# Statistical Analysis Plan

## Seqirus

**Protocol: CSLCT-QIV-15-03**

**Treatment: Seqirus split-virion quadrivalent inactivated influenza virus vaccine (Seqirus QIV)**

## A Phase 3, Randomized, Multicenter, Observer-blinded, Noninferiority Study to Evaluate the Immunogenicity and Safety of a Quadrivalent Inactivated Influenza Virus Vaccine (Seqirus QIV) with a US-licensed Quadrivalent Inactivated Comparator Influenza Virus Vaccine (Comparator QIV) in a Pediatric Population 6 Months Through 59 Months of Age

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# Abbreviations

| | |
|---|---|
| ACIP | Advisory Committee on Immunization Practices |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| CBER | Center for Biologics Evaluation and Research |
| CI | Confidence Interval |
| Comparator QIV | Comparator Quadrivalent Influenza Virus Vaccine |
| CSR | Clinical Study Report |
| DSMB | Data and Safety Monitoring Board |
| eCRF | Electronic Case Report Form |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GLM | General Linear Model |
| GMFI | Geometric Mean Fold Increase |
| GMT | Geometric Mean Titer |
| HI | Hemaglutinin Inhibition |
| ICH | International Conference on Harmonisation |
| ILI | Influenza-like Illness |
| Max | Maximum |
| MedDRA | Medical Dictionary for Regulatory Activities |
| Min | Minimum |
| N | Number of subjects |
| PP | Per Protocol |
| PT | Preferred Term |
| RCD | Reverse Cumulative Distribution |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SCR | Seroconversion rate |
| SD | Standard Deviation |
| Seqirus QIV | Seqirus Quadrivalent Influenza Virus Vaccine |
| SOC | System Organ Class |
| US | United States of America |
| VRBPAC | Vaccines and Related Biological Products Advisory Committee |
| WHO | World Health Organization |

# 1 Introduction

This document presents the statistical analysis plan (SAP) for Seqirus Protocol No. CSLCT-QIV-15-03: A Phase 3, Randomized, Multicenter, Observer-blinded, Noninferiority Study to Evaluate the Immunogenicity and Safety of a Quadrivalent Inactivated Influenza Virus Vaccine (Seqirus QIV) with a US-licensed Quadrivalent Inactivated Comparator Influenza Virus Vaccine (Comparator QIV) in a Pediatric Population 6 Months Through 59 Months of Age.

It 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 protocol Version 2.0 Amendment 1.0 dated 24 May 2016 and is compliant with ICH Harmonized Tripartite Guideline, 5 February, 1998, *Statistical Principles for Clinical Trials, E9*[2]*;* World Health Organization, WHO Technical Report, Series No. 924. 2004, Annex 1: *Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations*.[3]; and FDA CBER Guidance for Industry, May 2007, *Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines*[4].

The SAP provides the description of the analysis for the active study period and safety data through to the final evaluation (6 months following last study vaccination dose).

The DSMB analysis will be detailed in the Charter and follow definitions noted in this SAP.

In this SAP an interim analysis is defined as the analysis of immunogenicity and safety data collected from the active study period (Day 1 to Study Exit Visit).

A final analysis is defined as the analysis of immunogenicity and safety data collected from the active study period and safety data through to the final evaluation (6 months following last study vaccination dose).

A selection of outputs will be re-produced to capture additional safety data up to the final evaluation 6 months following last study vaccination dose. These outputs will include unsolicited AE tables, SAE tables, AESI tables and listing and overall safety summary (Table 14.3.1.1) only.

# 2 Study Objectives and Endpoints

## 2.1 Primary Objective and Endpoint

### 2.1.1 Primary Objective

The primary objective of this study is to demonstrate that vaccination with Seqirus QIV elicits an immune response that is not inferior to the US-licensed comparator QIV (Comparator QIV) containing the same virus strains as Seqirus QIV among a pediatric population 6 months through 59 months of age.

### 2.1.2 Primary Endpoints

The immunogenicity of study vaccines will be assessed 28 days after the last vaccine administration by measuring the hemagglutination inhibition (HI) antibody titers to the four viral strains included in the vaccines.

The noninferiority of Seqirus QIV compared to the US-licensed comparator QIV will be assessed by the eight co-primary endpoints of geometric mean titer (GMT) and seroconversion rate (SCR) for each viral strain included in the vaccines as follows:

- The GMT ratio* for the A/H1N1 strain;
- The GMT ratio for the A/ H3N2 strain;
- The GMT ratio for the B strain (Yamagata lineage);
- The GMT ratio for the B strain (Victoria lineage);
- The difference between the SCRs**for the A/H1N1 strain;
- The difference between the SCRs for the A/H3N2 strain;
- The difference between the SCRs for the B strain (Yamagata lineage);
- The difference between the SCRs for the B strain (Victoria lineage).

**The GMT ratio is defined as the geometric mean of the postvaccination (Study Exit Visit) HI titer for the US-licensed comparator over the geometric mean of the postvaccination (Study Exit Visit) HI titer for Seqirus QIV.*

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

## 2.2 Secondary Objectives and Endpoints

### 2.2.1 Secondary Objectives

The secondary objectives of the study are to assess the following:

1. To assess the safety and tolerability of Seqirus QIV, in two age strata: 6 months through 35 months, and 36 months through 59 months, as well as overall.

2. To characterize the immunogenicity of Seqirus QIV and the US-licensed comparator QIV in two age strata: 6 months through 35 months, and 36 months through 59 months, as well as overall.

### 2.2.2 Secondary Endpoints

**Secondary Safety Endpoints:**

- Frequency and severity of solicited local reactions and systemic adverse events (AEs) for 7 days after each vaccination dose;
- Frequency of cellulitis-like reactions for at least 28 days after each vaccination dose;
- Frequency and severity of unsolicited AEs for at least 28 days after each vaccination dose;
- Frequency of serious adverse events (SAEs) for at least 180 days after the last vaccination dose.

**Secondary Immunogenicity Endpoints:**

The humoral immune response will be assessed in terms of HI antibodies for both the Seqirus QIV and Comparator QIV. Serum HI antibody titers against the 4 influenza vaccine strains will be used to calculate:

- GMT: Geometric mean of HI titers prevaccination (Day 1) and postvaccination (Study Exit Visit);
- SCR: Percentage of subjects with either a prevaccination HI titer < 1:10 and a postvaccination HI titer ≥ 1:40 or a prevaccination titer ≥ 1:10 and a ≥ 4-fold increase in postvaccination titer;
- The percentage of subjects with a titer ≥40 (seroprotection rate) at Day 1 and at Study Exit Visit
- Geometric Mean Fold Increase (GMFI)***: Geometric mean fold titer rise from Day 1 to Study Exit Visit

****GMFI in antibody titer is defined as the geometric mean of the fold increase of postvaccination HI antibody titer over the prevaccination HI antibody titer.*

## 2.3 Exploratory Objectives and Endpoints

### 2.3.1 Exploratory Objectives

The exploratory objective of the study is:

- To assess the frequency of antipyretic use in the first 7 days post vaccination in two age strata: 6 months through to 35 months, and 36 months through 59 months, as well as overall according to treatment group.

### 2.3.2 Exploratory Endpoints

The exploratory endpoint of the study is:

- Frequency of antipyretic use in the 7 days after each vaccination dose.

# 3 Study Design

## 3.1 Discussion of Study Design

This phase 3 study is a randomized, observer-blinded, comparator controlled study of Seqirus QIV, administered intramuscularly into the deltoid region or the anterolateral aspect of the thigh, versus a US-licensed comparator QIV containing the same influenza strains recommended by the US Food and Drug Administration (FDA) and Vaccines and Related Biological Products Advisory Committee (VRBPAC) for the 2016-2017 season.

The study will be conducted during the 2016-2017 Northern Hemisphere influenza immunization season in male and female subjects 6 months through 59 months of age.

## 3.2 Study Treatment

Subjects who meet the entry criteria will be stratified by age and then randomized to one of the two treatment groups using a 3:1 allocation ratio to receive either Seqirus QIV or the US-licensed comparator QIV. Each subject will receive one 0.25 or 0.5 mL dose of Study Vaccine on Day 1. Subjects scheduled to receive a second dose will also receive one 0.25 or 0.5 mL dose of Study Vaccine after 28 days.

Cohort A: Subjects 6 months through 35 months of age will receive one or two 0.25 mL doses of Study Vaccine according to the current US Advisory Committee on Immunization Practices (ACIP) dosing recommendations. Each 0.25 mL dose contains 7.5 mcg hemagglutinin antigen (HA) from each of the following four influenza strains: A (H1N1)-like virus; A (H3N2)-like virus; B (Yamagata lineage) and B (Victoria lineage).

Cohort B: Subjects 36 months through 59 months of age will receive one or two 0.5 mL doses of Study Vaccine according to the current US ACIP dosing recommendations. Each 0.5 mL dose contains 15 mcg hemagglutinin antigen (HA) from each of the following four influenza strains: A (H1N1)-like virus; A (H3N2)-like virus; B (Yamagata lineage) and B (Victoria lineage).

The two treatment arms of Study Vaccine comprise:

- Seqirus QIV.

  Each 0.25 mL dose will contain 7.5 mcg HA from each of the following four influenza strains (recommended by the FDA's VRBPAC for the 2016-2017 influenza season in the US):

  - 7.5 mcg per 0.25 mL dose A/California/7/2009 (H1N1)pdm09-like virus;
  - 7.5 mcg per 0.25 mL dose A/Hong Kong/4801/2014 (H3N2)-like virus;
  - 7.5 mcg per 0.25 mL dose B/Brisbane/60/2008-like virus (B/Victoria lineage);
  - 7.5 mcg per 0.25 mL dose B/Phuket/3073/2013-like virus (B/Yamagata lineage).

  Each 0.5 mL dose will contain 15 mcg HA from each of the following four influenza strains (recommended by the FDA's VRBPAC for the 2016-2017 influenza season in the US):

  - 15 mcg per 0.5 mL dose A/California/7/2009 (H1N1)pdm09-like virus;
  - 15 mcg per 0.5 mL dose A/Hong Kong/4801/2014 (H3N2)-like virus;

- 15 mcg per 0.5 mL dose B/Brisbane/60/2008-like virus (B/Victoria lineage);
- 15 mcg per 0.5 mL dose B/Phuket/3073/2013-like virus (B/Yamagata lineage).

- The US-licensed comparator QIV.

  Each 0.25 mL dose will contain 7.5 mcg HA from each of the following four influenza strains (recommended by the FDA's VRBPAC for the 2016-2017 influenza season in the US):

  - 7.5 mcg per 0.25 mL dose A/California/7/2009 (H1N1)pdm09-like virus;
  - 7.5 mcg per 0.25 mL dose A/Hong Kong/4801/2014 (H3N2)-like virus;
  - 7.5 mcg per 0.25 mL dose B/Brisbane/60/2008-like virus (B/Victoria lineage);
  - 7.5 mcg per 0.25 mL dose B/Phuket/3073/2013-like virus (B/Yamagata lineage).

