is greater than 0.67 and the upper bound of the 95 % CI is less than 1.5 for all pairwise combinations of lots and for each strain.

Multiplicity:

For multiplicity of hypothesis tests, a stepwise closed testing approach will be applied. The stepwise closed testing procedure (1.A/California: lot 1/lot 2→lot 1/lot 3→lot 2/lot 3→2.A/Hong Kong:lot 1/lot 2….→3.B/Brisbane…→4.B/Phuket) will be stopped as soon as the first non-rejection of null hypothesis (H0).

8.2 SECONDARY IMMUNOGENICITY ENDPOINT(S) AND ANALYSES

8.2.1 Data Sets Analyzed

Immunogenicity analysis (GMTs, GMFRs, SC rates, and SP rates) will be based on the PP set, and repeated using the FAS as the sensitivity analysis.

8.2.2 Measurements

Immunogenicity will be evaluated by measuring the serum antibody response induced in subjects, using the HI test against the homologous vaccine strains. HI antibody response will be measured using titer values.

The homologous influenza strains are listed in Section 8.1.2.

8.2.3 Scheduled Collection

Immunogenicity data will be collected on Days 0 and 21.

8.2.4 Derived and Imputed Data

- For the purpose of endpoints calculation, all HI antibody responses below the lower limit of quantitation (BLQ, <10) will be attributed a value of 5.
- GMT and 95% confidence intervals for the vaccine lots are calculated as the antilog of the mean and 95% confidence limits of log (base 10) transformed total titer values.
- GMFR is the geometric mean of the ratio of GMTs (Day 21/Day 0).

- SC rate is the proportion of subjects with either a ≥ 4-fold increase in reciprocal HI titers between Day 0 and Day 21 or a rise of undetectable HI titer (i.e. <10) pre-vaccination (Day 0) to an HI titer of ≥40 on Day 21 post-vaccination.
- SP rate is the proportion of subjects attaining a reciprocal HI titer of ≥40 on Day 21 post-vaccination (the percentage of vaccine recipients with a serum HI titer of at least 1:40 following vaccination).

8.2.5 Data Summarization

The immunogenicity parameters will be summarized by the vaccine lots and by homologous influenza strains. Descriptive statistics and 95% CIs will be calculated for the immunological parameters.

8.2.6 Model Fitting

The GMT will be derived by using Analysis of Variance (ANOVA) with vaccine lot as main effect. The log (base 10) transformed titer will be used and the back-transformation for mean GMT will be calculated with two-sided 95% confidence limits, based on the ANOVA model. The model is shown below:

```
Proc mixed data=ADZ (with the appropriate pooled subset);
  class trtpn;
  model aval= trtpn;
  Lsmeans trtpn/ cl alpha=0.05;
Ods output LSMEANS-=_outmix;
run;
Quit;
Data   outmix;
Set   outmix;
GMT= 10**(Estimate);
GMT_LCL = 10**(Lower);
GMT_UCL = 10**(Upper);
Run;
```

where aval is the $\log_{10}$ transformed titer values.

For the SC and SP rates, the exact 95 % CI will be calculated using the following SAS® Code.

```
Proc freq data=ADZ(with the appropriate pooled subset);
```

```
    by trtpn;
    table SC/out=CNT binomial;  *SC or SP
    exact binomial;
    ods output binomialprop=bin (where=(name1 in ('XL_BIN', 'XU_BIN')));
run;
```

8.2.7 Secondary Analysis

- The GMTs, GMFRs, and SC and SP rates of HI antibody will be calculated for the combined vaccine lots (overall), using descriptive statistics and 95 % CI; GMTs will also be summarized for each vaccine lot.
- The GMTs for HI antibody for each individual vaccine lot will be derived using ANOVA model with vaccine lot as main effect.
- For the SC and SP rates, the point estimates and the corresponding exact two-sided 95 % CIs will be calculated for the combined lots (overall) to assess whether the CI meets the CBER criteria.

9. SAFETY

The analysis population used for safety analyses will be the SAS. Safety and tolerability endpoints (solicited local and systemic reactions, AEs, and vital signs) will be tabulated.

9.1 REACTIONS AND ADVERSE EVENTS

All subjects in the SAS will be included in the AE analysis.

9.1.1 Measurements

Both solicited reactions and unsolicited AEs will be collected.

Solicited Local and Systemic Reactions

Subjects will be monitored for both solicited local reactions (erythema, swelling and pain at the injection site) and solicited systemic reactions (fever, headache, fatigue, muscle aches, joint aches, chills, a feeling of general discomfort, swelling in the axilla, and swelling in the neck).

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

Unsolicited Adverse Events

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

A treatment-emergent AE (TEAE) is any AE that is new in onset or was aggravated in severity or frequency following the administration of study drug, up to and including the last visit of the study. Treatment emergence will be determined by comparing the AE start date/time with the actual date/time of vaccination. In the case that the AE start date/time are incomplete, treatment emergence will be imputed according to the algorithm in Section 6.3 of the SAP.

