Statistical Analysis Plan

Seqirus

V130_14

A Phase III, Randomized, Observer-blind, Multicenter Study to Evaluate the Efficacy, Immunogenicity and Safety of Seqirus' Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Compared to a Non-Influenza Vaccine when Administrated in Healthy Subjects aged 6 Months through 47 Months

[redacted]

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Clinical Development Commercialization Services

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Approvals

The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan as final. Programming of the tables, figures and listings based upon the specifications within this document can proceed.

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Version History

Version #	Description of Changes	Version Date
Version 1.0 Final	Final version	09 March 2021
Version 2.0 Final	Addition of Appendix C, deletion of site covariate for Cox PH model.	07 September 2021

Glossary of Abbreviations

Abbreviation	Term
AE	Adverse event
aVE	Absolute vaccine efficacy
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECDC	European Center for Disease Control
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HA	Hemagglutinin
HI	Haemagglutination Inhibition
HR	Hazard ratio
ID	Identification
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ILI	Influenza-Like Illness
IRT	Interactive Response Technology
LAR	Legally Acceptable Representative(s)
LL	Lower Limit
MedDRA	Medical Dictionary for Regulatory Activities
MenC	Meningococcal (Group C) Conjugate Vaccine
MN	Microneutralization
NOCD	New Onset of Chronic Disease
PD	Protocol Deviation
PPAS	Per Protocol Analysis Set
QIVc	Cell-derived Quadrivalent Influenza Vaccine
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCR	Seroconversion
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
VE	Vaccine Efficacy
WHO	World Health Organization

1 Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version	
Protocol	03 Sep 2020	3.0	
eCRF	13Feb20	4.0	

This document presents the SAP for Seqirus, Protocol No. V130_14: A Phase III, Randomized, Observer-blind, Multicenter Study to Evaluate the Efficacy, Immunogenicity and Safety of Seqirus' Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Compared to a Non-Influenza Vaccine when Administrated in Healthy Subjects aged 6 Months through 47 Months.

The aim of this study is to evaluate the efficacy of QIVc in the prevention of Reverse Transcription Polymerase Chain Reaction (RT-PCR) confirmed influenza A or B disease in children 6 through 47 months of age, compared to a non-influenza vaccine. Efficacy data from all planned influenza seasons will be combined. By successfully demonstrating that QIVc decreases influenza disease in this age group, it will have the potential to play an important role in the prevention of influenza worldwide.

This SAP describes the data and variables to be summarized and analyzed, including specifics of the statistical analyses to be performed. This analysis plan is based on the Version 3.0 of the protocol, dated 03 September 2020 and is compliant with ICH Harmonized Tripartite Guideline, 5 February, 1998, Statistical Principles for Clinical Trials, E9; World Health Organization, WHO Technical Report, Series No. 924. 2004, Annex 1: Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations; and FDA Center for Biologics Evaluation and Research (CBER) Guidance for Industry, May 2007, Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines.

The Data Monitoring Committee (DMC) analysis will be detailed in the Charter and follow definitions noted in this SAP.

The SAP provides the description of the analysis for the influenza cases during the active ILI surveillance period, the analysis of immunogenicity data and the analysis of safety data through to the final evaluation. Any deviations from the current statistical plan and changes in the conduct or planned analysis will be described and justified in the final Clinical Study Report (CSR).

2 Protocol Details

2.1 Study Objectives

In this study, efficacy will be evaluated in all subjects in association with first occurrence of influenza-like illness (ILI) symptoms occurring > 14 days after last vaccination and until the end of the influenza season in subjects 6 months through 47 months of age at enrollment.

Influenza like illness (ILI) is defined by the presence of a temperature ≥ 37.8°C (≥ 100.0°F) and at least one of the following symptoms on the same day: cough, sore throat, nasal congestion, rhinorrhea, earache or ear discharge.

Note: Defined as the end of May for Northern Hemisphere (NH) influenza season and end of November for Southern Hemisphere (SH) influenza season. For tropical countries, with no typical NH or SH influenza season, the season is defined by the use of the strains in the influenza vaccine formulation (i.e. strains as recommended for the NH or the SH influenza season).

2.1.1 Primary Efficacy Objectives

To demonstrate the absolute vaccine efficacy (aVE) of QIVc versus a comparator to prevent at least one of the following:

- RT-PCR confirmed illness caused by any influenza Type A and/or Type B virus, regardless of antigenic match.
- Culture confirmed illness caused by influenza virus strains antigenically matched to the influenza strains selected for the seasonal influenza vaccine.

2.1.2 Secondary Objectives

2.1.2.1 Secondary Efficacy Objective(s)

Objectives evaluating QIVc compared to a non-influenza vaccine:

- Prevention of culture confirmed illness caused by influenza virus strains antigenically dissimilar to the influenza strains selected for the seasonal vaccine.
- Prevention of culture confirmed illness caused by any Type A and/or Type B virus.
- Prevention of RT-PCR confirmed moderate-to-severe illness caused by any influenza Type A and/or Type B virus.

2.1.2.2 Secondary Immunogenicity Objective(s)

To evaluate the immune response after vaccination with QIVc, 4 weeks after last vaccination in a sub-set of subjects 6 months through 47 months of age in each study vaccine group.

2.1.2.3 Secondary Safety Objective(s)

To evaluate the safety and tolerability of QIVc among subjects 6 months through 47 months of age in each study vaccine group.

2.1.3 Exploratory Objectives

Exploratory objectives:

- To characterize the immune response by other assays.
- To use genotypic methods to characterize circulating strains of influenza collected during the study.

2.2 Overall Study Design

This multicenter phase III clinical study evaluates the efficacy, immunogenicity and safety of a cell-based quadrivalent subunit influenza virus-vaccine compared to non-influenza vaccine in subjects between 6 months through 47 months of age. The study features an observer blind design, parallel groups and 1:1 randomization between QIVc and a non-influenza vaccine (Meningococcal Group C Polysaccharide Conjugate Vaccine (MenC-vaccine)).

Based on previous influenza vaccination history, subjects will receive either one or two doses of either QIVc or comparator (non-influenza vaccine/placebo).

The study is designed to accrue an approximate number of subjects and a minimum number of cases over several influenza seasons. Each subject will participate until the end of the influenza season as defined in the protocol for the season in which the subject is enrolled but at least 180 days after last vaccination in the treatment period (defined below).

The study has a treatment period and a follow-up period.

For subjects with a previous influenza vaccination history (named also "previously vaccinated" subjects in the document):

- The treatment period begins at the time of vaccination (Day1) and ends 28 days after vaccination (Day 29) and will consist of 2 clinical visits and one reminder call to complete the Subject diary card.
- The follow up period begins 28 days after vaccination and ends at the time of study completion visit.

For subjects without or unknown previous influenza vaccination history (named also "not previously vaccinated" subjects in the document):

- The treatment period begins at the time of first vaccination (Day 1) and ends 28 days after the second vaccination (Day 57) and will consist of 3 clinical visits and two reminder calls to complete the Subject diary card, one after each vaccination.

- The follow-up period begins 28 days after second vaccination and ends at the time of study completion visit.

All subjects, irrespective of previous influenza vaccination history, will receive 1 safety follow-up call 90 days after last vaccination during the follow up period and the follow-up period will conclude with a study completion visit (clinic visit or call).
All subjects aged 6 through 11 months at enrollment, irrespective of randomization to investigational or comparator group, will receive a dose of the MenC vaccine at the end of the study.

The timing and frequency of the study visits are described in Schedule of Assessments (Appendix A).

The treatment arms of Study Vaccine comprise:

Study treatment:

Subjects who meet the entry criteria will be stratified by age and vaccination history and then randomized to one of the two treatment groups using a 1:1 allocation ratio to receive either Seqirus QIVc or the MenC-vaccine.

Investigational treatment

A cell-derived quadrivalent inactivated subunit influenza vaccine (QIVc) will be used as investigational vaccine.

Vaccination schedule:

- Subjects ≥ 12 months with a previous influenza vaccination history: One dose of QIVc at Visit 1.
- Subjects ≥ 12 months without a previous influenza vaccination history and subjects 6 through 11 months: One dose of QIVc at Visit 1 followed by one dose of QIVc at Visit 2.

Comparator treatment:

Meningococcal Group C Polysaccharide Conjugate Vaccine (MenC vaccine, Neisvac-C, Pfizer) will be used as a comparator.

Vaccination schedule:

- Subjects ≥ 12 months with a previous influenza vaccination history: One dose of MenC vaccine at Visit 1.
- Subjects ≥ 12 months without a previous influenza vaccination history and subjects 6 through 11 months: One dose of MenC vaccine at Visit 1 followed by one dose of placebo (saline for injection) at Visit 2.
- All subjects aged 6 through 11 months at enrollment, regardless of treatment assignment, will receive a dose of the MenC vaccine at Visit 5.

Withdrawn Subjects

Subjects may withdraw from the study at any time at their own request or request of the parent or legally appropriate representative, or they may be withdrawn at any time at the discretion of the investigator should any untoward effects occur and/or for safety reasons.
The reasons for premature withdrawal from the study include the following:

- Adverse event (AE)
- Death
- Withdrawal of consent
- Lost to follow-up
- Other
- Protocol deviation
- Study terminated by Sponsor

In accordance with International Conference on Harmonization (ICH) principles of Good Clinical Practice (GCP) the investigator always has the option to advise a subject to withdraw from the study if the subject's safety or wellbeing is compromised by his or her further participation in the study. Concern for the interests of the subject must always prevail over the interests of the study.