  Each 0.5 mL dose will contain 15 mcg HA from each of the following four influenza strains (recommended by the FDA's VRBPAC for the 2016-2017 influenza season in the US):

  - 15 mcg per 0.5 mL dose A/California/7/2009 (H1N1)pdm09-like virus;
  - 15 mcg per 0.5 mL dose A/Hong Kong/4801/2014 (H3N2)-like virus;
  - 15 mcg per 0.5 mL dose B/Brisbane/60/2008-like virus (B/Victoria lineage);
  - 15 mcg per 0.5 mL dose B/Phuket/3073/2013-like virus (B/Yamagata lineage).

## 3.3 Study Schedule

A summary of the assessments required at each study visit is described below. The timing and frequency of the study visits are also described in Schedule of Assessments (Section 3.3.4).

### 3.3.1 Screening

A screening examination should be performed up to 7 days before the intended date of dosing (Day 1). If a potential subject was not enrolled into the study within 7 days of the first screening visit, the potential subject may attend a second screening visit (for a maximum of two screening visits per subject). In the event that a potential subject is screened twice, a new subject number will be assigned and all screening assessments must be repeated at the second screening visit.

Subjects who complete all of these assessments and who fulfil the eligibility criteria (ie, eligible subjects) will be enrolled into the study. If the subject is not eligible for the study, the primary reason for screen failure must be entered in the eCRF.

### 3.3.2 Treatment Period

Visit 1 (Day 1) –Day of Vaccination (Either 1 or 2 Dose Schedule)

*Informed Consent*: The parent(s)/guardian(s) of subjects must provide written informed consent prior to any study-related procedures. Subjects with parent(s)/guardian(s) informed

consent will be issued a unique subject number, including those who prove to be screen failures.

*Prevaccination:* The following assessments will be performed and documented in the source notes:

- A review of the subject's medical history, including concomitant medications, vaccination history (including influenza vaccination),and documentation of any relevant medical history;
- Targeted physical examination as clinically indicated following the collection of medical history;
- Subject's axillary temperature and body weight;
- A review of the subject's eligibility according to the Inclusion/Exclusion criteria
- Collection of at least 3 mL blood sample.

Subjects who complete the above assessments and who fulfil the inclusion/exclusion criteria will be eligible for randomization. Eligible subjects will be assigned the next available, unique subject number and corresponding Study Vaccine.

*Vaccination:* As per the US ACIP guidelines for seasonal influenza vaccination, the subject's age and influenza vaccination history determines the dose and dosing regimen (a single vaccination or a two-vaccination regimen administered 28 days apart). The first vaccination will be administered at Visit 1 (Day 1) and the second vaccination, if scheduled, will be administered at Visit 2 (Day 29 + 4). The Investigator/delegate will administer the study vaccine according to the randomization code into the deltoid region of the arm or into the anterolateral aspect of the thigh, by intramuscular injection. If vaccination into the arm is selected, the injection will be administered where possible into the contralateral arm to which the blood sample was drawn.

Subjects will receive the following dose depending upon their age at the time of administration of the first dose of Study Vaccine:

- *Cohort A*, 6 months through 35 months of age: 0.25 mL
- *Cohort B*, 36 months through 59 months of age: 0.5 mL

*Postvaccination:*

- Subjects will be observed for at least 30 minutes postvaccination in case of an anaphylactic reaction. Appropriate medical treatment will be readily available in case of emergency.
- Parent(s)/guardian(s) will be issued with a digital thermometer and Local Reaction Measurement Card, and provided with electronic access to the 7-Day Diary (for recording solicited AEs), the Other Body Symptoms Diary (for recording unsolicited AEs), and the Medications Diary (for recording concomitant medications). The 7-Day Diary will be completed on the day of vaccination and for the subsequent 6 days following vaccination (total of 7 days). The Other Body Symptoms Diary and the Medication AE Diary will be completed on the day of vaccination until the next study visit.

- Parent(s)/guardian(s) will be reminded how to measure axillary temperature and record their child's temperature at the same time each evening, in addition to completing the diaries.
- Parent(s)/guardian(s) will be instructed to contact the Investigator/delegate immediately if the subject experiences any signs or symptoms with grade 3 intensity.
- Parents will be educated on how to recognize the signs/symptoms of an ILI and will be instructed to contact the investigator/delegate immediately if the subject experiences any signs or symptoms of an ILI from Day 1 until the Study Exit Visit.
- An appointment will be made for each subject to return to the clinic 28 + 4 days after Visit 1.

### 3.3.3 On-study Period

Diary Reminder Telephone Call (Day 3 + 2):

Sites will contact parent(s)/guardian(s) of subjects by telephone between Days 3 and 5 inclusive, to check that the electronic diaries are being completed daily, and to address any questions on how to complete them correctly.

Visit 2, Study Exit Visit (Single Dose Schedule) Day 29 + 4

Subjects who are scheduled to receive a single dose of study vaccine according to the previous immunization history, will exit the study at this visit. The following will be undertaken and recorded at the Exit Visit:

- Review of the electronic diary entries;
- Assessment of the occurrence of any SAEs and Adverse Events of Special Interest (AESIs);
- Targeted physical examination as clinically indicated;
- Collection of at least 3 mL blood sample.

OR

Visit 2, Second Vaccination (Two-Dose Schedule) Day 29 + 4

Subjects who are scheduled to receive 2 doses of study vaccine will require a second dose of study vaccine at this visit.

*Prevaccination:*

The following will be undertaken and recorded prior to administration of the second dose of study vaccine:

- Review of the electronic diary entries;
- Assessment of the occurrence of any SAEs and AESIs;
- Subject's ongoing eligibility will be reviewed;
- Targeted physical examination as clinically indicated;
- Subject's axillary temperature.

*Vaccination:*

Subjects will be injected according to the same procedure as for the first dose. Subjects who are scheduled to receive 2 doses of study vaccine and who turn 36 months of age between the two study vaccinations will receive a second dose of 0.25 mL of study vaccine.

*Postvaccination:*

- Subjects will be observed for at least 30 minutes after vaccination for the signs of an anaphylactic reaction;
- Parent(s)/guardian(s) will be reminded to complete the 7-Day Diary entries for the day of the second vaccination and for the subsequent 6 days following vaccination (total of 7 days), and to continue recording unsolicited AEs in the Other Body Symptoms Diary and concomitant medications in the Medications Diary from the day of the second vaccination until the Study Exit Visit.
- Parent(s)/guardian(s) will be reminded on how to measure axillary temperature and record their child's temperature at the same time each evening, in addition to completing the diaries.
- Parent(s)/guardian(s) will be instructed to contact the Investigator/delegate immediately if the subject experiences any signs or symptoms with grade 3 intensity.
- Parent(s)/guardian(s) will be reminded on how to recognize the signs/symptoms of an ILI and will be instructed to contact the investigator/delegate immediately if the subject experiences any signs or symptoms of an ILI from Visit 2 until the Study Exit Visit.
- An appointment will be made for each subject to return 28 + 4 days post-Dose 2 for a Study Exit Visit.

Diary Reminder Telephone Call (Day 3 + 2 after the second vaccination):

Sites will contact parent(s)/guardian(s) of subjects by telephone between Days 3 and 5 inclusive after the second vaccination, to check that the diaries are being completed daily, and to address any questions on how to complete them correctly.

Visit 3, Study Exit Visit (Two-dose Schedule)

The Study Exit Visit for the Two-dose Schedule will occur 28 + 4 days after the administration of the second dose of Study Vaccine (Visit 2). The following will be undertaken and recorded at this study visit:

- Review of the electronic diary entries;
- Assessment of the occurrence of any SAEs and AESIs;
- Targeted physical examination as clinically indicated;
- Collection of at least 3 mL blood sample.

Unscheduled Visit - Influenza-like Illness (ILI) Visit

Subjects reporting signs/symptoms of an ILI between Visit 1 and Study Exit Visit (Visit 2 or Visit 3) will be asked to attend an additional clinic visit within 72 hours of the symptoms meeting the case definition of an ILI, for confirmation of the ILI.

The criteria for an ILI are as follows:

- Elevated axillary temperature of ≥ 99.5°F (≥ 37.5°C) or a clear history of fever or chills; and
- At least one respiratory symptom, including sore throat, cough, wheezing, rhinorrhea/rhinitis; and
- At least one systemic symptom, including myalgia, headache, malaise and fatigue, nausea and/or vomiting, loss of appetite, and irritability.

To qualify as symptoms for the ILI case definition, symptoms should be either new, or for chronic symptoms, changed in severity or nature.

Influenza antiviral drugs (Symmetrel [amantadine], rimantadine, Tamiflu [oseltamivir] or Relenza [zanamivir]) should not be prescribed from any source until after the ILI assessment visit and the collection of respiratory specimens if indicated.

The site should perform an assessment to attempt to confirm a postvaccination ILI at the time of the ILI-assessment visit (the subject's temperature and clinical symptoms should be assessed). Additionally, the site may also confirm a postvaccination ILI through review of the AE diaries and/or illness history reported verbally by the subject at a time prior to the ILI visit. Information related to confirmation of a postvaccination ILI should be recorded in the subject's source notes.

Upon confirmation that the ILI case definition is met, the subject's temperature will be assessed and attempts will be made to diagnose influenza viral infection by obtaining nasal and throat swab specimens. These will be analyzed for laboratory confirmation of influenza A and/or B by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR).

Laboratory confirmation is more likely for specimens collected within approximately 3-4 days of illness onset, but nasal and throat swabs should be collected if the ILI assessment visit occurs up to 7 days after illness onset, to try to identify as many cases of laboratory confirmed influenza infection as possible. After 7 days following illness onset, the Investigator may choose whether to collect nasal and throat swabs, based on their clinical judgement of the potential value of testing specimens due to ongoing ILI symptoms.

Refer to the study-specific Nasal and Throat Swab Specimen Collection Instructions, for further details on collection, storage, handling and transportation of the nasal and throat swab specimens to the laboratory.

<u>Unscheduled Visit – Cellulitis-like Reaction</u>

Subjects reporting signs/symptoms of a Cellulitis-like Reaction between Day 1 and Study Exit Visit will be asked to attend an additional clinic visit within 24 hours (up to 3 days if on a weekend) of the symptoms meeting the definition of a cellulitis-like reaction.

The criteria for a Cellulitis-like Reaction are concurrent presence of all three of the following:

- Grade 3 injection site pain;
- Grade 3 injection site erythema;
- Grade 3 injection site induration.