Each AE report contains a description of the AE, the date and time of onset and resolution,

intensity, whether it is serious, any required treatment or action taken, outcome, relationship to the investigational vaccine, and whether the AE caused withdrawal from the study. Data will be recorded on the CRF by the total span of time covered for each event, rather than by a separate record for each report of the same event.

The intensity of all AEs will be graded as mild (1), moderate (2) severe (3), or potentially life-threatening (4). Their causal relationship with the study vaccine will be assessed by the Investigator (definitely not related, probably not related, possibly related, probably related or definitely related).

Unsolicited AEs will be coded using MedDRA 20.0 and analyzed by PT and System Organ Class (SOC).

All AEs will be evaluated to determine whether they should be considered as an NOCD or an SAE. In the context of this study, all NOCDs that may plausibly have an allergic, autoimmune, or inflammatory component are to be reported. An SAE is considered to be any untoward medical occurrence (whether or not considered to be related to the study vaccine) that, at any dose results in death; is life-threatening (at the time of the event); requires inpatient hospitalization (≥ 24 hours) or prolongation of existing hospitalization (elective hospitalizations/procedures for pre-existing conditions that have not worsened are excluded); results in persistent or significant disability/incapacity; is a congenital abnormality/birth defect; or is another medically important event (e.g. any cases of newly diagnosed cancer).

Hypersensitivity cases will be identified using a standardized MedDRA query (SMQ) for hypersensitivity.

9.1.2 Collection Schedule

Solicited local and systemic reactions will be collected from the time of vaccination through Day 7. Any solicited local or systemic reactions lasting beyond Day 7 will be considered an AE with a start date 8 days post-vaccination.

Solicited local and systemic reactions occurring within 15 minutes post vaccination will be considered as Immediate Complaints.

All AEs occurring within 21 days after vaccination will be recorded in the source documents or MA and reported in the “Adverse Event” form in the subject’s eCRF, irrespective of intensity or whether or not they are considered to be vaccination-related.

The SAEs and NOCDs will be followed up until complete resolution or stabilization.

Follow-up of unresolved SAEs, AEs leading to withdrawal, or NOCDs after the end of the study period will continue under the discretion of the Investigator.

9.1.3 Derived and Imputed Data

Every attempt will be made to get complete dates and times or best estimates for AEs which may occur or start outside of the clinic. AEs which begin during the subject's stay in clinic are expected to have complete dates and times. Incomplete AE dates and times will not be imputed.

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

Days from vaccination are calculated as date of event – date of vaccine +1.

9.1.4 Data Summarization

Immediate complaints, solicited local and systemic reactions, and AEs will be summarized according to the vaccine lot and overall.

Additional summaries will be provided for each vaccine lot and overall by severity and by relationship. The local and systemic signs and symptoms tabulations will also include the immediate complaints. The proportion of subjects with a non-zero grade will be included.

9.1.5 Model Fitting

No inferential tests will be used on these data.

9.1.6 Data Presentation

Displays of AEs by vaccine lot and overall will include:

- Overall Summary of Solicited Reactions and Unsolicited TEAEs
  This table will include the number and percentage of subjects who had solicited reactions or unsolicited TEAEs, who had immediate complaints, solicited local and systemic reactions, who had ≥severe reactions and events, who had serious events, and who were withdrawn due to an AE or who died.

The following summaries of immediate complaints (solicited local and systemic reactions occurring 15 minutes post vaccination) will be presented by vaccine lot and overall:

- Summary of incidence of immediate complaints.

- Summary of immediate complaints by symptom and maximum intensity (mild, moderate, severe, or potentially life-threatening).
- Summary of immediate complaints by symptom and relationship to vaccination (related or not related). The "related" category will include the Investigator causal assessments of definitely related, probably related, and possibly related; the "not related" category will include the Investigator causal assessments of probably not related and definitely not related.

The following summaries of solicited reactions will be presented by vaccine lot and overall:

- Summary of incidence of solicited reactions by symptom.
- Summary of solicited reactions by symptom and maximum severity (mild, moderate, severe, or potentially life-threatening). The "related" category will include the Investigator causal assessments of definitely related, probably related, and possibly related; the "not related" category will include the Investigator causal assessments of probably not related and definitely not related.
- Summary of solicited reactions by symptom and relationship to study vaccine (related or not related).
- Summary of severe and potentially life-threatening related solicited reactions

The following summaries of unsolicited TEAEs will be presented by vaccine lot and overall:

- Summary by MedDRA SOC and PT.
- Summary by severity (mild, moderate, severe, or potentially life-threatening), MedDRA SOC, and PT.
- Summary by relationship to study vaccine (related or not related), MedDRA SOC, and PT. The "related" category will include the Investigator causal assessments of definitely related, probably related, and possibly related; the "not related" category will include the Investigator causal assessments of probably not related and definitely not related.
- Summary of severe and potentially life-threatening related TEAEs by MedDRA SOC and PT.
- Summary of serious TEAEs by MedDRA SOC and PT.
- Summary of NOCDs by SOC and PT.