If a subject is withdrawn from the study or further participation is declined, they will continue to have access to medical care and will be treated as per routine medical practice.

Randomization

All enrolled subjects will be randomly assigned to one of the two study groups (QIVc or comparator) in a pre-specified ratio of 1:1, with stratification factors such as age cohort (6 through 23 months / 24 through 47 months, with a at least 30% of the subjects between 6 through 23 months of age and at least 30% of the subjects between 24 through 47 months of age), previous influenza vaccination history. For immunogenicity assessments, a subset of subjects (a maximum of 222 subjects per influenza season) will be assigned to the immunogenicity subset at a 1:1 ratio to QIVc or comparator respectively with stratification factors such as age cohort, and previous influenza vaccination history.

Enrolled subjects will be randomized through a randomization and trial supply management (RTSM) system. The list of randomization assignments is produced by the RTSM system and approved by Seqirus according to applicable Seqirus Standard Operating Procedure (SOP).

If for any reason, after signing the Informed Consent Form (ICF), the subject who is eligible and enrolled fails to be randomized, this is called a randomization failure. The

reason for all randomization failures will be recorded in the Screening and Enrollment Log.

If for any reason, after randomization the subject fails to undergo treatment, this is an Early Termination and the early termination study procedures must be applied, including reason should be recorded. The information on these Early Termination subjects should be kept distinct in the source documentation from randomization failures.

Blinding

The trial is designed as an observer-blind study. During the treatment period of the study, designated and trained unblinded nurse(s), physician(s), or other qualified health care professional will be responsible for administering the study vaccines to the subjects. They will be instructed not to reveal the identity of the study vaccines either to the subject's parent(s)/ Legally Acceptable Representative(s) (LAR)/delegate or to the investigative site personnel (i.e., investigator and study nurse) involved in the monitoring of conduct of the trial, except in an emergency if unblinding in Interactive Response Technology (IRT) is not possible. Vaccine administration should be shielded from the subject's parent(s)/LAR(s) and blinded study personnel. The unblinded personnel should not be involved in data collection or data review such as safety assessments and/or collect study data after the vaccinations. Study vaccines will be assigned through an Interactive Response technology system.

To maintain the blind in the study, all subjects aged 6 through 11 months at enrolment will receive a MenC vaccine at visit 5. According to the MenC (Neisvac-C) vaccine prescribing information subjects that received their first dose < 12 months of age should receive a second dose, at least 6 months after the first dose, to complete their primary immunization. For subjects aged ≥12 months at first vaccination, only one dose of the MenC vaccine is necessary. To meet these requirements and to maintain the blind in the study, all subjects aged 6 through 11 months at enrollment will receive a dose of the MenC vaccine at visit 5.

Except in the case of medical necessity, a subject's treatment should not be unblinded without the approval of the Sponsor. In such instance, every effort should be made to contact the Sponsor prior to unblinding. If unblinding occurs, by either accidental unblinding or emergency unblinding for a serious adverse event, prior to completion of the study, the investigator must promptly contact the Sponsor and document the circumstances in IRT. In case of an emergency, the information can be retrieved by the Investigator from the IRT system either via web or phone (a 24/7 backup service). If the subject or blinded site staff is unblinded by the Investigator, the subject could be removed from an Analysis Set.

Investigators, Seqirus study team, all laboratory personnel involved in processing samples and performing laboratory assays and others who are directly involved in the conduct of the trial or in the analysis of the final trial results, or have contact with study centers, will remain blinded to the treatment codes and interim analysis results until the database has been locked for final analysis.

If a subject is unblinded during the study, it is to be reported as major Protocol Deviation (PD), except for subjects unblinded by Pharmacovigilance due to suspected unexpected serious adverse reactions (SUSAR). The unblinding will be documented appropriately.

2.3 Sample Size and Power

This study is planned using a group sequential design, with one or more interim analyses for efficacy using O'Brien-Fleming efficacy bounds. The statistical test performed will depend on the number of RT-PCR confirmed influenza cases and the number of culture confirmed influenza cases, so the sample size estimate is only for operational reasons (an estimate of number of subjects needed to assess the endpoint).

For the primary efficacy endpoint for RT-PCR confirmed illness (1a), assuming an attack rate in the comparator group of 8% and an influenza vaccine efficacy of 40%, an estimated sample size of minimally 2,974 evaluable subjects (or 1,487 evaluable subjects per study group) with a minimum total of 191 cases are needed to have at least 90% power to reject the null hypothesis that the VE is less or equal to 0% at the significance level alpha=0.0125 and the risk of infection contained entirely within period covered by follow-up. For the primary efficacy endpoint for vaccine antigenically matched strains (1b), assuming an attack rate in the comparator groups of 4%, a VE of 50%, α=0.0125, a minimum of 3,446 evaluable subjects and a minimum number of 104 cases are needed to have at least 90% power to reject the null hypothesis that the VE is less or equal to 0% at the significance level alpha= 0.0125. These results assume that the hazard ratio is constant throughout the study and that Cox proportional hazard regression is used for the analysis. The following table summarises the power calculations assumptions and the number of cases required to meet primary efficacy endpoints.

Table 1. Power calculation for Multiple Primary Endpoints

Primary Objective	VE Success Criteria	Assumed VE	Alpha (α)	Influenza attack rate in comparator group	Power	Minimum number evaluable subjects per Treatment Group	Minimum total subjects Enrolled	Minimum number of ILIs to demonstrate LL 97.5% CI for VE is > 0%
1a	0%	40%	0.0125	8%	>90%	1,487	3,306	191
1b	0%	50%	0.0125	4%	>90%	1,723	3,830	104

Accounting for 10% early dropout and uncertainty about the assumed parameters, an approximate number of 3,830 subjects are planned to be enrolled (or 1,915 subjects per study group) to demonstrate that the lower limit (LL) of the two-sided 97.5% CI for the VE is greater than 0% for the primary endpoint assessment.

The study is designed to accrue a minimum of 191 RT-PCR confirmed influenza cases and a minimum of 104 culture confirmed influenza cases antigenically matched to the strains selected for the seasonal vaccine.

If the overall/pooled influenza attack rate differs from the predicted and/or influenza strain circulation within a study season has drifted or shifted away from the strains selected for the seasonal vaccine, an adjustment of the prospectively specified number of cases, and number of subjects may be required. Extraneous real-life information, from (but not limited to) the influenza surveillance systems of the European Center for Disease Control (ECDC), US Center for Disease Control and Prevention (CDC) or World Health Organization (WHO) may be used to re-assess the influenza event rate.

Sample Size for Secondary Immunogenicity Objectives (Immunogenicity Sub-set):

Per season, with a 1:1 allocation, approximately 100 evaluable subjects from the active arm and 100 evaluable subjects from the comparator arm will be enrolled into the immunogenicity sub-set. Assuming a 10% drop out rate approximately 222 subjects will be allocated to the immunogenicity sub-set per influenza season.

Sample Size for Safety:

With a Safety Population of 1,723 evaluable subjects in the safety set of QIVc, AEs with population rates of 1 in 1,000 have an 82.2% probability of being detected. Events with population rates of 1 in 575 have a 95% chance of being observed with n=1,723). Events with population rates of 1 in 2,000 have a 57.8% chance of being observed with n=1,723.

Sample size calculations were performed using PASS v12.0.2.

3 Efficacy and Safety Variables

3.1 Primary Efficacy Endpoint(s)

Endpoints evaluating QIVc compared to a non-influenza vaccine:

- 1a. First occurrence of RT-PCR confirmed influenza, due to any influenza Type A and/or B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, occurring at > 14 days after the last vaccination and until the end of the influenza season, in association with protocol-defined ILI symptoms.
- 1b. First occurrence of culture confirmed influenza, due to influenza Type A and/or B virus antigenically matched by ferret antigenicity testing to the influenza strains selected for the seasonal influenza vaccine, occurring at > 14 days after the last vaccination and until the end of the influenza season, in association with protocol defined ILI symptoms.

Note: Last vaccination is defined as the last vaccination administered during the treatment period of the study.

3.2 Secondary Safety Endpoints

The measures for assessing safety and tolerability are as follows:

1. Percentage of subjects with solicited local and systemic AEs will be assessed for 7 days following each vaccination in the QIVc group and the comparator group.
2. Percentage of subjects with any unsolicited AEs will be assessed in the QIVc group and in the comparator group until 28 days after each vaccination.
3. Percentage of subjects with Serious Adverse Events (SAEs), New Onset of Chronic Diseases (NOCDs), AEs leading to withdrawal from the study or vaccination, and all medications associated with these events will be reported in the QIVc group and in the comparator group.
4. Percentage of subjects with medically-attended AEs within 30 days after ILI onset will be reported in the QIVc group and in the comparator group.

3.3 Secondary Efficacy Endpoints

Secondary efficacy endpoints evaluating QIVc compared to a non-influenza vaccine:

1. The efficacy endpoint for the objective 2 is first occurrence of culture confirmed influenza caused by influenza virus strains antigenically dissimilar to the influenza strains selected for the seasonal vaccine occurring at > 14 days after the last vaccination and until the end of the influenza season, in association with protocol defined ILI symptoms.