Investigational site staff attending the subject will confirm if he or she meets or has met the cellulitis-like illness case definition postvaccination according to reported symptoms and, if applicable, will perform other clinical investigations as relevant according to routine clinical practice. Additionally, investigational site staff will assess for the presence of ulceration,

abscess, or necrosis at the injection site, which will inform the application of study enrolment halting rules. In the event of a possible cellulitis-like reaction, sites should identify a local laboratory to perform any laboratory analyses to investigate, confirm, and manage any confirmed cellulitis-like reactions, and document any results in the source notes.

End of Study - Postvaccination Safety Follow-up Telephone Call (Day 90+7 and 180+7 after Last Vaccination)

Serious adverse events will be collected for at least 180 days after administration of the last vaccination dose. Subjects will be contacted by telephone at 90 (+7) and 180 (+7) days after the last vaccination dose to obtain this information.

### 3.3.4 Schedule of Assessments

**Schedule of Assessments – Single Dose Regimen**

| Assessment | | Visit 1 | Phone call | Visit 2 | Phone call | Phone call |
|---|---|---|---|---|---|---|
| | Pre-Study | Vaccination | Diaries Reminder | Exit Visit | SAE Follow-up | SAE Follow-up |
| | Day -7 to -1 | Day 1 | Day 3 + 2 | Day 29 + 4 | Day 90 + 7 | Day 180 + 7 |
| Invitation to participate | ✓[1] | | | | | |
| Informed consent | ✓[1] | | | | | |
| Demographics and influenza vaccination history | ✓[1] | | | | | |
| Medical history and baseline medication use | ✓[1] | | | | | |
| Targeted physical examination *(if necessary)* | ✓[1] | | | ✓ | | |
| Body weight | ✓[1] | | | | | |
| Axillary temperature | | ✓ | | | | |
| Review of eligibility criteria | | ✓ | | | | |
| Blood sample for immunogenicity testing | | ✓ | | ✓ | | |
| Vaccination | | ✓ | | | | |
| Provision of study supplies and instructions | | ✓ | | | | |
| Solicited Diary review | | | ✓ | ✓ | | |
| Unsolicited/Concomitant Medications Diary review | | | ✓ | ✓ | | |
| Assessment for cellulitis-like reaction, influenza-like illness *(if applicable)* [2] | | ← ✓ → | | | | |
| Review of adverse events and concomitant medications | ← ✓ → | | | | | |
| Review of SAEs *(if applicable)* | ← ✓ → | | | | | |

**Notes to the schedule of assessments:**

[1] These may be performed on or up to 7 days before the day of vaccination.

[2] Elevated axillary temperature of ≥ 99.5°F (≥ 37.5°C) (or a clear history of fever/chills), and at least one respiratory symptom (including sore throat, cough, wheezing, rhinorrhea/rhinitis) and at least one systemic symptom (including myalgia, headache, malaise, nausea and/or vomiting, loss of appetite, and irritability).

**Schedule of Assessments – Two Dose Regimen**

| Assessment | | Visit 1 | Phone call | Visit 2 | Phone call | Visit 3 | Phone call | Phone call |
|---|---|---|---|---|---|---|---|---|
| | Pre-Study | Vaccination | Diaries Reminder | Vaccination | Diaries Reminder | Exit Visit | SAE Follow-up | SAE Follow-up |
| | Day -7 to -1 | Day 1 | Day 3 + 2 | Day 29 + 4 | Day 3 + 2 after 2nd dose | Day 29 + 4 after 2nd dose | Day 90 + 7 after 2nd dose | Day 180 + 7 after 2nd dose |
| Invitation to participate | ✓[1] | | | | | | | |
| Informed consent | ✓[1] | | | | | | | |
| Demographics and influenza vaccination history | ✓[1] | | | | | | | |
| Medical history and baseline medication use | ✓[1] | | | | | | | |
| Targeted physical examination *(if necessary)* | ✓[1] | | | ✓ | | ✓ | | |
| Body weight | ✓[1] | | | | | | | |
| Axillary temperature | | ✓ | | ✓ | | | | |
| Review of eligibility criteria | | ✓ | | ✓ | | | | |
| Blood sample for immunogenicity testing | | ✓ | | | | ✓ | | |
| Vaccination | | ✓ | | ✓ | | | | |
| Provision of study supplies and instructions | | ✓ | | ✓ | | | | |
| Solicited Diary review | | | ✓ | ✓ | ✓ | ✓ | | |
| Unsolicited/Concomitant Medications Diary review | | | ✓ | ✓ | ✓ | ✓ | | |
| Assessment for cellulitis-like reaction, influenza-like illness *(if applicable)* [2] | | ← | — | ✓ | — | → | | |
| Review of adverse events and concomitant medications | ← | — | — | ✓ | — | → | | |
| Review of SAEs *(if applicable)* | ← | — | — | ✓ | — | — | — | → |

**Notes to the schedule of assessments:** [1] These may be performed on or up to 7 days before the day of vaccination. [2] Elevated axillary temperature of ≥ 99.5°F (≥ 37.5°C) (or a clear history of fever/chills), and at least one respiratory symptom (including sore throat, cough, wheezing, rhinorrhea/rhinitis) and at least one systemic symptom (including myalgia, headache, malaise, nausea and vomiting, loss of appetite, and irritability).

## 3.4 Concomitant Medication

Subjects are not to be enrolled into the study if they receive any prohibited therapy or any therapy in a prohibited dosage that cannot be discontinued or reduced to a permitted dose before enrolment.

The following therapies are NOT PERMITTED before and/or during the active study period (Day 1 to Exit Visit) for the periods outlined below and as specified in the study exclusion criteria:

- Current or recent immunosuppressive or immunomodulatory therapy, as follows:
  - Chronic or long term systemic corticosteroids: ≥ 0.125 mg/kg/day of oral prednisolone or equivalent daily;
  - Sporadic systemic corticosteroids: ≥ 0.5 mg/kg/day of oral prednisolone or equivalent for one or more short courses of > 3 days in the three months preceding vaccination and/or during the active study period.
- Administration of immunoglobulin and/or any blood products within the 3 months preceding study vaccination, or planned administration during the active study period;
- Participation in a clinical trial or use of an investigational compound (ie, a new chemical or biological entity not licensed for clinical use) within 28 days prior to the first dose of Study Vaccine, or within 28 days after receiving the final indicated dose of Study Vaccine, or plans to enter a clinical trial during this period;
- Vaccination with a licensed or investigational influenza vaccine within the 6 months prior to receiving the first dose of Study Vaccine and during the study;
- Vaccination with a licensed live or inactivated vaccine 21 days prior to receiving the Study Vaccine, or plans to receive any licensed vaccine prior to the Study Exit Visit;

- Treatment with warfarin or other anticoagulants in the 3 weeks preceding vaccination, contraindicating intramuscular vaccination (with the exception of antiplatelet agents).
- Prophylactic antipyretics on the day of vaccination or for the first 7 days postvaccination. Antipyretic use for the treatment of AEs during the study period is permitted, and will be documented as concomitant medications.
- The use of topical anesthetic cream (eg, EMLA Cream) on the vaccination site before or after administration of the Study Vaccine is prohibited. Topical anesthetic cream use at the blood draw site is permitted.

If any of the above therapies are received during the active study period, the subject will not be withdrawn from the study unless required for medical reasons, but immunogenicity results pertaining to this subject may be excluded from assessment prior to unblinding following medical review of the potential for the therapies to impact on immunogenicity results.

## 3.5 Study Analysis Populations

There will be four analysis populations defined for the study analyses:

### 3.5.1 Full Analysis Set

The Full Analysis Set (FAS) will comprise all subjects who provide informed consent and who were randomized to treatment. Screening failures will not be included in the FAS. However, the number of screening failures will be summarized in the disposition tables and all screening failures will be listed.

The FAS will be used to produce summaries and listings of subject characteristics. Subjects will be analysed according to the treatment they were randomised to.

### 3.5.2 Safety Population

#### 3.5.2.1 Overall Safety Population

The Overall Safety Population will comprise all subjects in the FAS who received at least one dose or partial dose of Study Vaccine and have provided any evaluable follow-up safety data.

The Overall Safety Population will be used to produce summaries and listings of overall and unsolicited safety data after any vaccination. Subjects will be analysed according to the treatment they received.

#### 3.5.2.2 Solicited Safety Population

The Solicited Safety Population will comprise all subjects in the FAS who received at least one dose or partial dose of Study Vaccine and have provided any evaluable data on solicited events.

#### 3.5.2.2.1 Solicited Safety Population after the First Vaccination

The Solicited Safety Population after the First Vaccination will comprise all subjects in the FAS who received at least one dose or partial dose of the first vaccination of Study Vaccine and have provided any evaluable data on solicited events after the first vaccination. This safety population will be used in the assessment of solicited AEs after the first vaccination.

#### 3.5.2.2.2 Solicited Safety Population after the Second Vaccination

The Solicited Safety Population after the Second Vaccination will comprise all subjects in the FAS who received at least one dose or partial dose of the second vaccination of Study Vaccine and have provided any evaluable data on solicited events after the second vaccination. This safety population will be used in the assessment of solicited AEs after the second vaccination.

### 3.5.2.3 Criteria for Defining Safety Populations

Follow-up safety data is defined as any safety information that is recorded for a subject in a Study Diary or in the subject's medical notes.