The following summary of hypersensitivity events will be presented by vaccine lot and overall:

- Summary by MedDRA SOC and PT.

AEs will be listed by subject, treatment (lot) and day of onset for all AEs. Solicited reactions including Immediate Complaints will be displayed in Listing 16.2.7.1. Unsolicited AEs will be listed in Listing 16.2.7.2, NOCDs will be listed in Listing 16.2.7.4, and hypersensitivity will be listed in Listing 16.2.7.5.

9.2 VITAL SIGNS

All subjects in the SAS will be included in the vital signs analysis.

9.2.1 Measurements

Vital signs will consist of blood pressure (systolic and diastolic blood pressure, measured in millimeters of mercury (mmHg)), heart rate (beats per minute (bpm)), and oral temperature (degrees Celsius (°C)).

9.2.2 Collection Schedule

Vital sign parameters will be measured as part of screening procedures (prior to eligibility assessment on Day 0) and after the post-vaccination surveillance period.

9.2.3 Derived and Imputed Data

No derived or imputed data are calculated for vital signs. Missing data will not be replaced using any imputation method.

9.2.4 Data Summarization and Presentation

Vital signs data will be summarized by vaccine lot and assessment time using standard summary statistics. Vital signs data will be listed in Listing 16.2.8.2.

9.3 PHYSICAL EXAMINATION

9.3.1 Measurements

Results of normal, abnormal and Not Clinically Significant (NCS), or abnormal and Clinically Significant (CS) will be collected for the physical examination. Abnormal CS findings will be reported in Medical History or as an AE as applicable.

9.3.2 Collection Schedule

A history/symptom-directed physical examination will be performed on Day 0 prior to vaccination, and it can also be conducted on Day 21, if deemed necessary by the Investigator.

9.3.3 Derived and Imputed Data

No derived or imputed data are calculated for physical examination.

9.3.4 Data Summarization and Presentation

Physical examination abnormalities will not be summarized. Physical examination data will be listed in Listing 16.2.8.3.

9.4 OTHER SAFETY VARIABLES

9.4.1 Pregnancy Test

A urine dipstick pregnancy test will be performed prior to vaccination and during the Day 21 visit. This data will be listed in Listing 16.2.8.1.

10. INTERIM ANALYSES

No interim analysis is scheduled.

11. CHANGE FROM ANALYSIS PLANNED IN PROTOCOL

There were no changes to the planned analysis from version 1.3 CP-PRO-QVLP-011 protocol dated 08-Aug-2017, in effect at the start of the study.

12. PROGRAMMING CONSIDERATIONS

12.1GENERAL CONSIDERATIONS

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

12.2TABLE, LISTING AND FIGURE FORMAT

12.2.1 General

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

- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

12.2.2 Headers

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

  Medicago R&D Inc.

  Protocol CP-PRO-QVLP-011

- All output should have Page n of N at the top right corner of each page. TLFs should be internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

- The date (date output was generated) should appear along with program name as the last footer on each page.

12.2.3 Display Titles

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

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

12.2.4 Column Headers

- Column headings should be displayed immediately below the solid line described above in initial upper-case characters.
- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if

applicable). For numeric variables, include "unit" in column or row heading when appropriate.

- Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.

12.2.5 Body of the Data Display

12.2.5.1 General Conventions

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

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

12.2.5.2 Table Conventions

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

Severity Rating	N
mild	3
moderate	8
severe	0

  Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).
- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.
- An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.

- Unless otherwise specified, the estimated mean and median for a set of values should be printed out to 1 more significant digit than the original values, and SDs should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

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

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

12.2.5.3 Listing Conventions

- Listings will be sorted for presentation in order of subject number, visit/collection day, and visit/collection time.
- Missing data should be represented on subject listings as either a hyphen ("-") with a corresponding footnote ("- = unknown or not evaluated"), or as "N/A", with the footnote "N/A = not applicable", whichever is appropriate.
- Dates should be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates should be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

- All observed time values must be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

12.2.5.4 Figure Conventions

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

12.2.6 Footnotes

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

13. QUALITY CONTROL

SAS® programs are developed to produce clinical trial outputs such as analysis data sets, summary tables, data listings, figures or statistical analyses. A SAS® Programming and Quality Control (QC) Plan will be prepared prior to the start of programming, and will specify all QC SOPs and Work Instructions (WIs), which will describe the quality control procedures that are performed for all SAS® programs and outputs.

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Statistical Analysis Plan

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17. MOCK-UPS

The following mock-ups can be provided upon request:

- Planned Table Shells
- Planned Listing Shells
- Planned Figure Shells