2. The efficacy endpoint for the objective 3 is first occurrence of culture confirmed influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, occurring at > 14 days after the last vaccination and until the end of the influenza season, in association with protocol-defined ILI symptoms.
3. The efficacy endpoint for the objective 4 is first occurrence of RT-PCR confirmed moderate-to-severe influenza due to any influenza Type A and/or Type B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, occurring at > 14 days after the last vaccination and until the end of the influenza season.

Note: Last vaccination is defined as the last vaccination administered during the treatment period of the study.

3.4 Secondary Immunogenicity Endpoints

The measures for immunogenicity are determined by a haemagglutination inhibition [HI] and a microneutralisation (MN) assay prior to vaccination (Visit 1) and 28 days after last vaccination (Day29/57) for all four influenza strains. For each assay the measures include:

1. Pre and post-vaccination geometric mean titers (GMTs);
2. Seroconversion rates (SCR): Defined as the percentage of subjects with either a prevaccination HI (or MN) titer < 1:10 and a postvaccination HI (or MN) titer ≥ 1:40, or a prevaccination HI (or MN) titer ≥ 1:10 and a ≥ 4-fold increase in postvaccination HI (or MN) titer;
3. Geometric mean ratio (GMR): GMR is the geometric mean of the fold increase of post-vaccination HI (or MN) titer over the pre-vaccination HI (or MN) titer.

4 Analysis populations

4.1 All Enrolled Set

All screened subjects who provided informed consent, received a subject ID, and provided demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study.

4.2 All Exposed Set

All subjects in the All Enrolled Set who received a study vaccination

4.3 Safety Set

Solicited Safety Set (solicited local adverse reactions, solicited systemic adverse events and other solicited adverse events)

All subjects in the Exposed Set with any solicited AE data indicating the occurrence or lack of occurrence of solicited adverse events (e.g., use of analgesics/antipyretics medication) i.e., a subject does not have to have any solicited adverse events to be included in this population. The Solicited Safety will be split into Solicited safety after vaccination 1 and Solicited safety after vaccination 2 and overall.

Unsolicited Safety Set (unsolicited adverse events)

All subjects in the Exposed Set with unsolicited adverse event data. All subjects in the Exposed Set who had gone through any adverse event assessments i.e., a subject did not have to have any adverse events to be included in this population.

Overall Safety Set

All subjects who are in the Solicited Safety Set and/or Unsolicited Safety Set.

In case of vaccination error, subjects will be analyzed as "treated" (i.e., according to the vaccine a subject receives, rather than the vaccine to which the subject is randomized).

Subjects randomized in the wrong stratum will be reassigned to the correct stratum and will be analyzed using corrected stratum for all safety sets (i.e., solicited safety set, unsolicited safety set and overall safety set).

If a subject is unblinded during the study, he/she will be included in all safety sets.

4.4 Full Analysis Set (FAS), Efficacy/ Immunogenicity Set

FAS, Efficacy

All subjects in the All Enrolled Set who are randomized, who received at least one dose of study vaccination and are evaluated for efficacy at more than 14 days after the last vaccination.

FAS, Immunogenicity

All subjects in the All Enrolled Set who are randomized, who received at least one study vaccination and provide evaluable serum samples at both baseline (Day 1) and 28 days after last vaccination (Day29/57).

Last vaccination is at Visit 1 for "previously vaccinated" subjects and at Visit 2 for "not previously vaccinated" subjects.

In case of vaccination error, subjects in the FAS sets will be analyzed "as randomized" (i.e., according to the study vaccine a subject was designated to receive, which may be different from the study vaccine the subject actually received).

If a subject is unblinded during the study, he/she will be included in the FAS.

4.5 Per Protocol Set (PPS), Efficacy/Immunogenicity Set

All subjects in the FAS Efficacy/Immunogenicity who:

- Correctly receive the study vaccine (i.e., receive the study vaccine to which the subject is randomized and at the scheduled time points).
- Have no protocol deviations leading to exclusion (see section 4.5.1) as defined prior to unblinding / analysis.
- Are not excluded due to other reasons defined prior to unblinding or analysis.

PPS are sub-sets of FAS and should be always defined even if the objectives do not require it. Examples for subjects excluded due to other reasons than protocol deviations are:

- Subjects who withdrew informed consent.
- Subject who has a lab confirmed influenza case between first vaccination and 14 days after last vaccination.

Exclusions will be considered by objective/time point, i.e., sometimes not all data of a subject but only part of the subject's data will be removed from the PPS analysis.

In case of vaccination error, subjects in the FAS will be analyzed "as randomized" and the subject who received a wrong vaccination (not the vaccine the subject was assigned to) will be excluded from the PPS. If a subject receives a vaccine from the wrong kit number, but the same as the one the subject was randomized to, the subject will not be removed from the PPS. Subjects randomized in the wrong stratum will be excluded from the PPS.

If a subject is unblinded during the study, he/she will be excluded from the PPS.

If the percentage of vaccinated subject excluded from the FAS immunogenicity is greater than 5%, a secondary analysis based on the PPS immunogenicity will be performed to complement the FAS. The exploratory immunogenicity objectives will be analyzed on the FAS immunogenicity only.

4.5.1 Major Protocol Deviations Leading to Exclusion from the PPS Analysis

A protocol deviation (PD) is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. PDs can be either observable or programmable. Programmable PDs are those PDs that can be programmed from the data recorded in the clinical database. Observable PDs are PDs identified by Clinical Research Associates (CRAs) or other team members.

PDs will be classified as major and minor using a prespecified list of types of deviations. Major PDs are defined in accordance with ICH E3 as important PDs related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment resulting in the potential to jeopardize the safety or rights of the trial subjects or the scientific value of the trial.

All PDs will be evaluated before unblinding and most will be classified into the following categories:

- Subject randomized and did not satisfy entry criteria
- Subject developed withdrawal criteria during the study but was not withdrawn.
- Subject received the wrong treatment or incorrect dose
- Subject took an excluded concomitant medication
- Key study procedures missed or performed out of window

The impact of major PDs on the efficacy, immunogenicity and/or safety results will be investigated by assessing the robustness of the study results.

Major PDs will lead to exclusion of the subject or part of the subject's data from at least one analysis set.

The number of subjects in any and by PD category will be summarized by treatment group, center and overall. Individual subject listings will be provided in an appendix, sorted by subject and by PD category.

Prior to unblinding the analysis, designated Seqirus staff will develop a memo that describes the PDs that led to exclusions from analysis sets. This Exclusion Memo will be signed off by at least the Biostatistician and the Clinical Scientist and will be included in the trial master file.

Prematurely terminating study participation for reasons such as withdrawal of consent or occurrence of AEs (including death) is not considered as a PD. Any missing assessments that should have otherwise been collected for that subject later in the study is also not considered as a PD.

Deviations from the protocol will be documented on an ongoing basis by the study monitors and lead CRA or designee throughout the study period.

At the time of database lock, prior to unblinding and while the major PDs are being reviewed, the project manager or designee will forward all relevant documentation highlighting PDs to the study statistician. These deviations will be included in the protocol deviation document for agreement and will be listed with the PDs in the clinical study report (CSR).

PD listings will be reviewed by Seqirus prior to the finalization of the population datasets, which will occur prior to unblinding. The list will be used to determine which subjects should be excluded from either the FAS or the PPS.

4.6 Special Subpopulations

Not Applicable.

5 DATA Handling

5.1 Time points and Visit Windows

Assessments required at each study visit is described in Schedule of Assessments (Appendix A)

Day 1 is defined as the day of first dose of the vaccination.

Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1

All data will be analyzed using nominal study visits as defined in the Study Schedule see (Appendix A) and electronic case report form (eCRF).

Throughout the study, unscheduled visits are planned for subjects who manifest influenza-like illness (ILI) symptoms during the influenza season. The data collected at those visits will not be reallocated to one of the clinic visits, but rather the actual date will be listed.

(Protocol Table 1.3).

The following visit windows will be used.

Table 2: Visit windows for subjects without or unknown previous influenza vaccination history (two dose regimen)

Study part	Scheduled visit	Time interval (days)
Treatment period	Clinic Visit V1	Day 1
	Diary Reminder Call	V1 + 2 Days (-1/+1 Day)
	Clinic Visit V2	V1 + 28 Days (+7 Days)
	Diary Reminder Call	V2 + 2 Days (-1/+1 Day)
	Clinic Visit V3	V2 + 28 Days (+7 Days)
Follow-up Period	Safety Follow-up Call V4	V2 + 90 Days (+7 Days)
	Clinic Visit V5	End of influenza season or V2 + 180 Days (+14 Days) (whichever is longer)
	Clinic Visit V6	V5 + 28 Days (+7 Days)

Table 3: Visit windows for subjects with a previous influenza vaccination history (one dose regimen)

Study part	Scheduled visit	Time interval (days)
Treatment period	Clinic Visit V1	Day 1
	Diary Reminder Call	V1 + 2 Days (-1/+1 Day)
	Clinic Visit V2	V1 + 28 Days (+7 Days)
Follow-up Period	Safety Follow-up Call V3	V1 + 90 Days (+7 Days)
	Clinic Visit V4	End of influenza season or V1 + 180 Days (+14 Days) (whichever is longer)

Visit window deviations will be reviewed prior to unblinding.

5.2 Missing Values – Missing Visits.

Missing, unused and spurious data will be dealt with as such. There is no intention to implement any procedure for replacing missing data.