The following criteria will be used to define NO follow-up safety data (not included in the Overall Safety Population):

- "Were any unsolicited AEs experienced that were not recorded in the diary?" = BLANK (no entries) AND
- "Were any new SAEs reported?" (Day 90 & 180) = BLANK AND
- "Was the subject confirmed to have experienced symptoms meeting cellulitis-like reaction criteria?" = BLANK AND
- Any AE/SAE form = BLANK AND
- Unsolicited Diary Other Body Symptoms = BLANK (no entries) AND
- Solicited Diary Local Symptoms= BLANK (all 7 days after first and second vaccination) AND
- Solicited Diary Temperature= BLANK (all 7 days after first and second vaccination) AND
- Solicited Diary Systemic Symptoms = BLANK (all 7 days after first and second vaccination)
- Site Entered Local Symptoms = BLANK (all 7 days after first and second vaccination) AND
- Site Entered Temperature= BLANK (all 7 days after first and second vaccination) AND

- Site Entered Systemic Symptoms = BLANK (all 7 days after first and second vaccination)

The following criteria will be used to define subjects with follow-up safety data (included in the Overall Safety Population):

- "Were any unsolicited AEs experienced that were not recorded in the diary?" = YES OR
- "Were any unsolicited AEs experienced that were not recorded in the diary?" = NO OR
- "Were any new SAEs reported?" = YES (Day 90 & 180) OR
- "Were any new SAEs reported?" = NO (Day 90 & 180) OR
- "Was the subject confirmed to have experienced symptoms meeting cellulitis-like reaction criteria?" = YES OR
- "Was the subject confirmed to have experienced symptoms meeting cellulitis-like reaction criteria?" = NO OR
- Any AE/SAE form = ANY FIELD HAS DATA OR
- Unsolicited Diary Other Body Symptoms = ANY FIELD HAS DATA (on any of the 28 days) OR
- Solicited Diary Local Symptoms= ANY FIELD HAS DATA (on any of the 7 days after first or second vaccination) OR
- Solicited Diary Temperature= ANY FIELD HAS DATA (on any of the 7 days after first or second vaccination) OR
- Solicited Diary Systemic Symptoms = ANY FIELD HAS DATA (on any of the 7 days after first or second vaccination)
- Site Entered Local Symptoms= ANY FIELD HAS DATA (on any of the 7 days after first or second vaccination) OR
- Site Entered Temperature= ANY FIELD HAS DATA (on any of the 7 days after first or second vaccination) OR
- Site Entered Systemic Symptoms = ANY FIELD HAS DATA (on any of the 7 days after first or second vaccination)

The following criteria will be used to define NO safety data on solicited events (not included in the Solicited Safety Population):

- Solicited Diary Local Symptoms= BLANK (all 7 days after first and second vaccination) AND
- Solicited Diary Temperature= BLANK (all 7 days after first and second vaccination) AND

- Solicited Diary Systemic Symptoms = BLANK (all 7 days after first and second vaccination)
- Site Entered Local Symptoms = BLANK (all 7 days after first and second vaccination) AND
- Site Entered Temperature= BLANK (all 7 days after first and second vaccination) AND
- Site Entered Systemic Symptoms = BLANK (all 7 days after first and second vaccination)

The following criteria will be used to define subjects with safety data on solicited events (included in the Solicited Safety Population):

- Solicited Diary Local Symptoms= ANY FIELD HAS DATA (on any of the 7 days after first or second vaccination) OR
- Solicited Diary Temperature= ANY FIELD HAS DATA (on any of the 7 days after first or second vaccination) OR
- Solicited Diary Systemic Symptoms = ANY FIELD HAS DATA (on any of the 7 days after first or second vaccination)
- Site Entered Local Symptoms= ANY FIELD HAS DATA (on any of the 7 days after first or second vaccination) OR
- Site Entered Temperature= ANY FIELD HAS DATA (on any of the 7 days after first or second vaccination) OR
- Site Entered Systemic Symptoms = ANY FIELD HAS DATA (on any of the 7 days after first or second vaccination)

The criteria used to define Solicited Safety Population, limited to the first vaccination data, will be used to define subjects with safety data on solicited events after the first vaccination. The (additional) following criteria to those noted above will be applied

- Did subject receive the vaccination? = Yes

The (additional) following criteria to those noted above will be used to define subjects with safety data on solicited events after the second vaccination

The criteria used for Solicited Safety Population, limited to the second vaccination data, will be used to define subjects with safety data on solicited events after the second vaccination. The (additional) following criteria to those noted above will be applied

- Dose Group= Two Doses
- Did subject receive the vaccination? = Yes (for both doses)

### 3.5.3 Evaluable Population – Immunogenicity Analysis

The Evaluable Population for immunogenicity analyses will comprise all subjects in the FAS who:

- receive vaccine at Visit 1;
- provided serology specimens which provided valid serology assay results from both Visit 1 and the Study Exit Visit (Visit 2 or 3);

- did not experience a laboratory-confirmed influenza illness between Visit 1 and Study Exit Visit (Visit 2 or 3); and
- did not receive any prohibited medication during the study that is medically assessed to potentially impact immunogenicity results.

### 3.5.4 Per-Protocol Population

The Per-Protocol Population (PPP) will comprise all subjects in the Evaluable Population who do not have any protocol deviations that were medically assessed as potentially impacting on immunogenicity results.

The Per Protocol Population will be the primary population of interest for the primary immunogenicity analysis and a supporting analysis will be performed using the Evaluable Population.

Membership of the PPP will be determined prior to unblinding the study.

Primary and secondary immunogenicity analyses will be completed using the Per-Protocol Population. Duplicate tables of primary and secondary immunogenicity analyses may also be produced based on the Evaluable population if there is >1% difference in the total number of subjects in either of the two age-strata (6 through 35, and 36 through 59 months) between the Per-Protocol Population and the Evaluable Population. The decision to produce tables based on the Evaluable Population will be made by Seqirus after population sets are finalised and prior to unblinding. Analysis on antipyretics frequency will be performed on the Per-Protocol Population.

The study biostatistician will provide information on proposed datasets to Seqirus for review. Protocol deviation listings will also be reviewed by Seqirus prior to the finalisation of the population datasets, which will occur prior to unblinding. The lists will be used to determine which subjects should be excluded from either the Evaluable or the Per Protocol Population, with documentation of the reason for exclusion.

## 3.6 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 or Seqirus for safety, behavioural or administrative reasons (eg, due to an adverse event, protocol deviation, loss to follow-up, subject noncompliance to protocol procedures, and study termination).

In accordance with 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.

## 3.7 Randomisation

A randomization scheme will be used to ensure that the balance between the treatment groups is maintained. To ensure the study blind is maintained, delegates from the Interactive

Response Technology (IRT) company, in association with a Seqirus statistician/delegate not directly involved in the analysis of study results, will prepare the study randomization code. The Stability and Environmental Monitoring group at Seqirus will keep a checked final copy of the randomization code on file. Emergency Code Break IRT access will be provided to the investigational site for use in case of an emergency.

Eligible subjects will be randomized by means of IRT to one of the 2 treatment groups in a 3:1 ratio (Seqirus QIV: Comparator QIV) and will be proportionally balanced in the two age strata (6 through 35 months and 36 through 59 months), with no more than 60% of the total sample size represented in one age stratum. The IRT system will manage randomization and provide to the sites a subject randomization number. The number will correspond to the appropriate study treatment.

## 3.8 Blinding

Investigational site staff including the investigator and all personnel performing study assessments will be blinded to treatment allocation (observer-blind). The subject and parent(s)/ guardian(s) will also remain blinded to treatment allocation.

As there is a visual difference between the Seqirus QIV and the Comparator QIV pre-filled syringes, personnel who prepare and administer the Study Vaccine will be considered unblinded and excluded from involvement in other study procedures, with the exception of other Study Vaccine related activities, such as receipt, preparation and accountability management.

All Seqirus study staff, excluding those in the Seqirus Stability and Environmental Monitoring group and Quality Assurance group, will also be blinded to treatment allocation. Study monitors will be blinded to subject treatment allocation and will remain blinded when performing Study Vaccine accountability.

The randomization code will be unblinded four times:

1. at the time of the safety analysis after a third of subjects or a minimum of 300 subjects in the 36 months through 59 months of age cohort have been enrolled;
2. at the time of the safety analysis after a third of subjects or a minimum of 300 subjects in the 6 months through 35 months of age cohort have been enrolled
3. at the time of the interim analysis when all subjects have completed all immunogenicity assessments and all solicited and unsolicited adverse event reporting;
4. and finally, once all data (including extended follow-up for recording SAEs and AESIs) have been entered into the study database for each subject and the database has been locked.

The randomization code will be provided to the Biostatistics group once written authorization of database lock has been received.

The first unblinding will occur after a third of subjects or a minimum of 300 subjects in the 36 months through 59 months of age cohort are enrolled. A Data and Safety Monitoring Board (DSMB) will review and assess available unblinded safety data in a closed session. The Seqirus team will remain blinded.

The second unblinding will occur after a third of subjects or a minimum of 300 subjects in the 6 months through 35 months of age cohort are enrolled. The DSMB will review and

assess available unblinded safety data in a closed session. The Seqirus team will remain blinded.

Unblinding of the randomization code will also occur once all subjects have completed all immunogenicity assessments and all solicited and unsolicited adverse event reporting. This will facilitate timely analysis of immunogenicity and safety data including all solicited AEs. The results may be communicated to regulatory authorities and relevant personnel within Seqirus but not to personnel directly involved in monitoring the study or interacting with investigators. The results will not be communicated to investigators. Seqirus Safety personnel participating in review of the interim analysis will have no further involvement in the assessment of any SAEs occurring after interim database lock.

A final clinical study report will present all immunogenicity and safety data collected from the active study period and safety data through to the final evaluation (180 days following the last vaccination dose).

Seqirus Safety personnel may unblind the randomization code for an individual subject at any time to facilitate assessment of suspected unexpected serious adverse reactions (SUSARs) experienced by any subject for expedited reporting to regulatory authorities. To maintain integrity of the study blind the Seqirus Safety personnel responsible for assessment of SUSARs are excluded from the Seqirus study team.

## 3.9 Sample Size

Seqirus QIV will be tested against a US-licensed comparator QIV. The treatment randomization ratio is 3:1 (Seqirus QIV: Comparator QIV).

This study is designed to achieve at least 80% power to demonstrate noninferiority for all of the 8 co-primary endpoints, seroconversion rates for 4 strains, GMT for 4 strains using a one-sided alpha of 0.025 for each comparison. No adjustment for multiple endpoints was made. For comparisons of SCR a noninferiority margin of 10% (Comparator QIV-Seqirus QIV) will be employed. It is assumed that the SCR for all strains for QIV is 50% and that there is no difference between Seqirus QIV and Comparator QIV.

For comparison of GMT ratio a noninferiority margin of 1.5 (Comparator QIV/ Seqirus QIV, equivalent to a difference on the log scale of 0.405465108) will be employed. It is assumed that there is no difference between Seqirus QIV and Comparator QIV (ie, a ratio of 1, difference on the log scale of 0) and that the standard deviation of log (titer) is 1.4.

Under these assumptions and with n evaluable = 1500 in the Seqirus QIV group and 500 in the Comparator QIV the power for 4 GMT ratio endpoints is 99.95% and the power for 4 SCR endpoints is 89.70%. The overall global power of the 8 endpoints is then 89.7% x 99.95% = 89.66%.

This provides a total N evaluable = 2000 (with 10% dropouts N=2222).

Sample size calculations were performed using SAS v9.3 and PASS v12.0.02.

Table 3.9-1 summarises the list of all primary endpoints with strains, the planned noninferiority margin and underlying assumptions used for the sample size computations.