Titer values recorded as <1:10 will be summarized as 1:5.

No imputation of missing solicited or unsolicited AEs will be used. The percentage of subjects with missing solicited AE assessments (e.g. missing Patient Diary) and

missing Safety Phone Calls or Safety Assessments will be reported for each time period.
Missing immunogenicity values are considered missing completely at random (MCAR) and therefore will not contain information that impact the result of the analysis (i.e., not informative). Therefore, the key secondary analysis will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

Exclusions of Individual Values for Safety Analyses

Some local and systemic AEs will be directly measured by the subject and will not be subject to a reconciliation process, even if they are biologically implausible. Therefore, these implausible measurements will be removed from the analysis but included in listings.

Implausible measurements are summarized in the table below:

Table 4: Implausible Solicited Adverse Events

Parameter	Implausible measurements
Body temperature	≤ 33°C or ≥ 42°C
Erythema Measurements	≥ 450 mm or < 0 mm
Induration Measurements	≥ 250 mm or < 0 mm
Ecchymosis Measurements	≥ 250 mm or < 0 mm

6 Statistical Methods

6.1 General Principles

All data processing, summarization and analyses will be performed using [redacted] SAS Environment / Version 9.3 (or later) of the SAS® statistical software package.

The FAS will be used for summaries of baseline characteristics and background data; the Safety population will be used for all safety analyses; the analysis population for primary and secondary vaccine efficacy analyses will be based on the FAS Efficacy and repeated on the PPS Efficacy.

In general, summary descriptive statistics of continuous data will be presented as number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max). For categorical variables, statistical summaries will include counts and percentages relative to the appropriate population.

Two-sided 95% (or 97.5%) confidence intervals (CI) will be provided for descriptive statistics, as warranted. The 95% or 97.5% CI for percentages will be exact CIs based upon the binomial distribution. Geometric means and 95% CIs will be calculated by

taking the anti-logs of the means and 95% CI of the log transformed immunogenicity parameters.

Statistics will be displayed for the following:

- QIVc
- Comparator
- Overall

Summaries by age strata will be:

- 6 through 23 months
- 24 through 47 months

In the summary tables, the strains will be displayed as follows:

- A/H1N1
- A/H3N2
- B/Yamagata
- B/Victoria

All data will be listed.

6.2 Subject Disposition and Data Sets Analyzed

The number of subjects enrolled into the study, in each study population, who completed the study, and the reasons for any premature discontinuation from the study will be presented in summary tables by treatment group, by age strata (6 through 23 months, 24 through 47 months) and overall. The number in the enrolled set will be used as the denominator.

The number of subjects who are excluded from each of the FAS and Per-Protocol populations will be summarized by treatment group, by age strata (6 through 23 months, 24 through 47 months) and overall.

The primary reason for discontinuing the study product, or withdrawing a subject from the study, will be summarized by treatment group, by age strata and overall.

6.3 Protocol Deviations

Major protocol deviations will be tabulated by vaccine group on the All Enrolled Set and will also be listed for subjects who have been entered into the study and assigned a subject number.

6.4 Demographics and Other Baseline Characteristics

All baseline and demographic characteristics will be summarized by vaccine group, age strata, and overall on the Enrolled, Exposed, FAS (Efficacy, Immunogenicity),

PPS (Efficacy, Immunogenicity) and Safety Sets. This will include age (months), gender, race, ethnicity, weight, height, BMI, medical history, season, country and previous vaccination status.

Derived variables:

Body Mass Index will be calculated according the following formula:
Body Mass Index (kg/m^2): Mass (kg) / Height2 (m^2)

6.4.1 Medical History

Medical history will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or higher and will be displayed by system organ class and preferred term, using the MedDRA internationally agreed order.

The numbers and percentages of subjects with medical history will be presented by MedDRA system organ class (SOC) and preferred term (PT) by vaccine group and overall. Medical history data will be tabulated for Enrolled Set.

For prior vaccination history, the number and percentage of subjects who have ever been vaccinated, who have received at least 2 Seasonal Influenza Vaccinations prior to current influenza season and who have been assigned to receive 1 or 2 vaccinations during the study, based on the previous vaccination history, will be summarized.

Adverse events that occur between the time the ICF was signed and administration of first vaccination are recorded on the AE form. These events will be reported as an output in the Medical History.

6.4.2 Prior and Concomitant Medications

Medications will be coded using the WHO Drug dictionary version B3 MARCH 2019 or higher.

A prior medication is a medication used only before the first study vaccination (i.e. medication end date < first study vaccination date). Concomitant medications are all medications taken during the study period, including those started before but ongoing at vaccination.

When start and/or end dates of a medication intake are missing, the medication is considered as concomitant with the study vaccination schedule.

If the study vaccination date is missing, then the medication is considered as concomitant with the study vaccination schedule, provided that the study vaccine was administered to the subject.

Use of concomitant medication will be tabulated by treatment, age cohort, therapeutic area, and preferred drug name on the Enrolled Set.

Prior medications will only be listed.

6.5 Efficacy

6.5.1 Primary Efficacy Endpoints Analysis

The primary efficacy analysis will be based on the FAS Efficacy. Eligible subjects for FAS analysis are subjects who are randomized and received at least one study vaccine and will be analyzed according to their randomized study vaccine (intent-to-treat analysis). Absolute vaccine efficacy will only be assessed for RT-PCR confirmed influenza episodes (primary efficacy endpoint 1a) and culture confirmed antigenically matched influenza episodes (primary efficacy endpoint 1b) with first onset of illness occurring at > 14 days after the last vaccination was administered in the treatment period until the end of the influenza season. Additionally, the primary objective will be evaluated in PPS Efficacy.

Time-to-event methodology based on a proportional hazard model will be used for all efficacy analyses to estimate the hazard ratio (HR). Absolute vaccine efficacy (aVE) against first occurrence RT-PCR confirmed influenza cases will be determined using a standard formula: aVE = 1 - HR where HR is the hazard ratio for RT-PCR influenza confirmed cases in the QIVc group versus the comparator group. The HR will be estimated by a proportional hazards regression model, described below. For which the following null (H0) and alternative (H1) hypotheses will be tested:

$$H0: 1 - HR \leq 0 \text{ versus } H1: 1 - HR > 0$$

where HR is a hazard ratio of QIVc versus comparator and VE is vaccine efficacy. For both primary efficacy objectives, the HR and the related 97.5% CI of HR, for onset of first RT-PCR confirmed influenza will be estimated by a proportional hazards regression model with treatment effect as a fixed effect and stratifying covariates as random effect:

$$h_i(t|X) = h_0(t) \exp(\beta^T X + b^T Z),$$

with t denoting time to the influenza, β is the effect of treatment group indicated by X, b is random effect (assumed as a multivariable random gaussian variable with zero mean and diagonal covariance matrix), Z is random effect covariate (reflecting randomization strata).
Subjects that did not experience an event during observation period (be > 14 days after last vaccination up to end of influenza season) and subjects that dropped out from the study during observational period will be censored (right censoring) at the last available date in the eCRF prior to the end of influenza season.

The estimate of the hazard ratio, the respective estimate for absolute VE and the pertaining two-sided CIs will be calculated based on this model, including treatment group (2 treatments), age strata (2 categories, 6 through 23 months or 24 through 47 months), gender (male or female), vaccination history (yes or no) and country. If

the study continues over several seasons, estimates will be also adjusted for the factor season(s).

In case of one or two (interim) analyses, confidence levels at each stage will be adjusted to provide 97.5% overall coverage.

For each of the multiple primary objectives, estimates for hazard ratio in Cox Proportional Hazard (PH) model will be calculated using Maximum Likelihood (ML) method. In case of problems with convergence (algorithm does not converge or converges to infinite estimates) penalized ML approach will be used (Heinze and Schemper).

Vaccine efficacy VE = 1 – HR, that is, 1- exp($\hat{\beta}$) with $\hat{\beta}$ with 100(1- α) percent confidence interval as: [1- exp($\hat{\beta}$) + Z(s.e. ($\hat{\beta}$))); 1- exp ($\hat{\beta}$) - Z(s.e. ($\hat{\beta}$)))]. Z is the 100(1- α) percent point of the standard normal distribution, and s.e. denotes the standard error of β.

The hazard ratio is the predicted ratio of cases of Influenza A and/or B disease in subjects receiving QIVc and comparator within each of the strata of interest. The term β_g is the estimate of treatment effect (or regression coefficient) between QIVc and comparator within each of the stratum.

The estimate of the hazard ratio, the respective estimate for absolute VE and pertaining two-sided 97.5% CIs will be calculated based on this model. If the study continues over several seasons, estimates will be also adjusted for the factor season(s). Factor country might be added to the model if appropriate. In case of more than one interim analysis confidence level for the estimates at the final stage will be adjusted. In case interim analyses will be performed a k-stages group - sequential test procedure for time-to-event data will be implemented. As the K-stage interim analysis for absolute VE introduces a multiple test problem, alpha will be adjusted as described in Section 6.8 Interim Analysis via an error-spending function. For this group sequential test procedure parameters like information level and/or standard error at each stage will be calculated by the above described model and then used to calculate the actual group sequential test that compared the test statistic at each stage with the respective boundaries. Repeated CIs for each stage and also the final estimator and the respective CI can be retrieved by the group sequential test method to maintain simultaneous coverage probability.