**Table 3.9-1 Summary of Assumptions Used for Sample Size Calculations**

| | **H1N1** | **H3N2** | **B strains** |
|---|---|---|---|
| Test significance level, alpha (1-sided) | 2.50% | 2.50% | 2.50% |
| Noninferiority Margin for the SCR comparison (%) | 10 | 10 | 10 |
| Assumed true SCR | 50% | 50% | 50% |
| Power for SCR comparison tests for each strain (%) | 97.32% | 97.32% | 97.32% |
| Global Power for 4 SCR Endpoints | **89.70%** | | |
| | | | |
| Noninferiority Margin for the GMT ratio | 1.5 | 1.5 | 1.5 |
| Common Standard Deviation of $\log_e$(titre) | 1.4 | 1.4 | 1.4 |
| Power for GMT ratio tests for each strain (%) | 99.99% | 99.99% | 99.99% |
| Global Power for 4 GMT ratio Endpoints | **99.95%** | | |
| | | | |
| Global Power for 8 Co-primary Endpoints | **89.66%** | | |

# 4 Statistical Methodology

## 4.1 Planned Analyses

The FAS will be used for summaries of baseline characteristics and background data; the Safety population will be used for all safety analyses; the PPP will be used for the primary and secondary analyses; and the Evaluable population (if required, see Section 3.5.4) will be used for supporting analysis of the primary endpoint, and all other immunogenicity endpoints.

Descriptive statistics will be used to present all safety and immunogenicity results: number of observations (n), mean, standard deviation (SD), median, minimum (min), maximum (max) for continuous data and frequency and percentage for categorical data. Ninety-five percent confidence intervals (CIs) will also be presented for some immunogenicity criteria. 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. Exact CIs based upon the binomial distribution will be calculated for percentages.

Statistics will be displayed for the following:

- Seqirus QIV
- Comparator QIV
- Overall

Summaries by age strata will be:

- 6 through 35 months
- 36 through 59 months

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

- A/H1N1 for *A/California/7/2009 (H1N1)pdm09-like virus*
- A/H3N2 for *A/Hong Kong/4801/2014 (H3N2)-like virus*
- B/Yamagata for *B/Phuket/3073/2013-like virus (B/Yamagata lineage)*
- B/Victoria for *B/Brisbane/60/2008-like virus (B/Victoria lineage)*

All data will be listed.

## 4.2 Interim Analysis

An interim analysis is defined as the analysis of immunogenicity and safety data collected from the active study period (Day 1 to Study Exit Visit). Details of the summaries and analyses to be performed are provided in subsequent sections, with tables and listings to be produced highlighted in Section 5.3 and Section 5.4.

A Data and Safety Monitoring Board (DSMB) review of safety data will be conducted after approximately one third of subjects (or a minimum of 300 subjects) in the 36 through 59 months age group have received the first vaccination and have had an opportunity to enter at least the first 7 days of safety data post-vaccination.

Recruitment in the 36 through 59 months age cohort will not be halted during the period of the data cut and DSMB review. Enrolment in the younger age cohort (subjects 6 months through 35 months of age) will only commence after the DSMB has reviewed the safety data and recommended that the study may proceed.

A second safety data cut will be performed when approximately one third of subjects (or a minimum of 300 subjects) in the 6 through to 35 months age cohort have received the first vaccination and have had an opportunity to enter at least the 7 days of safety data post-vaccination. A DSMB meeting will be convened to review and assess the available safety data. Recruitment in the 6 through 35 months age cohort will not be halted during the period of the data cut and DSMB review.

Halting rule triggers may lead to additional DSMB safety data review as defined in the DSMB Charter.

An interim CSR will be produced from data generated from Visit 1 through to the Exit Visit.

A final consolidated CSR will present all immunogenicity and safety data collected from the active study period and safety data through to the final evaluation (180 days following the last vaccination dose).

## 4.3 Disposition of Subjects

The number of subjects screened, 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 35 months, 36 through 59 months) and overall. The number in the full analysis set will be used as the denominator.

The number of subjects who are excluded from each of the Evaluable and Per-Protocol populations will be summarized by treatment group, by age strata (6 through 35 months, 36 through 59 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.

The number of screen failures, and reason for screen failure will also be displayed.

## 4.4 Baseline and Demographic Characteristics

All baseline and demographic characteristics will be summarised by treatment group, age strata, and overall. This will include age, gender, race, ethnicity, weight, pre-vaccination temperature, medical history, and previous vaccination history.

Medical history will be coded according to MedDRA version 19, and will be displayed by system organ class and preferred term, using the MedDRA internationally agreed order.

For prior vaccination history, the number and percentage of subjects who have ever been vaccinated, who have been vaccinated in the 2015/2016 season, and have been assigned to receive 1 or 2 vaccinations during the study, will be summarised.

## 4.5 Exposure

The number and percentage of subjects that received vaccination, the side/site/route of each vaccination, and received vaccinations according to protocol will be summarised by treatment group, by age strata, and overall, for Visit 1 and Visit 2.

## 4.6 Concomitant Medication

Incidence of concomitant medication will be presented by treatment, age strata, therapeutic area and preferred drug name.

Concomitant medications are all medications taken during the study period, including those started before but ongoing at vaccination.

Where a medication start date is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

**Note:**

Medications are coded using WHO Drug dictionary version March 2016.

Prior medications will be listed only.

## 4.7 Primary and Secondary Analysis

### 4.7.1 Primary Endpoints

Serum HI antibody levels of all participants will be determined in triplicate (HI1, HI2 and HI3) on serum separated from the whole blood. Pre- and post-vaccination samples will be titrated in duplicate, simultaneously. The titer assigned to each sample shall be the geometric mean of three independent determinations i.e. Assigned titer=exp[(log(HI1) +log(HI2) +log(HI3))/3

GMT and SCR will be based on the following:

- HI antibody titer for each strain: All analyses involving HI antibody titer (namely group GMT within a treatment group) will be performed on the log scale and the resultant summary statistic back-transformed to derived GMT
- Seroconversion: For each strain the subjects will be classified as ‘seroconverted’ if either they have a pre-vaccination HI antibody titer < 1:10 and a post-vaccination HI antibody titer ≥ 1:40 or a pre-vaccination HI antibody titer ≥ 1:10 and a ≥ 4-fold increase in post vaccination HI antibody titer. Otherwise they will be classified as ‘not seroconverted’

### 4.7.2 Method of Analysis for Primary Outcome

**Primary Objectives**

The primary objective of this study is to demonstrate that vaccination with Seqirus QIV elicits an immune response that is not inferior to that of a US-licensed comparator QIV containing the same virus strains as Seqirus QIV, among a pediatric population 6 through 59 months of age.

**Primary Endpoints**

Co-primary immunogenicity endpoints of GMT and SCR for each virus strain contained in the vaccine will be assessed among a pediatric population 6 through 59 months of age.

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

The non-inferiority of Seqirus QIV compared to the US-licensed comparator QIV will be assessed by the 8 co-primary endpoints of GMT and SCR.

In line with the FDA Guidance on seasonal inactivated influenza vaccines (*Guidance for Industry Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines 2007*), Seqirus QIV will be considered to be non-inferior to the US-licensed comparator QIV if, for each of the four strains, the following statistical criteria are met:

- The upper bound of the two-sided 95% confidence interval (CI) on the ratio of the GMTs does not exceed 1.5. The GMT ratio will be calculated by GMT US-licensed comparator QIV / GMT Seqirus QIV
- The upper bound of the two-sided 95% CI on the difference between the SCRs does not exceed 10%. The difference in SCRs will be calculated by (Seroconversion US-licensed comparator QIV–Seroconversion Seqirus QIV). The 95% CI will be computed based on the binomial distribution.

To determine the GMT ratio (adjusted analysis) a general linear model (GLM) will be fitted on log transformed (natural log) post-vaccination HI titer as the outcome variable and terms for covariates: vaccine treatment, pre-vaccination HI titer, age stratum, gender, vaccination history, age-by-vaccine interaction and study site. Potential covariate interaction effects will also be examined in the fit of the GLM. From the model an adjusted difference in least square means (on the log scale) will be produced with 95% confidence limits. The estimated difference and the confidence limits will be back transformed to obtain an *adjusted* GMT ratio with 95% confidence limits. Each of the four strains will be analysed separately. The adjusted GMT ratio will be the result for which the non-inferiority assessment of the HI GMT co-primary endpoint will be based on.

The complete set of covariates that will be used in the model to calculate the adjusted GMT ratio will include treatment group (2 treatments), pre-vaccination mean GMT titer (value), age strata (2 categories, 6 through 35 months or 36 through 59 months), gender (male or female), influenza vaccination received prior year (Yes or No), Number of Dose (1 vs 2), and investigator site (site identifier).

The GLM specification is:

- Adjusted Analysis GMT Model: Log-transformed Post-vaccination HI Titer = Vaccine + Age Strata + Gender + Vaccination History [y/n] + Log-transformed Pre-vaccination HI Titer + Site + Number of Dose [1/2] + Age Strata*Vaccine.

For any strain, the interaction term *Age Strata*Vaccine* will be removed from the fit of the model if it is assessed to be not significant.

The measure of the *unadjusted* GMT ratio based on post-vaccination GMTs only will also be presented.

The PPP will be the primary analysis population for the primary immunogenicity analysis and a supporting analysis may be performed using the evaluable population according to the criteria outlined in Section 3.5.4.

If all 8 co-primary endpoints result in a conclusion of non-inferiority then overall non-inferiority of Seqirus QIV compared to the US-licensed comparator QIV will be concluded.

This assessment will be conducted overall (the primary endpoint).

In mathematical notation the statistical hypotheses to be tested for the primary immunogenicity analysis corresponds to:

H0: $R_i > 1.5$, for any strain
Ha: $R_i \leq 1.5$, for all strain

and

H0: $D_i > 10$, for any strain
Ha: $D_i \leq 10$, for all strain

where $R_i$ is any of the 4 strain-specific post immunogenicity dose GMT ratios:

- (US-licensed comparator QIV) / (Seqirus QIV) for B/Yamagata strain
- (US-licensed comparator QIV) / (Seqirus QIV) for B/Victoria strain
- (US-licensed comparator QIV) / (Seqirus QIV) for A/H1N1 strain
- (US-licensed comparator QIV) / (Seqirus QIV) for A/H3N2 strain

and $D_i$ is the 4 strain-specific post-dose SCR difference, namely

- (US-licensed comparator QIV) - (Seqirus QIV) for B/Yamagata strain
- (US-licensed comparator QIV) - (Seqirus QIV) for B/Victoria strain
- (US-licensed comparator QIV) - (Seqirus QIV) for A/H1N1 strain
- (US-licensed comparator QIV) - (Seqirus QIV) for A/H3N2 strain

No adjustment will be made for multiple comparisons.

### 4.7.3 Secondary Endpoints - Immunogenicity

The humoral immune response will be assessed in terms of HI antibodies for both Seqirus QIV and the QIV comparator. Serum HI antibody titers against the 4 influenza vaccine strains will be used to calculate:

- GMTs: Geometric mean of HI titers pre-vaccination (Day 1) and post-vaccination (Study Exit Visit);

- SCRs: Percentage of subjects with either a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and a ≥ 4-fold increase in post-vaccination titer;
- The percentage of subjects with a titer ≥40 (seroprotection rate) at Day 1 and at Study Exit Visit;
- Geometric mean fold increase (GMFI)*: Geometric mean fold titer rise from Day 1 to Study Exit Visit

**GMFI in antibody titer is defined as the geometric mean of the fold increase of post-vaccination HI antibody titer over the pre-vaccination HI antibody titer.*

For each treatment group (each age strata as well as overall) summary tables, by strain, will be presented for GMT (mean and 95% CIs), number and percentage of subjects with a titer ≥40 at Day 1 and Study Exit Visit, Day 29, SCR (number and percentage of subjects at Study Exit Visit ) and GMFI (mean and 95% CIs).

All secondary immunogenicity endpoint summaries described above will be presented overall, and by age strata, by gender, by race, and by ethnicity.

The distribution of antibody titers 6 through 35 months of age, 36 through 59 months of age, as well as overall (for each vaccine) will be displayed graphically using reverse cumulative distribution (RCD) curves. RCD curves following the first and second vaccinations will also be displayed by age strata.

#### 4.7.3.1 Influenza-Like-Illness

For influenza-like illness the number and percentage of subjects experiencing at least one episode will be presented with 95% CIs. The relative risk and 95% CI based on unconditional exact method will also be presented for Seqirus QIV/Comparator QIV. P-value for Cochran Mantel Haenszel test for general association will be also reported. Analysis will be performed using the Full Analysis Set.

Influenza-like illness will be obtained from 'Did subject experience fever and at least 1 other influenza-like symptom?'

Laboratory results will be listed.

### 4.7.4 Secondary Endpoints - Safety

AEs will be monitored after vaccination as per the following;

- Frequency and severity of solicited local adverse reactions and systemic adverse events (AEs) for 7 days (ie, day of vaccination and 6 subsequent days) after each vaccination dose;
- Frequency of cellulitis-like reaction for at least 28 days after each vaccination dose;
- Frequency and severity of unsolicited AEs for at least 28 days (ie, day of vaccination and 27 subsequent days) after each vaccination dose;
- Frequency of serious adverse events (SAEs) for at least 180 days after the last vaccination dose.

#### 4.7.4.1 Total Adverse Events

The total number of AEs (including solicited and unsolicited AEs, SAEs, and AESIs) will be summarised by treatment (i.e. Seqirus QIV/Comparator QIV/Overall), by presenting the number and percentage of subjects having one or more events, and the relationship and severity of each event. Each summary will be presented for total AEs, solicited local AEs, solicited systemic AEs, and unsolicited AEs. The number of subjects with an SAE or AESI, a related SAE or AESI, who discontinued due to an AE or an SAE or an AESI, or had an SAE resulting in death, will also be presented. Summaries will be repeated by Age Strata, Gender, Race, and Ethnicity.

Related events are defined as events that are related to study medication or with an unknown relationship.

An adverse event of special interest [AESI] is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

AESIs include the following:

| **AESI** | **Preferred Term** |
|---|---|
| Bell's Palsy | VIIth nerve paralysis |
| Encephalomyelitis | Encephalomyelitis |
| Guillain-Barre Syndrome | Guillain-Barre Syndrome |
| Optic Neuritis | Optic Neuritis |
| Thrombocytopenia | Thrombocytopenia |
| Transverse Myelitis | Myelitis transverse |
| Vasculitis | Vasculitis |
| Demyelinating disorders | Acute disseminated encephalomyelitis (ADEM)<br>Encephalomyelitis<br>Acute haemorrhagic Leukoencephalitis (AHL)<br>Acute hemorrhagic encephalomyelitis (AHEM)<br>Acute necrotizing hemorrhagic leukoencephalitis (ANHLE)<br>Leukoencephalitis<br>Multiple sclerosis<br>Primary progressive multiple sclerosis<br>Progressive multiple sclerosis<br>Progressive relapsing multiple sclerosis<br>Relapsing-remitting multiple sclerosis<br>Neuromyelitis optica (NMO)<br>Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)<br>Demyelinating polyneuropathy<br>Lewis-Summer syndrome |
| Febrile convulsion | Febrile convulsion |
| Febrile delirium | Delirium febrile |

#### 4.7.4.2 Solicited Adverse Events

Solicited AEs are those events specifically sought for and recorded by the parent(s)/guardian(s) in the 7-Day Diary, entered on the day of vaccination and the subsequent 6 days.

Solicited Local AEs include pain, induration/swelling, and erythema/redness. All solicited local AEs will be assessed as related to the Study Vaccine.

Solicited Systemic AEs include fever (temperature ≥37.5ºC), nausea and/or vomiting, and diarrhea. For subjects less than 36 months of age at the time of the first dose of study vaccine solicited Systemic AEs also include loss of appetite and irritability. For subjects 36 months of age and older at the time of the first dose of study vaccine solicited Systemic AEs also include headache, myalgia, and malaise and fatigue.

For all solicited AEs the following summaries will be presented by treatment group. In addition, the summaries will be presented by dose (i.e. After 1st Vaccination, After 2nd Vaccination):

- The number and percentage of subjects reporting at least one occurrence of each type of adverse event will be presented with 95% CIs.
- The number and percentage of subjects experiencing at least one local reaction will be presented with 95% CIs.
- The number and percentage of subjects experiencing at least one systemic adverse event will be presented with 95% CIs.

For each of these summaries the relative risk and 95% CIs will be presented for Seqirus QIV/ Comparator QIV.

All summaries will be presented overall and by maximum intensity. Analyses by treatment group will be repeated by age strata, by gender, by race, and by ethnicity where specified.

Separate summaries will be presented for Related Solicited Systemic Adverse Events, overall and by maximum intensity after any vaccination.

For all solicited events, the day of onset will be determined according to the day they are first recorded (day 1 to day 7). Summaries will be presented with the number (and percentage) of subjects experiencing at least one event by onset day.

For all solicited events, the duration (in days) will be determined as the number of consecutive days where severity is ≥1. A subject may experience multiple events of a solicited AE. Separate events will be defined as ≥1 day without the event being recorded. Summaries will be presented with the number (and percentage) of subjects experiencing at least one event by duration. Number of events will also be presented.

Summaries of onset and duration will be presented by treatment group and repeated by age strata. In addition, the summaries will be presented by dose.

Severity will be determined as follows:

## Solicited Local Reactions

| **Reaction** | **Grading** | | | |
|---|---|---|---|---|
| | **0** | **1** | **2** | **3** |
| Pain at the vaccination site | None | For subjects less than 36 months of age at the time of the first dose of study vaccine: | | |
| | | Minor reaction on touch | Cried/protested on touch | Cried when limb was moved/ spontaneously painful |
| | | For subjects 36 months of age and older at the time of the first dose of study vaccine: | | |
| | | Does not interfere with daily activities | Interferes with daily activities | Prevents daily activity |
| Redness at the vaccination site (erythema) | Absent | < 10 mm | ≥ 10 to ≤ 30 mm | > 30 mm |
| Induration/Swelling at the vaccination site | Absent | < 10 mm | ≥ 10 to ≤ 30 mm | > 30 mm |

## Solicited Systemic AEs

| **Symptom** | **Grading** | | | |
|---|---|---|---|---|
| | **0** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** |
| Fever | <99.5°F (<37.5°C) | ≥99.5 – <100.4°F (≥37.5 – <38.0°C) | ≥100.4 – <101.3°F (≥38.0 – <38.5°C) | ≥101.3°F (≥38.5°C) |
| Nausea and/or Vomiting | None | Adverse events easily tolerated by the subject, causing minimal discomfort and does not interfere with daily activities | Adverse event sufficiently discomforting to interfere with daily activities | Adverse event prevents normal everyday activities or requires significant medical intervention |
| Diarrhea | | | | |
| For subjects less than 36 months of age at the time of the first dose of study vaccine: | | | | |
| Loss of appetite | None | Adverse events easily tolerated by the subject, causing minimal discomfort and does not interfere with daily activities | Adverse event sufficiently discomforting to interfere with daily activities | Adverse event prevents normal everyday activities or requires significant medical intervention |
| Irritability | | | | |
| For subjects 36 months of age and older at the time of the first dose of study vaccine: | | | | |
| Malaise and fatigue | None | Adverse events easily tolerated by the subject, causing minimal discomfort and does not interfere with daily activities | Adverse event sufficiently discomforting to interfere with daily activities | Adverse event prevents normal everyday activities or requires significant medical intervention |
| Headache | | | | |
| Myalgia | | | | |

#### 4.7.4.3 Cellulitis-like Reaction

Cellulitis-like reaction is defined as concurrent:

- Grade 3 injection site pain;
- Grade 3 injection site erythema/redness;
- Grade 3 injection site induration/swelling.

The number and percentage of subjects experiencing cellulitis-like reaction will be presented with 95% CIs. The relative risk and 95% CIs will also be presented for Seqirus QIV/Comparator QIV.

The number and percentage of subjects with Cellulitis-like reaction during the time period Day 1 to Day 7, and Day 1 to Day 29/Exit Visit after each vaccination (1st and 2nd), and after any vaccination will be presented.

#### 4.7.4.4 Unsolicited Adverse Events

Unsolicited AEs will be coded using MedDRA v19. The number (and percentage) of subjects experiencing at least one event (ie, the incidence) of unsolicited AEs will be summarized by MedDRA system organ class (SOC) and preferred term (PT), overall and by maximum intensity. For summaries by maximum intensity, if a subject experiences more than one event in the same system organ class and preferred term, the event with the maximum intensity will be summarised. Maximum intensity will be ranked as follows: severe > moderate > mild > unknown. All summaries will be presented by treatment group (i.e. Seqirus QIV/Comparator QIV/Overall), and repeated by age strata, gender, race, and ethnicity where specified.

Summaries will be presented for:

- Any AEs
- Any AEs by maximum intensity
- Any AEs by relationship to Study Vaccine
- Any SAEs
- Any discontinuations due to AEs
- Any deaths
- Any AESIs

All tables listing events by MedDRA SOC will use the internationally agreed order of MedDRA SOCs:

- Infections and infestations
- Neoplasms benign, malignant and unspecified (incl cysts and polyps)
- Blood and lymphatic system disorders
- Immune system disorders
- Endocrine disorders
- Metabolism and nutrition disorders
- Psychiatric disorders

- Nervous system disorders
- Eye disorders
- Ear and labyrinth disorders
- Cardiac disorders
- Vascular disorders
- Respiratory, thoracic and mediastinal disorders
- Gastrointestinal disorders
- Hepatobiliary disorders
- Skin and subcutaneous tissue disorders
- Musculoskeletal and connective tissue disorders
- Renal and urinary disorders
- Pregnancy, puerperium and perinatal conditions
- Reproductive system and breast disorders
- Congenital, familial and genetic disorders
- General disorders and administration site conditions
- Investigations
- Injury, poisoning and procedural complications
- Surgical and medical procedures
- Social circumstances
- Product issues

Only treatment emergent AEs (commencing after exposure to study treatment) will be included in the unsolicited AE and SAE summaries. Non-treatment emergent events (starting prior to exposure to study treatment) will be included in the subject listings and flagged but not included in the above summaries. Where an AE start date is partially or fully missing, and it is unclear as to whether the AE is treatment emergent, it will be assumed that it is.