Success Criteria for the Multiple Primary Efficacy Objectives:

The primary objective of efficacy is considered demonstrated if efficacy is demonstrated for at least one of the two primary efficacy endpoints, if the lower limit of the two-sided 97.5% CI of VE is greater than 0% in subjects 6 months through 47 months of age.

In case an interim analysis will be performed the 97.5% CI will be adjusted accordingly. If an interim analysis is performed and the trial continues, then all the subsequent analysis will be tested at a reduced alpha level, i.e. what's left from the interim analysis.

6.5.2 Secondary Efficacy Endpoints Analysis

The analysis population for all secondary efficacy objectives will be based on the FAS Efficacy and repeated on the PPS Efficacy.

The secondary measure of efficacy is the estimate of absolute efficacy of QIVc versus a comparator to prevent moderate-to-severe RT-PCR influenza confirmed cases caused by any influenza Type A and/or Type B virus.

Moderate-to-severe ILI episode is defined as ILI episode complicated by one of the following:

- physician confirmed lower respiratory tract illness,
- physician confirmed acute otitis media, or hospitalization in the Intensive Care Unit (ICU),
- physician-diagnosed serious extra-pulmonary complication of influenza or supplemental oxygen requirement for more than 8 hours.

Secondary efficacy objectives are not associated with any hypothesis testing.

The model specification used to estimate absolute vaccine efficacy for the secondary objectives are similar to the model used for the primary efficacy endpoints.

Example SAS code is shown in Appendix B.

6.5.3 Subgroup Analysis

The efficacy analyses will be performed by stratifying for the following subgroups:

- Subjects aged "6 through 23 months" and "24 through 47 months".
- Subjects "previously influenza vaccinated" and "not-previously influenza vaccinated".
- Subjects by race.
- Subjects by gender.
- Subjects by country or region.
- Subjects by season/year treated.

6.6 Immunogenicity

6.6.1 Secondary Immunogenicity Endpoints Analysis

Secondary immunogenicity objectives will be evaluated based on the PPS Immunogenicity HI, PPS Immunogenicity MN, FAS Immunogenicity HI and FAS Immunogenicity MN.

No statistical testing will be performed for the comparative secondary immunogenicity objectives.

All statistical analyses for HI (or MN titers) will be performed on the logarithmically (base 10) transformed values. Individual HI titers below detection limit (<10) will be set to half of that limit (5). Individual MN titers below the lower limit of quantification (LLOQ), will be set to half of that limit (1/2* LLOQ).
Crude estimates for GMTs, GMRs and pertaining 2-sided 95% CIs will be calculated assuming log-normal distribution of the titers and will be completed by providing minimum, maximum and median titers for each study vaccine group.

Binary data (i.e., percentages of subjects with SCR and with titer ≥ 1:40) will be summarized for each group using crude estimates and will be reported together with 2- sided 95% CIs calculated according to Clopper's and Pearson's (1934) method. No multiplicity adjustment to the CI levels will be implemented.

For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, the key secondary analysis will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

Derived variables:
Values below the limit of quantification (LQ = 10) recorded as "< LQ" and values lower than the limit of quantification have been set to half that limit (5).

The rate of seroconversion is defined as the percentage of subjects with either a prevaccination HI (or MN) titer < 1:10 and a post vaccination HI (or MN) titer ≥ 1: 40 or a prevaccination HI (or MN) titer ≥ 1:10 and a ≥ 4-fold increase in post vaccination HI (or MN) titer.

Seroconversion is defined as binary variable for subjects with non-missing values prevaccination and post-vaccination as:

= 1, if seroconverted (defined as the percentage of subjects with either a pre-vaccination HI (or MN) titer < 1:10 and a post-vaccination HI (or MN) titer ≥

1:40 or a pre-vaccination HI (or MN) titer ≥ 1:10 and a minimum 4-fold rise in post-vaccination HI (or MN) antibody titer)
= 0, otherwise

Geometric Mean Titer

Serum HI (or MN) antibody levels of all participants will be measured in serum separated from whole blood. Pre- and post-vaccination samples will be titrated, simultaneously. The titer assigned to each sample shall be the geometric mean of n independent determinations

GMT will be based on the following:

- HI(or MN) antibody titer for each strain: All analyses involving HI (or MN) antibody titer (namely group GMT within a vaccine group) will be performed on the log scale and the resultant summary statistic back-transformed to derived GMT

The GMT will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(t_i)}{n}\right\}}$$

where n, t_1, t_2, K, t_n are n observed immunogenicity titers.

The 95% CIs for GMT will be calculated as $10^{\{M-t_{0.975,n-1}SE)\}}, 10^{\{M+t_{0.975,n-1}SE)\}}$; where M and SE are the means and standard error of logarithm base 10 -transformed titers, respectively.

Geometric Mean Ratio

GMRs measure the changes in immunogenicity titers within subjects.

The GMR will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}\left(t_{ij}/t_{ik}\right)}{n}\right\}} = 10^{\left\{\frac{\sum_{i=1}^{n}(\log_{10}(t_{ij})-\log_{10}(t_{ik}))}{n}\right\}}$$

where, for n subjects, t_{ij} and t_{ik} are observed immunogenicity titers for subject i at time-points j and k, j ≠ k. The 95% CI for GMR will be calculated as $10^{\{M-t_{0.975,n-1}SE)\}}, 10^{\{M+t_{0.975,n-1}SE)\}}$; where M and SE are the means and standard error of log 10(t_{ij}) - log 10(t_{ik}) respectively.

6.6.2 Season Subgroup Analysis

The immunogenicity analyses will be performed for each season by stratifying for the following subgroups:

- Subjects aged "6 through 23 months" and "24 through 47 months".
- Subjects with pre-vaccination HI (or MN) titer <1:10 and pre-vaccination HI (or MN) titer ≥ 1:10.
- Subjects "previously influenza vaccinated" and "not-previously influenza vaccinated".
- Subjects by race.
- Subjects by sex.
- Subjects by country or region.

6.7 Safety

6.7.1 Secondary Safety Endpoints Analysis

6.7.1.1 Extent of Exposure

The number of subjects actually receiving vaccination will be summarized by study vaccine group on the Enrolled Set.

6.7.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

Definitions

For details refer to section 7.1.1 of Study Protocol.

Analyses

All solicited adverse events will be summarized according to defined severity grading scales using Solicited Safety Set.

Frequencies and percentages of subjects experiencing each adverse event will be presented for each symptom severity. Summary tables showing the occurrence of any local or systemic adverse event overall and at each time point will also be presented.

Post-vaccination solicited adverse events reported for 7 days after each vaccination will be summarized for the interval day 1-7 by maximal severity and by vaccine group, excluding the 30-minute measurement, which will be summarized separately. Local and systemic AEs:

Injection-site erythema, ecchymosis and induration will be summarized according to categories based on linear measurements: Type I: None (0 mm), Any (1-9 mm, 10-25 mm, 26-50 mm, >50 mm).

Injection site tenderness and systemic adverse events (except fever) occurring up to 7 days after each vaccination will be summarized according to "mild", "moderate" or "severe" categorization. Severity grades are defined in Table 4 below.

Table 5 Solicited Systemic AE Grading

Symptom	**Grading**			
	0 (None)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Solicited Local AEs*				
Tenderness		For subjects less than 24 months of age at the time of the first dose of study vaccine:		
Tenderness		Minor reaction on touch	Cried/protested on touch	Cried when limb was moved/ spontaneously painful
Tenderness		For subjects 24 months of age and older at the time of the first dose of study vaccine:		
Tenderness		Does not interfere with daily activities	Interferes with daily activities	Prevents daily activity
Solicited Systemic AEs**				
Change of eating habits	None	Eating less than normal for 1 - 2 feeds / meals	Missed 1 or 2 feeds / meals	Missed more than 2 feeds / meals
Sleepiness	None	shows an increased drowsiness	sleeps through feeds / meals	sleeps most of the time and it is hard to arouse him/ her

Vomiting (throwing up)	None	1 - 2 times in 24 hours	3 - 5 times in 24 hours	6 or more times in 24 hours or requires intravenous hydration
Diarrhoea (loose stools)	Fewer than 2 loose stools in 24 hours	2-3 loose stools in 24 hours	4-5 loose stools in 24 hours	6 or more loose stools in 24 hours or requires intravenous hydration
Irritability	None	Requires more cuddling and is less playful than usual	More difficult to settle	Unable to console
Shivering	None	Present but does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Temperature***	<38°C	≥38°C to <39°C	≥39°C to <40°C	≥40°C

* Injection-site erythema, ecchymosis, and induration will be summarized according to categories based on linear measurements: Type I: none (0 mm), Any (1-9 mm, 10-25 mm, 26-50 mm, >50 mm).

** Use of antipyretics and analgesics will be summarized by frequency, by type of use (prophylactic versus treatment) and percentage of subjects reporting use.

*** Body temperature will be summarized by 0.5°C and 1.0°C increments from 36.0°C to ≥40°C and will be broken down by route of measurement and by age cohort.

Each solicited local and systemic adverse event will also be further summarized as "none" versus"any". "Any" will include reactions with a diameter of at least 1 mm. Fever is defined as temperature ≥ 38.0°C (≥ 100.4°F).

Implausible measurements will be left out of the analysis, see Section 5.2 of this SAP.

Other solicited AEs:

Use of antipyretics and analgesics will be summarized by frequency, by type of use (prophylactic versus treatment) and percentage of subjects reporting use.

Body temperature will be summarized by 0.5°C and 1.0°C increments from 36.0°C up to ≥ 40°C and will be broken down by route of measurement and by age cohort.

6.7.1.3 Analysis of Unsolicited Adverse Events

Definitions

All AEs will be characterized according to the date of occurrence related to the first vaccination as follows:

- **Non-Treatment Emergent:** start date before the date of first injection of study vaccine. These are reported in the Medical History output.
- **Treatment Emergent**: start date on or after the date of injection of study vaccine or, AE increase in severity, including to "serious" AE.

If start date is equal to the first date of injection, then "timing" variable ("Did event start before or after vaccination?") will be used to define whether the AE occur before or after the injection.

If an AE happened on the same day of first injection and the time stamp is missing, then the AE is assumed to be treatment emergent.

If an AE start date is missing or unknown, the AE will be considered as emergent.

When start and/or end dates of an AE are only partially known, AEs will be categorized as emergent before, during, or after vaccination phase using the following rules:

- If the partial end date is before (<) the first vaccination (i.e., year or year & month is/are before the first study vaccination year or year & month) then the AE is not treatment-emergent.
- If the partial start date is equal or after (≥) the first study vaccination (i.e., year or year & month is/are after or the same as the first study injection year or year & month) then the AE is considered treatment-emergent.

The **maximum event severity** is the greatest severity associated with a preferred term (PT) for a reported AE according to the following order: Mild < Moderate < Severe. Unknown/ Missing severity is considered as severe.

Multiple AEs with the same PT for the same subject are counted only once.

Vaccination-related AEs are those for which the cause has been evaluated by the investigator, and recorded as related.

Analysis of Unsolicited Adverse Events

This analysis applies to all Treatment Emergent adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in AE Case Report Form (CRF), with a start

date on or after the date of first vaccination. AE starting prior to the first vaccination will be reported in the Medical History output.

The original verbatim terms used by investigators to identify AEs in the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The AEs will then be grouped by MedDRA preferred terms into frequency tables according to SOC. All reported AEs, as well as AEs judged by the investigator as at least possibly related to study vaccine, will be summarized presenting the number and percentage of subjects having one or more events according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group and period (as defined in section 2.2): treatment period, follow up period and total observation period (Day 1 until study end). When an AE occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories:

- SAE
- NOCD
- Adverse events/Serious Adverse events that are possibly or probably related to vaccine
- Adverse event leading to study withdrawal or early termination
- Adverse events leading to a medically-attended visit within 30 days after the onset of ILI episode
- Adverse events leading to a medically-attended visit during the treatment period
- Adverse event resulting in death

Data listings of all adverse events will be provided by subject. In addition, adverse events in the categories above will be provided as listed data.

6.7.2 Adverse Events

Summaries of unsolicited adverse events are described in section 6.7.1

6.7.3 Other Safety parameters

Body weight and temperature, recorded prior to vaccination, will be provided as a by–subject listing.

Physical Examination Findings will be provided as a by-subject listing.

6.7.4 Subgroup Analysis

The safety analyses for QIVc and comparator vaccine will be performed by stratifying for the following subgroups:

- Subjects aged “6 through 23 months” and “24 through 47 months”.

- Subjects "previously vaccinated" and "not-previously vaccinated".
- Subjects by race.
- Subjects by gender.
- Subjects by country or region.
- Subjects by season/year treated.

6.8 Interim Analysis

As the circulation of influenza viruses is seasonal and the event rates of influenza are difficult to predict, this study is group sequentially designed to allow for analyses of interim data to enable early study termination when a statistically robust demonstration of efficacy is observed.

An event-driven interim analysis may be performed if deemed necessary by the Sponsor.

In the event an interim is performed, the goal of the interim analysis is to be able to stop the study for early evidence of efficacy. For this analysis a restricted unblinding will be done, i.e. only external Data Monitoring Committee (DMC) members and Contract Research Organization (CRO) employees executing the unblinding receive access to the randomization codes and unblinded data for the purpose of preparing the interim analyses. Interim analyses are only intended to determine if the trial has met criteria for efficacy. Further details regarding the interim analysis are described in the DMC Charter and in Appendix C.

Primary Efficacy Analysis:

Nasopharyngeal swab samples in this study will be analyzed in batches and the number of RT-PCR confirmed influenza cases and its antigenic match to the influenza vaccine strain will be reviewed on a regular basis (blinded review) throughout the study.

An interim analysis for efficacy may be performed, if deemed necessary by the Sponsor:

- If the number of RT-PCR confirmed influenza cases is less or equal to 95 overall, no interim analysis for efficacy will be done and the study will be extended because the probability to make a conclusion for efficacy is too low.
- If the number of RT-PCR confirmed influenza cases is greater or equal to 96 but less than 191, an unblinded interim analysis for efficacy may be performed. To maintain the overall alpha, $\alpha = 1.25\%$ (1-sided), for the hypotheses testing for the primary objectives, an error-spending-function will be used. The benefit of using an error-spending-function is that no maximum number of analysis stages and the timing of the analyses need to be pre-specified, what in practice

means that the duration of the study in terms of number of seasons can be left open. In this case α-boundaries, forming the adjusted probabilities for the type I error, are calculated using error-spending function and if the p-value for one primary objective is lower than the respective α-boundary the trial stops early (i.e., without reaching the targeted number of cases of 191) for efficacy. Otherwise, the trial continues enrollment. Decisions to stop or continue the trial will be made based on discussions between the DMC and Senior Management.

- If the number of RT-PCR confirmed influenza cases is greater or equal to 191, the study may be unblinded and the final analysis may be performed by the Sponsor. If the trial proceeds to the final analysis (upon reaching 191 cases) the boundaries for acceptance or rejection are identical to the assumed type I and type II errors for the overall design, and the trial stops to either reject or accept the null hypothesis of either one or / and the other of the primary objectives.

In case the DMC states that the observed data provides already the full information level needed for the final test decision, then the final analysis can be done on full alpha level and no further enrollment is needed. However, if the decision of the group-sequential test is to continue the study then it is on the DMC to determine the number of subjects needed to be enrolled. The monitoring committee should not be influenced by the individual results of the study vaccine groups observed at an interim analysis stage when planning further subjects' accrual or the times of future analysis. Only the overall number of cases is allowed to be used for further planning.

The following formula for determination of sample sizes for further enrollment may be used:
$N_{total} = (C_{planned} - C_{observed}) / [(ER_{QIVc} + ER_{comp})/2]$,
where N_{total} denotes the total number of subjects needed for further enrollment, $C_{planned}$ is the overall number of cases needed for the test, i.e 191 cases, $C_{observed}$ are the at that stage observed number of cases overall, and ER are the respective attack rates assumed for each group. A consideration of early dropout and uncertainty about assumed parameters will be accounted for number of enrolled subjects.

The method of stopping rules given above is statistical and should be completed by clinical and strategic stopping rules that allow the DMC to make a decision on a broader picture of the data which includes safety endpoints and the other endpoints of the study.

For the analysis of early stopping for efficacy, an error-spending function will be applied to provide statistical stopping rules for efficacy (α-boundaries) for the first

interim analysis and second interim analysis, if necessary, based on the information accumulated until that specific interim stage, i.e. based on the accumulated variance of the parameter of interest. If there is early evidence of safety issues we will stop the study early for a fatal event, if a subject requires an emergency surgery or if a subject experiences permanent or irreversible disability, unless it can be shown that the event is unrelated to participation in the clinical study. The study will be stopped for a death, emergency surgery or if a subject experiences permanent or irreversible disability, unless it can be shown that the event is unrelated to participation in the clinical study.

These boundaries will be calculated on a p-value.

At each interim stage, α-boundaries, forming the adjusted probabilities for the type 1 error, are calculated using an error-spending function. If the p-value for the test of primary objective is lower than the respective α-boundary, the trial will be stopped for efficacy at this stage.

The cumulative O'Brien-Fleming type error-spending-function (Lan and DeMets, 1983, option ERRFUNCOBF in SAS® PROC SEQDESIGN) will be used for α-boundaries; the error-spending function is defined as:

$$E(t;a) = \begin{cases} 1 & \text{if } t \geq 1 \\ \frac{1}{a}\,2\,(1-\Phi(\frac{z_{(1-a/2)}}{\sqrt{t}})) & \text{if } 0 < t < 1 \\ 0 & \text{otherwise} \end{cases}$$

where a equals α for α spending function and β for beta spending function, and t is the information fraction, i.e. $t = C_{observed} / C_{planned}$.

If the trial proceeds to the final analysis without an interim analysis, the boundary for rejection of null hypothesis is identical to the type 1 error (that is, the 0.025/2 one-sided alpha level) with power specified for the overall design, and the trial stops to either reject or not reject the null hypothesis of the primary objective.

Additional interim analyses may be requested at a future date (by the DMC), particularly if the first interim analysis is conducted soon after 96 cases of influenza have been reported. In this case, the DMC may request that a second interim analysis be conducted to allow for greater accuracy to determine if the trial should stop or continue.

Table 6 shows the needed total number of cases at each stage of the two-stage design together with boundaries for early stopping efficacy, calculated on p-value scale using the cumulative error spending function. With half the information collected at the stage of interim analysis (that is, with exactly 96 confirmed ILIs) the

trial would stop early for efficacy if the p-value is lower than 0.0004120. Otherwise the trial will be continued, and more subjects will be enrolled. The actual boundaries used for decision making would depend on number of confirmed ILIs occurring and reported for Interim Analysis.