All the AEs starting on the day of or before the exit visit (Day 29 + 4) will be included in the summaries of unsolicited AEs. AEs starting after the exit visit will be included in the subject listings and flagged but not included in the above summaries. Where an AE start date is partially or fully missing, and it is unclear as to whether the AE starts prior to the exit visit, it will be assumed that it does.

In the interim analysis, SAEs started after the exit visit will be excluded from the analysis. SAEs up to day of the safety follow-up call, irrespective of the date will be included in the final safety analysis.

If sufficient numbers of cases of AEs occur, more formal statistical analyses of event rates, duration or severity may be conducted.

Deaths will be presented by time period (Day 1 to Study Exit Visit, and Day 1 to Day 180 after last vaccination dose), by treatment, subject number, preferred term, and relationship.

All other AE information collected (e.g. outcome, action taken) will be listed as appropriate.

### 4.7.5 Exploratory endpoints

The exploratory objective of the study is:

- To assess the frequency of antipyretic use in the first 7 days post-vaccination in two age strata: 6 months through to 35 months, and 36 months through 59 months, as well as overall according to treatment group.

Antipyretics are among medications coded under the WHO Drug dictionary ATC code N02B. Namely they include the following drug names:

- Ibuprofen
- Acetaminophen

The number and percentage of subjects consuming antipyretics during the time period Day 1 to Day 7 after each vaccination (1st and 2nd), and after any vaccination will be presented along with the exact 95% confidence limits and the number of medications used.

Descriptive statistics, i.e. number of observation, mean, SD, median, minimum, maximum will be presented to summarize the total days of individual antipyretics use in the subjects with antipyretics use. Summaries will be presented with the number (and percentage) of subjects by days of use.

Results will be presented by treatment, overall and by age strata.

Where a medication start date/end date is partially or fully missing, and it is unclear as to whether the medication is concomitant during the time period Day 1- Day 7 after each vaccination, it will be assumed that it is concomitant. Where it is unclear whether the medication has been taken in a day, it will be assumed that it has been taken.

**Note:**

Medications are coded using WHO Drug dictionary version March 2016.

## 4.8 Safety Analysis

### 4.8.1 Adverse Events

Summaries of adverse events are described above.

### 4.8.2 Body Weight and Temperature

Body weight and temperature, recorded prior to vaccination, will be listed.

### 4.8.3 Physical Examination

Results from physical examination will be listed.

## 4.9 Adjustment for Covariates

The complete set of covariates that will be used to calculate the adjusted GMT ratio will include treatment group (2 treatments), pre-vaccination mean GMT titer (value), age strata (2 categories, 6 through 35 months or 36 through 59 months), gender (male or female), influenza vaccination received prior year (Yes or No), number of doses (1 or 2) and investigator site (site identifier) as described in Section 4.7.2.

## 4.10 Protocol Deviations

Major protocol deviations (major deviations, see Section 4.10.1) will be listed, even if they are assessed not to influence any of the immunogenicity or safety results for subjects who have been entered into the study and assigned a subject number.

The following criteria will exclude a subject from the evaluable population. These will be listed in the deviation listing:

- Not provided both pre- and post-vaccination blood samples
- Laboratory-confirmed influenza infection during the active period (Day 1 to Exit Visit)
- Received prohibited medication during the active study period which medically assessed to potentially impact immunogenicity results

**Note**: Other reasons for deviation may be added to this list, but will be done prior to unblinding of the study. The reasons highlighted will be used in defining the evaluable population and per-protocol population.

### 4.10.1 Protocol Deviations Definitions and Procedure

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

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

*Major protocol deviations* are deviations that could significantly affect the subject's safety, rights, or welfare and/or significantly impact the completeness, accuracy and reliability of the study data. Examples of major protocol deviations include:

- enrolling subjects in violation of inclusion/exclusion criteria defined in the protocol,
- failing to collect pre-vaccination or post-vaccination blood samples
- Subject took prohibited medication during active period (Day 1 to Exit Visit) in the study;
- Administration of second dose of study vaccine when contraindicated as described in the protocol;
- Failure to obtain written Informed Consent from a parent/legal guardian prior to initiating study procedures
- Blood sample handling issues which would affect immunogenicity results e.g. samples freeze/thawed; samples not processed within allowed time frames;
- Failure to report a SAE to Seqirus within timeframe specified in the protocol;

- Subject received an Investigational product which had significant temperature deviations outside pre-specified range in the protocol

*Minor protocol deviations* are deviations that do not significantly affect the subject's safety, rights, or welfare and/or significantly impact the completeness, accuracy and reliability of the study data. Examples of minor protocol deviations include:

- a blood sample not being drawn at an interval specified by the Study Protocol;
- Subject Lost to follow-up;
- Randomization errors which did not affect immunogenicity results or compromised subjects safety;
- Subject completed e-diary outside of allowed time window;
- Missed study procedures with the exception of pre-vaccination and/or post-vaccination blood samples;
- Subject failed to complete and/or submit e –diary (solicited and/or unsolicited);
- Study procedures outside allowed time window;
- Study visit outside allowed time window;
- Safety follow up phone call missed/outside allowed time window;
- Subject's initials missing/ boxes checked instead of initialled, corrections not initialled/dated: MINOR if corrected at following subject visit; MAJOR if not corrected;
- Subject did not complete "time" field on ICF;
- Discrepancies between ICF time and source document time;

Protocol deviation listings will be reviewed by Seqirus prior to the finalisation 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 Evaluable or the Per Protocol Population.

## 4.11 Missing Values – Missing Visits

Titer values recorded as <10 will be summarised as 5.

When solicited AEs occur, if entries are missing for only some of the days, then the intensity will be imputed as the maximum of the previous and next non-missing value for calculation of the aggregated value.

## 4.12 Deviations from SAP

Any deviations from the original statistical plan will be described and justified in the final CSR, whether written post interim or final analysis.

## 4.13 Changes in Conduct or Planned Analyses from the Protocol

The term 'sex' has been replaced with 'gender' throughout the analysis section. The safety population has been refined for overall, solicited safety, solicited safety after 1st vaccination and solicited safety after 2nd vaccination.

The term Number of Doses (1 vs 2) has been included as an additional covariate in the GLM model fitting.

There will be no separate summary tables for SAEs by maximum intensity and relationship, discontinuations due to AEs related to Study Vaccine, or discontinuations due to SAEs. These details will be in listings only.

Unsolicited AEs will be presented overall and not after each vaccination dose, as stated in the secondary endpoints. The wording in the endpoint should have been 'Frequency and severity of unsolicited AEs for at least 28 days (ie, day of vaccination and 27 subsequent days) after the last vaccination dose'.

## 4.14 Algorithms/SAS Codes

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

- **Tables that need frequency counts:**

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

**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:**

- **Code to create 95% CIs within group for continuous variables:**

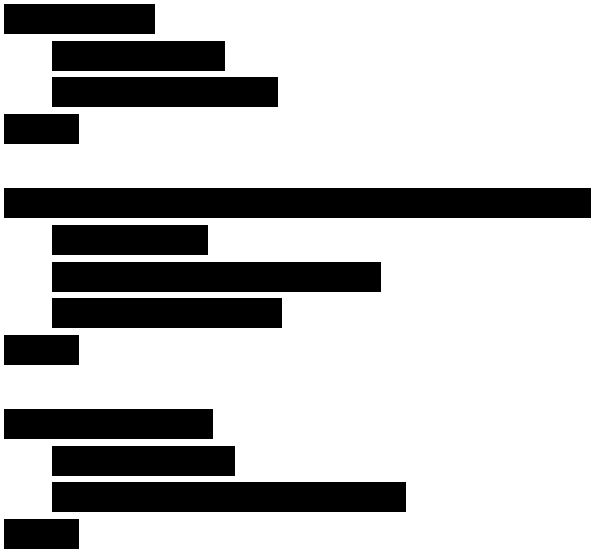
- **Tables that need exact 95% CIs for relative risk, risk difference and Cochran Mantel Haenszel Statistics:**

**Notes**: Estimates are computed for 2x2 tables only

- **Tables that require analysis of (co)variance and 95% CIs between arms for continuous variables:**

**Note**: (Treatment order: 1=drug 1,2= drug 2)

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



# 5 Tables and Listings

## 5.1 Table Format

All output will be produced using SAS version 9.2 or a later version.

In the top left portion of each table/listing, a *table/listing number* followed by the *title* of the table/listing will be presented. After the title line, optional *sub-title* or *population* information can be presented. Horizontal lines will appear before and after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page.

The *sponsor name*, *protocol number,* programmers User ID, status of the table/listing (i.e. draft or final) and *SAS program name* will appear bottom left in a string and the *page number* will appear on the bottom right corner of each table/listing. The *date and time of creation* of table/listing will appear bottom left under the sponsor name. The source listing number will appear bottom left.

A *landscape layout* is proposed for both table and listing presentations.

The *left* and *right margins* of all tables and listings will be a minimum of 2.1 cm from the left and 1.9cm from the right. The *top and bottom margins* will be a minimum 2.92cm. *Header and footer* will be both 1.27 cm.

There is no special requirement of *font type* and *size*, but an *8-point* font size for tables and *7*or *8-point* for listings is proposed using *Courier New* font. A maximum SAS line size=141 and page size=44 for *8-point* font size, and line size=161 and page size=50 for *7-point* will be used so as to fit on both UK and US paper sizes.

In a listing, in the case that a subject's record has been continued to the next page, an appropriate identification (e.g., the subject ID number) must be presented at the beginning of that page.

## 5.2 Conventions

Unless otherwise specified, in summary tables of continuous variables, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data. Wherever possible data will be decimal aligned.

Unless otherwise specified frequency tabulations will be presented by number and percentage, where the percentage is presented in brackets to 1 decimal place. However, if percentages are small the following will be implemented: Percentages between 0.05% and 0.1% will be rounded to 0.1%. Percentages less than 0.05% will be displayed as <0.1%.

P-values, if applicable, will be presented to 3 decimal places. If a p-value is less than 0.05 but is greater than or equal to 0.01, then an asterisk (*) will be added next to this value. If a p-value is less than 0.01 but is greater than or equal to 0.001, then two asterisks (**) will be added next to this value. Finally, if the p-value is less than 0.001 then three asterisks (***) will be added next to this value and it will be presented as <0.001. If the rounded result is a value of 1.000, it will be displayed as >0.999. Any date information in the listing will use the *date9.* format, for example, 07MAY2002. In the listing, a unit associated with a variable will be presented only once within parentheses either below or next to that variable in the heading

portion. If a parameter has multiple units, each unit will be displayed only once, as applicable.