Table 6: Example of a Two Stages Group-Sequential Design

	Stage 1 First	Stage 2 Final
Number of Events	96	192
Alpha Boundary on p-value scale (equivalent to Type 1 error, 1-sided), early stopping for efficacy	0.0004120	0.01236

The stopping rules are statistically determined and should be complemented by clinical and strategic stopping rules that allow the DMC to make a decision on a broader picture of the data. Another interim look at the data with appropriate adjustment of type 1 error might be recommended before reaching the targeted 191 cases.

The comparison of the test statistic with its boundary values will be performed by using the SAS® SEQTEST procedure. The boundary information tables calculated by PROC SEQDESIGN (https://support.sas.com/documentation/onlinedoc/stat/131/seqdesign.pdf) at an analysis stage are structured for input to the SEQTEST procedure. At each subsequent stage, the boundary values are derived by using the test information tables created by the SEQTEST procedure at the previous stage. These test information tables are also structured for input to the SEQTEST procedure. PROC SEQTEST can also be used to compute parameter estimates, confidence limits, and p-values after the trial stops.

For the interim analyses, a restricted unblinding will be done, i.e., only DMC members and unblinded CRO employees responsible for the analyses will receive access to the randomization codes and unblinded data for the purpose of preparing the interim analyses (further information on handling of the blinding for the interim analyses can be found in protocol section 3.3). The results of the interim analyses are only for DMC purposes and will not be reported in the CSR.

7 Changes in Planned Analysis

The term 'sex' has been replaced with 'gender' throughout the analysis section.
The definition of FAS Overall has been added to this SAP for baseline and background data description purpose.

8 Data Issues

Not applicable.

9 References

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Appendix A: Schedule of Assessments

The schedule chart is the master representation of the clinical trial. In case of (apparent) inconsistencies in the clinical trial protocol the information provided here is the binding one.

Treatment and Follow-up Period for subjects without or unknown previous influenza vaccination history (two dose regimen)

		Treatment Period					Follow-up Period[b,c]		
Visit Type		Clinic Visit[a]	Diary Reminder Call[a]	Clinic Visit[a]	Diary Reminder Call[a]	Clinic Visit[a]	Safety Follow-up Call[a]	Clinic Visit[a]	
Study Day			V1 + 2[d]	V1 + 28	V2 + 2[c]	V2 + 28	V2 + 90	End of influenza season or 180 days after last vaccination [e, *]	V5 + 28
Visit Number		V1		V2		V3	V4	V5	V6[c]
Visit Window (Days)		n/a	-1/+1	0 to +7	-1/+1	0 to +7	0 to +7	0 to +14	0 to +7
Study Event	**References**								
Screening and Safety									
Informed Consent[f]	Section 5.1.1	√[f]							
Review of Systems[g]	Section 5.1.2	√[g]							
Medical History[g]	Section 5.1.2	√[g]							
Demographic Information[g]	Section 5.1.2	√[g]							
Physical Examination[g]	Sections 5.1.2 and 5.3.1	√[g]		√[g]		√		√	
Exclusion/Inclusion Criteria[g]	Section 4	√[g]		√[g]					

Influenza and MenC Vaccination History[g]	Section 5.1.2	√[g]						√[g]	
Randomization[g]	Section 5.1.4	√[g]							
Subject Diary Card Training	Section 5.2.1	√		√					
Subject Diary Card Reminder	Section 5.2.2		√		√				
Subject Diary Card Review and Collection	Section 5.3.1			√[g]		√			
Assess all AEs[g]	Section 7.1	√[g]		√[g]		√			
Collection of information on SAEs	Section 7.1.4	At any time during the study period							
Assess AEs Leading to Withdrawal, NOCDs	Sections 7.2 and 7.1.3						√	√	√
Collect Relevant Medications and Vaccinations	Sections 5.1.2 and 6.5	At any time during the study period							
Immunogenicity									
Serology Blood Draw[g,h]	Section 3.5	√[g,h]				√[h]			
Collect Relevant Medications and Vaccinations	Sections 5.1.2 and 6.5	At any time during the study period							
Study Treatment									
Vaccination	Section 5.2	√		√					
30 Minutes Post Injection Assessment	Section 5.2.1	√		√					
Efficacy									
ILI Symptom Assessment and Documentation Training[i]	Section 5.2.5	√[i]							
ILI Reminder Calls[j]	Section 5.4.1	← √[j] →							
Study Completion Procedures									
Procedures	Section 5.5							√	
Vaccination[k]	Section 5.5 and 6.2							√[k]	

30 Minutes Post Injection Assessment[k]	Section 5.2.1							√[k]	

a) In the exceptional case where calls or clinic visits are not feasible in some countries, study site personnel may visit the subject's homes to inquire about signs and symptoms of illness in the subject collect a NP swab specimen or perform other study assessments (see Section 5 Study Procedures), when agreed upon by the Sponsor and in line with country specific requirements and/or regulations.

b) Visit 5 is a call for subjects aged 12 months and older at enrollment, and is a clinic visit for subjects 6 through 11 months at enrollment

c) Study completion is at visit 6 ONLY for subjects aged 6 through 11 months at enrollment, who are enrolled in a country WITHOUT a NeisVac-C (MenC) vaccine marketing authorization. Visit 6 can be call. For all other subjects' study completion is at visit 5; visit 6 is not required.

d) A subject diary reminder call is a call approximately 2 days after vaccination

e) Performed at End of Influenza Season but at least 180 days after last vaccination date

f) Informed Consent Form can be collected before Study day 1

g) Procedures that should be completed before vaccination

h) Blood draws are only applicable for subjects randomized into the immunogenicity sub-set. Collect blood samples before vaccination

i) ILI Symptom Assessment and Documentation Training includes use of ILI Booklet to be completed if an ILI occurs

j) Performed until End of Influenza Season

k) Subjects aged 6 through 11 months at enrollment will receive a dose of the MenC vaccine at study completion visit.
*Should an ILI be identified and a NP swab obtained, it is recommended to postpone the study completion visit, to allow for the ILI follow-up visit to occur (see Section 5.5, Study Completion)

Treatment and Follow-up Period for subjects with a previous influenza vaccination history (one dose regimen)

Visit Type		Treatment Period			Follow-up Period	
		Clinic Visit[a]	Diary Reminder Call[a]	Clinic Visit[a]	Safety Follow-up Call[a]	Clinic Visit[a, b, *]
Study Day Visit		1	V1 + 2[c]	V1 + 28	V1 + 90	End of influenza season or 180 days after last vaccination[d]
Number		V1		V2	V3	V4
Visit Window		n/a	-1/+1	0 to +7	0 to +7	0 to +14
Study Event	**References**					
Screening and Safety						
Informed Consent[e]	Section 5.1.1	√[e]				
Review of Systems[f]	Section 5.1.2	√[f]				
Medical History[f]	Section 5.1.2	√[f]				
Demographic Information[f]	Section 5.1.2	√[f]				
Physical Examination[f]	Sections 5.1.2 and 5.3.1	√[f]		√[f]		
Exclusion/Inclusion Criteria[f]	Section 4	√[f]				
Influenza and MenC Vaccination History[f]	Section 5.1.2	√[f]				√[f]
Randomization[f]	Section 5.1.4	√[f]				
Subject Diary Card Training	Section 5.2.1	√				
Subject Diary Card Reminder	Section 5.2.2		√			
Subject Diary Card Review and Collection	Section 5.3.1			√[f]		
Assess all AEs[f]	Section 7.1	√[f]		√[f]		
Collection of information on SAEs	Section 7.1.4	At any time during the study period				

Assess AEs Leading to Withdrawal, NOCDs	Sections 7.2 and 7.1.3				√	√
Collect Relevant Medications and Vaccinations	Sections 5.1.2 and 6.5	At any time during the study period				
Immunogenicity						
Serology Blood Draw[f,g]	Section 3.5	√[f,g]		√[g]		
Study Treatment						
Vaccination	Section 5.2	√				
30 Minutes Post Injection Assessment	Section 5.2.1	√				
Efficacy						
ILI Symptom Assessment and Documentation Training[h]	Section 5.2.5	√[h]				
ILI Reminder Calls[i]	Section 5.4.1	← √[i] →				
Study Completion Procedures						
Study Completion	Section 5.5					√

a) In the exceptional case where calls or clinic visits are not feasible in some countries, study site personnel may visit the subject's homes to inquire about signs and symptoms of illness in the subject, collect a NP swab specimen or perform other study assessments (see Section 5 Study Procedures), when agreed upon by the Sponsor and in line with country specific requirements and/or regulations.

b) Study completion visit is a call for subjects aged 12 months and older at enrollment, and is a clinic visit for subjects 6 through 11 months at enrollment

c) A subject diary reminder call is a call approximately 2 days after vaccination

d) Performed at End of Influenza Season but at least 180 days after last vaccination

e) Informed Consent Form can be collected before Study day 1

f) Procedures that should be completed before vaccination

g) Blood draws are only applicable for subjects randomized into the immunogenicity sub-set. Collect blood samples before vaccination

h) ILI Symptom Assessment and Documentation Training includes use of ILI Booklet to be completed if an ILI occurs

i) Performed until End of Influenza Season

*Should an ILI be identified and a NP swab obtained, it is recommended to postpone the study completion visit, to allow for the ILI follow-up visit to occur (see Section 5.5, Study Completion)