All tables will have their source listing referenced in a footnote. Listings should be sorted by treatment group, subject and visit and have the source data received by data management referenced in a footnote. All tables and listings will be converted into Microsoft Word documents and collated into two complete documents.

## 5.3 Tables

Tables based on the Evaluable Population will be conducted, depending on the difference in absolute numbers of subjects between the two populations (see Section 3.5.4).

All Tables and Listings will be produced for the interim analysis after Study Exit Visit. If there are no events to summarise in a table/listing, the output will be produced displaying a message, for e.g. 'There were no xxxx events recorded'. Flagged (*) Tables and Listings will be repeated for the final analysis. Flagged (**) Tables and Listings will be produced for the final analysis only.

### 5.3.1 Demographic and Baseline

Table 14.1.1.1 Subject Disposition
Table 14.1.1.2 Subject Disposition: By Age Strata
Table 14.1.2.1 Demographics and Baseline Characteristics
Table 14.1.2.2 Demographics and baseline characteristics: By Age Strata
Table 14.1.3.1 Medical History
Table 14.1.3.2 Medical History: By Age Strata
Table 14.1.4.1 Previous Vaccination History
Table 14.1.4.2 Previous Vaccination History: By Age Strata
Table 14.1.5.1 Exposure
Table 14.1.5.2 Exposure: By Age Strata
Table 14.1.6.1 Concomitant Medications
Table 14.1.6.2 Concomitant Medications: By Age Strata

### 5.3.2 Immunogenicity

Table 14.2.1.1 Primary Analysis of Geometric Mean Titer (GMT)
Table 14.2.1.2 Primary Analysis of Geometric Mean Titer (GMT) (Evaluable Population)
Table 14.2.2.1 Primary Analysis of Seroconversion Rate (SCR)
Table 14.2.2.2 Primary Analysis of Seroconversion Rate (SCR) (Evaluable Population)
Table 14.2.3.1 HI Titer Pre-Vaccination (Day 1) and Post-Vaccination (Study Exit Visit)
Table 14.2.3.2 HI Titer Pre-Vaccination (Day 1) and Post-Vaccination (Study exit): By Age Strata
Table 14.2.3.3 HI Titer Pre-Vaccination (Day 1) and Post-Vaccination (Study exit): By Gender
Table 14.2.3.4 HI Titer Pre-Vaccination (Day 1) and Post-Vaccination (Study exit): By Race
Table 14.2.3.5 HI Titer Pre-Vaccination (Day 1) and Post-Vaccination (Study exit): By Ethnicity
Table 14.2.4.1 HI Titer Fold Increase
Table 14.2.4.2 HI Titer Fold Increase: By Age Strata
Table 14.2.4.3 HI Titer Fold Increase: By Gender
Table 14.2.4.4 HI Titer Fold Increase: By Race
Table 14.2.4.5 HI Titer Fold Increase: By Ethnicity
Table 14.2.5.1 Seroconversion Rate (SCR)
Table 14.2.5.2 Seroconversion Rate (SCR): by Age Strata

Table 14.2.5.3 Seroconversion Rate (SCR): by Gender
Table 14.2.5.4 Seroconversion Rate (SCR): by Race
Table 14.2.5.5 Seroconversion Rate (SCR): by Ethnicity
Table 14.2.6 Influenza-Like Illness
Table 14.2.7.1 Antipyretics
Table 14.2.7.2 Antipyretics: by Age Strata

### 5.3.3 Safety

*Table 14.3.1.1.1 Summary of All Solicited and Unsolicited Adverse Events
*Table 14.3.1.1.2 Summary of All Solicited and Unsolicited Adverse Events: By Age Strata
**Table 14.3.1.1.3 Summary of All Solicited and Unsolicited Adverse Events: By Gender
**Table 14.3.1.1.4 Summary of All Solicited and Unsolicited Adverse Events: By Race
**Table 14.3.1.1.5 Summary of All Solicited and Unsolicited Adverse Events: By Ethnicity
**Table 14.3.1.1.6 Summary of All Solicited and Unsolicited Adverse Events (Solicited Safety Population)

Table 14.3.1.2.1 Solicited Local Symptoms Overall and by Maximum Intensity: After Any Vaccination
Table 14.3.1.2.2 Solicited Local Symptoms Overall and by Maximum Intensity: After Any Vaccination By Age Strata
Table 14.3.1.2.3 Solicited Local Symptoms Overall and by Maximum Intensity: After 1st Vaccination
Table 14.3.1.2.4 Solicited Local Symptoms Overall and by Maximum Intensity: After 2nd Vaccination
Table 14.3.1.2.5 Solicited Local Symptoms Overall and by Maximum Intensity: After 1st Vaccination By Age Strata
Table 14.3.1.2.6 Solicited Local Symptoms Overall and by Maximum Intensity: After 2nd Vaccination By Age Strata
Table 14.3.1.2.7 Solicited Local Symptoms Overall and by Maximum Intensity: After Any Vaccination By Gender
Table 14.3.1.2.8 Solicited Local Symptoms Overall and by Maximum Intensity: After Any Vaccination By Race
Table 14.3.1.2.9 Solicited Local Symptoms Overall and by Maximum Intensity: After Any Vaccination By Ethnicity

Table 14.3.1.3.1 Solicited Systemic Adverse Events Overall and by Maximum Intensity: After Any Vaccination
Table 14.3.1.3.2 Solicited Systemic Adverse Events Overall and by Maximum Intensity: After Any Vaccination By Age Strata
Table 14.3.1.3.3 Solicited Systemic Adverse Events Overall and by Maximum Intensity: After 1st Vaccination
Table 14.3.1.3.4 Solicited Systemic Adverse Events Overall and by Maximum Intensity: After 2nd Vaccination
Table 14.3.1.3.5 Solicited Systemic Adverse Events Overall and by Maximum Intensity: After 1st Vaccination By Age Strata
Table 14.3.1.3.6 Solicited Systemic Adverse Events Overall and by Maximum Intensity: After 2nd Vaccination By Age Strata
Table 14.3.1.3.7 Solicited Systemic Adverse Events Overall and by Maximum Intensity: After Any Vaccination By Gender
Table 14.3.1.3.8 Solicited Systemic Adverse Events Overall and by Maximum Intensity: After Any Vaccination By Race
Table 14.3.1.3.9 Solicited Systemic Adverse Events Overall and by Maximum Intensity: After Any Vaccination By Ethnicity

| | |
|---|---|
| *Table 14.3.1.9.4 | Summary of Unsolicited Adverse Events by Maximum Intensity and Relationship by System Organ Class and Preferred Term: Comparator QIV |
| *Table 14.3.1.9.5 | Summary of Unsolicited Adverse Events by Maximum Intensity and Relationship by System Organ Class and Preferred Term: Comparator QIV Strata 6 through 35 months |
| *Table 14.3.1.9.6 | Summary of Unsolicited Adverse Events by Maximum Intensity and Relationship by System Organ Class and Preferred Term: Comparator QIV Strata 36 through 59 months |
| *Table 14.3.1.10.1 | Serious Adverse Events by System Organ Class and Preferred Term |
| Table 14.3.1.11 | Discontinuations Due to Adverse Events by System Organ Class and Preferred Term |
| *Table 14.3.1.12 | Adverse Events of Special Interest by System Organ Class and Preferred Term |
| *Table 14.3.1.13 | Deaths by Preferred Term |

## 5.4 Listings

| | |
|---|---|
| Listing 16.1.7 | Randomisation |
| Listing 16.2.1.1 | Subject Disposition |
| Listing 16.2.1.2 | Eligibility |
| Listing 16.2.2.1.1 | Protocol Deviations - Analysis Populations |
| Listing 16.2.2.1.2 | Site Log of Protocol Deviations |
| Listing 16.2.4.1 | Subject Demography |
| Listing 16.2.4.2 | Medical History |
| Listing 16.2.4.3 | Previous Vaccination Against Influenza |
| Listing 16.2.4.4 | Concomitant Medications |
| Listing 16.2.5.1 | Treatment Administration |
| Listing 16.2.5.2 | Visit Dates |
| Listing 16.2.6.1 | HI Titer Levels and Immunogenicity Results |
| Listing 16.2.6.2 | Cellulitis-like Reaction |
| Listing 16.2.6.3 | Solicited Diary (Symptoms at Injection Site) |
| Listing 16.2.6.4 | Solicited Diary (Temperature) |
| Listing 16.2.6.5 | Solicited Diary (General Body Symptoms) |
| Listing 16.2.6.6 | Solicited Events Site Entered (Symptoms at Injection Site) |
| Listing 16.2.6.7 | Solicited Events Site Entered (Temperature) |
| Listing 16.2.6.8 | Solicited Events Site Entered (General Body Symptoms) |
| *Listing 16.2.7.1 | Adverse Events |
| *Listing 16.2.7.2 | Severe Adverse Events |
| *Listing 16.2.7.3 | Related Adverse Events |
| *Listing 16.2.7.4 | Serious Adverse Events |
| *Listing 16.2.7.5 | Adverse Events of Special Interest |
| Listing 16.2.8.1 | Influenza-Like Illness Lab Data |
| Listing 16.2.8.2 | Nasal & Throat Swab Specimens |
| Listing 16.2.8.3 | Clinical Signs |
| Listing 16.2.8.4 | Physical Examination |
| *Listing 16.2.8.5 | Safety Follow-up |

## 5.5 Figures

| | |
|---|---|
| Figure 14.2.1 | Geometric Mean Titer (GMT) Reverse Cumulative Distribution Curve – Overall |

Figure 14.2.2 Geometric Mean Titer (GMT) Reverse Cumulative Distribution Curve – by Age Strata
Figure 14.2.3 Geometric Mean Titer (GMT) Reverse Cumulative Distribution Curve – by Vaccination and Age Strata
Figure 14.2.4 Geometric Mean Titer (GMT) Reverse Cumulative Distribution Curve – By Study Treatment
Figure 14.2.5 Geometric Mean Titer (GMT) Reverse Cumulative Distribution Curve – By Study Treatment and Age Strata

Tables, Listings and Figures will follow the format of: CSLCT-QIV-13-02 Final Version 1 TLFs.

## 5.6 Appendices

Not applicable.

## 5.7 References

1. Clinical Study Protocol CSLCT-QIV-15-03 Protocol v2.0 Amendment 1.0 24 May16.pdf
2. ICH Harmonized Tripartite Guideline, 5 February, 1998, Statistical Principles for Clinical Trials, E9
3. World Health Organization, WHO Technical Report, Series No. 924. 2004, Annex 1: *Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations*
4. FDA CBER Guidance for Industry, May 2007, *Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines*
5. ICH guideline (Guidance for Industry, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting – ICH-E2A), 27 October, 1994