Unscheduled visit(s) related to a protocol defined ILI episode

	Visit	Unscheduled Clinic Visit[b]	ILI Follow-up Call[c, *]
	Type ILI	I[d]	+ 30
	Onset	n/a	n/a
	Day Visit	0 to +6	0 to +7
Study Event	**References**		
Efficacy			
ILI Booklet Review and Collection	Section 5.4.2	√	
Assess ILI symptoms	Sections 5.4.3 and 7.2	√	√
ILI Nasopharyngeal Swab Collection[d]	Sections 3.5 and 5.4.2	√[d]	
Assess Relevant Medications and	Sections 5.1.2, 5.4.3 and 6.5	√	√
Assess Medically-Attended AEs[e]	Sections 5.4.3 and 7.1.2	√[e]	√[e]
Physical Examination	Sections 5.1.2 and 5.3.1	√	
ILI Symptom Assessment and Documentation	Section 5.2.5	√[f]	

a) Influenza-like illness (ILI) is defined by the presence of a temperature ≥ 37.8°C (≥ 100.0°F) and at least one of the following symptoms on the same day: cough, sore throat, nasal congestion, rhinorrhea, earache or ear discharge
b) In the exceptional case that the subject cannot visit the study center, a home visit can be made
c) In countries, in the exceptional case where calls are not feasible, study site personnel may visit the subject's homes to inquire about signs and symptoms of illness in the subject.
d) Subject will be asked to come to the study site within the first 24 hours or as soon as possible following ILI onset to ensure optimal viral yield
e) A "medically-attended adverse event" is an adverse event requiring hospitalization, or emergency room visit, or visit to/by a health care provider
f) ILI Symptom Assessment and Documentation Training includes use of ILI Booklet to be completed if an ILI occurs
*Should an ILI be identified and a NP swab obtained, it is recommended to postpone the study completion visit, to allow for the ILI follow-up visit to occur (see Section 5.5, Study Completion)

Appendix B: Example SAS® code for analyses

- **Tables that need descriptive statistics – continuous variables:**

```
PROC UNIVARIATE DATA=dset NOPRINT;
    VAR var1 var2 var3 …varn;
    BY byvar; (optional)
    OUTPUT OUT=outname
    N=n MEAN=mean MIN=min MAX=max MEDIAN=median STD=std;
RUN;
```

- **Tables that need frequency counts:**

```
PROC FREQ DATA=dset NOPRINT;
    BY byvar; (optional)
    TABLES var1*var2;
    OUTPUT OUT=outname;
RUN;
```

- **Tables that need exact 95%CIs between groups for proportions:**

```
PROC FREQ DATA=dset;
    BY byvar; (optional)
    TABLES var1 * var2 / binomial(exact) MEASURES ALPHA=0.05;
RUN;
```

Notes: 1 Estimates are computed for 2x2 tables only
2 This code also gives exact 95% CIs within group for binomial proportions

- **Tables that need 95% CIs within group for binomial proportions:**

```
PROC FREQ DATA=dset;
    BY byvar; (optional)
    TABLES var1;
    EXACT BINOMIAL;
RUN;
```

- **Code to create 97.5% CIs within group for continuous variables:**

```
DATA outdata;
    SET outname;
    LCL=mean-(TINV(0.975,n-1)*(std/SQRT(n)));
    UCL=mean+(TINV(0.975,n-1)*(std/SQRT(n)));
RUN;
```

- **Table to estimate the Hazard Ratio (HR) for all Efficacy Analysis:**

```
PROC PHREG DATA=data;
MODEL (T1) *CENSOR(0)= trt agegrp vachis /rl alpha=0.025;
RANDOM agegrp vachis;  STRATA trt;
RUN;
```

- **General linear model (adjusted analysis):**

```
PROC GLM DATA= dset  OUTSTAT=outset;
    CLASS classification variables;
    MODEL <log transformed response> = <treatment group> <Age group>
<Sex><vaccination history> <log transformed base>  <siteid>
<agegroup*treatmentgroup> / SOLUTION;
    LSMEANS treatmentgroup / STDERR PDIFF CL ALPHA=0.05;
    BY byvar; (optional)
    WHERE condition (optional)
RUN;
QUIT;
```

- **The geometric mean is the antilog of the arithmetic mean of the logs:**

```
DATA dset;
    SET dset old;
    LOGx = LOG(x);
RUN;

PROC UNIVARIATE DATA=dset NOPRINT;
    VAR LOGx;
    OUTPUT OUT=outname
    MEAN=logmean;
RUN;

DATA outname;
    SET outname;
    geomean = EXP(logmean);
RUN;
```

Appendix C: Interim Analysis Strategy Plan

Study V130_14 uses a group sequential design based on pre-specified criteria and has an independent, external Data Monitoring Committee (DMC) to monitor safety and efficacy. V130_14 is an event-driven study based upon the multiple primary endpoints of the (a) first occurrence of RT-PCR confirmed influenza regardless of antigenic match and (b) first occurrence of culture confirmed illness caused by influenza virus strains antigenically matched to the influenza vaccine strains.

As described in the Protocol and in the SAP, event-driven interim analyses may be performed if deemed necessary by the Sponsor with the goal to be able to stop the study for early evidence of efficacy. If an IA is to be performed, the unblinded CRO biostatistician designated for the study will execute the analysis and prepare a report for the DMC. The interim analysis report will be reviewed by the DMC in a closed session, and, the DMC will then make a recommendation to the Sponsor to continue, modify or end the study. A decision tree flowchart that outlines the strategy to perform interim analyses (IA) can be found in Figure 1.

In the event the Sponsor deems an IA for efficacy is necessary, the number of RT-PCR cases specified in the protocol is: *If the number of RT-PCR confirmed influenza cases is greater or equal to 96 but less than 191, an unblinded interim analysis for efficacy may be performed.* As shown in Figure 1, at the time of the first interim analysis, an efficacy analysis for culture confirmed cases antigenically matched to vaccine strains will also be performed. Outcome of the first IA would be one of the following:

- If vaccine efficacy meets success criteria for at least one of the two primary efficacy endpoints, namely LB VE > 0%, the study stops early.
- If vaccine efficacy is lower than the pre-defined success criteria for both endpoints, namely LB VE < =0 %, the study will continue until accrual of a minimum number of 191 RT-PCR confirmed influenza cases and 104 matched cases, unless with the DMC a second interim analysis is recommended.

If the first IA does not meet success criteria, the study continues. Because of seasonal variability of proportion of circulating strains matched to vaccine strains and the current uncertainty of influenza activity (attack rate) due to the COVID-19 pandemic, a second interim analysis may be performed. In the case a second IA is deemed necessary by the Sponsor, the timing would be when at least 52 matched cases have been accrued. Whether an analysis is done for RT-PCR confirmed cases at the time of a second IA depends upon the number of cases: if at the time of a second IA for matched cases, the number of RT-PCR cases is greater or equal to 300, a final analysis for RT-PCR cases will be performed. If at this time the number of RT-PCR cases is less than 300, then an analysis of RT-PCR cases will not be performed unless the success criteria of LB VE > 0% is met for the matched cases. Then the study stops and final analysis for all RT-PCR cases will be performed.

The sponsor may choose not to perform a second IA and proceed to a final efficacy analysis when the number of RT-PCR confirmed influenza cases is greater than or equal to 191 RT-PCR confirmed influenza cases and when the number of culture confirmed cases antigenically matched to the influenza strains is greater than or equal to 104 cases.

Table 1 summarize the interim analysis strategy. Further details regarding the interim analysis plan are specified in the decision tree in Figure 1.

Table 1: Interim Analysis Strategy

Interim Analysis Number	Endpoints for Interim Analysis	Anticipated Timing of Interim Analysis	Success criteria	Purpose of Interim Analysis
First	(a) First occurrence of RT-PCR confirmed influenza, due to any influenza Type A and/or B virus regardless of antigenic match to the influenza strains selected for the seasonal influenza vaccine, occurring at > 14 days after the last vaccination and until the end of the influenza season (b) First occurrence of culture confirmed influenza, due to influenza Type A and/or B virus antigenically matched by ferret antigenicity testing to the influenza strains selected for the seasonal influenza vaccine, occurring at > 14 days after the last vaccination and until the end of the influenza season	If the number of RT-PCR confirmed influenza cases is greater or equal to 96 but less than 191	Lower bound* Vaccine Efficacy greater than 0%	Stop for efficacy
Second (*if recommended by the Sponsor and the DMC*)	First occurrence of culture confirmed influenza, due to influenza Type A and/or B virus antigenically matched by ferret antigenicity testing to the influenza strains selected for the seasonal influenza vaccine, occurring at > 14 days after the last vaccination and until the end of the influenza season	At least 50% (i.e 52 cases) of the required culture confirmed cases for the antigenically matched endpoint has accrued	Lower bound* Vaccine Efficacy greater than 0%	Stop for efficacy†

**lower bound* of the appropriately *alpha-adjusted* confidence interval for VE

† If the number of RT-PCR confirmed influenza cases are ≥ 300 cases at the time of a second interim analysis, a final analysis for RT-PCR cases will be performed. See Flowchart for further details.

Table 1: Decision Tree Flowchart : Interim Analysis Strategy Plan