CLINICAL STUDY PROTOCOL V130_10

Version 4.0, dated 09 DEC 19

A Phase 3, Randomized, Observer-Blind, Multicenter, Noninferiority Study to Evaluate Safety and Immunogenicity of a Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) and a United States-licensed Quadrivalent Influenza Virus Vaccine (QIV) in Healthy Subjects 6 Months Through 47 Months

A Phase 3 Safety and Immunogenicity Study of QIVc in Healthy Pediatric Subjects

IND number 15744

Table of Contents

List of Tables

PROTOCOL SYNOPSIS V130_10

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus	V130_10	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) US-licensed Egg-Based Quadrivalent Influenza Vaccine (QIV)

Title of Study:

A Phase III, Randomized, Observer-Blind, Multicenter, Noninferiority Study to Evaluate Safety and Immunogenicity of a Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) and a United States-licensed Quadrivalent Influenza Vaccine (QIV) in Healthy Subjects 6 Months through 47 Months

Study Period: Approximately 180 days (6 months) after last vaccination date	**Clinical Phase:** Phase 3

Background and Rationale:

Influenza is an infectious disease caused by the influenza virus, an orthomyxovirus with two clinically relevant types (Type A and B). Influenza Type A/H1N1, A/H3N2, and Type B/Victoria and B/Yamagata strains have circulated and caused disease in humans on a global basis since 1977 (Fiore et al. 2010), with a high susceptibility to severe influenza in children (Izurieta et al. 2000; Bourgeois et al. 2006). Children <5 years, and particularly those <2 years of age, are at high risk of infection and are a priority for annual seasonal influenza vaccination throughout the world (World Health Organization[WHO] 2012; American Academy of Pediatrics Commitee on Infectious Diseases 2016). With vaccination as the recommended method to prevent influenza, both childhood influenza disease burden and community viral transmission could be reduced (Mertz et al. 2016).

One of the challenges of protecting children against influenza is providing a vaccine with an antigenic match against the circulating strains in a given influenza season. Since 1983, two evolutionarily distinct lineages of influenza B viruses have co-circulated in the human population globally (Rota, 1990) and influenza B viruses account for roughly 20% of total influenza events in all regions of the world (Ciani et al. 2015). As only one B lineage is selected for inclusion in current trivalent influenza vaccines (TIVs) and

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
Seqirus	V130_10	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) US-licensed Egg-Based Quadrivalent Influenza Vaccine (QIV)

there has been no demonstrated cross protection between the two lineages (Peltola et al. 2003; Hu et al. 2004), there is the risk of a mismatch for the influenza B strain (Couch 2007; Belshe, 2010; Orsi et al. 2018). Since patients infected with influenza B are usually younger than patients infected with influenza A, the effectiveness of vaccination in children seems more dependent on adequate matching (Jayasundara et al. 2014; Ciani et al. 2015; Orsi et al. 2018). To address this problem, quadrivalent influenza vaccines (QIV) have been developed containing B strains from both lineages.

Seqirus' Flucelvax Quadrivalent (QIVc) is a cell based quadrivalent inactivated subunit influenza vaccine prepared from virus propagated in Madin Darby Canine Kidney (MDCK) cells, and approved by the Food and Drug Administration (FDA) for use in children 4 years and older. QIVc has a formulation with two influenza A strains and two influenza B strains updated annually as recommended by the WHO for a specific influenza season, and addresses the unmet medical need of better vaccine antigenic matching against co-circulating influenza B strains. A shift from egg- to cell-culture based manufacturing platforms has several advantages, allowing for the possibility to work directly with wild-type viruses, avoiding the generation of egg-adaptive mutations in the HA protein, increasing surge capacity in the event of a pandemic, and providing better manufacturing control through a closed-system fermentation process (Lambert and Fauci 2010).

The purpose of this study is to demonstrate that vaccination with QIVc elicits an immune response that is not inferior to that of a United States (US)-licensed QIV containing the recommended strains for the season, in children 6 months through 47 months of age.

The data from this study will be used to support the licensure of QIVc for use in children 6 months through 47 months of age.

Study Objectives:

Immunogenicity Objectives

The immunogenicity objectives will be evaluated based on antibody responses against all strains 4 weeks after last vaccination in subjects 6 months through 47 months of age.

Primary Immunogenicity Objective:

1. To demonstrate that vaccination with QIVc elicits an immune response that is not inferior to that of a US-licensed QIV, in subjects 6 months through 47 months of age, as measured by hemagglutination inhibition (HAI) assay for A/H1N1, B/Yamagata and B/Victoria strains and by microneutralization (MN) assay for A/H3N2 strain, using cell-derived target viruses

Secondary Immunogenicity Objectives:

1. To describe the immunogenicity of QIVc and US-licensed QIV by HAI assay for A/H1N1, B/Victoria, and B/Yamagata strains, and by MN assay for A/H3N2 strain, using egg-derived target viruses

2. To describe the immunogenicity of QIVc and US-licensed QIV by HAI assay for A/H1N1, B/Victoria, and B/Yamagata strains and by MN assay for A/H3N2 strain, using cell-derived target viruses

3. To describe the immunogenicity of QIVc and US-licensed QIV by MN assay for A/H1N1, B/Victoria, and B/Yamagata strains, in a subset of subjects

Secondary Safety Objective:

1. To evaluate the safety and reactogenicity of QIVc and US-licensed QIV

Exploratory Immunogenicity Objectives:

1. To evaluate the homologous cell-mediated immunity (CMI) response, prevaccination and postvaccination, in a small population of subjects

2. To further describe the immune response to vaccination, additional immunogenicity analyses may be conducted such as HAI assay for A/H3N2 using cell- and egg-derived target virus

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus	V130_10	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) US-licensed Egg-Based Quadrivalent Influenza Vaccine (QIV)

Study Design:

This phase 3 clinical study is a randomized, observer-blind, comparator controlled, multicenter study of QIVc versus a US-licensed QIV in children 6 months through 47 months of age. The study features a 2:1 randomization between QIVc and US-licensed QIV. Based on influenza vaccination history, subjects will receive either 1 or 2 doses of either QIVc or US-licensed QIV comparator (see Table 1-1 for previously vaccinated subjects and Table 1-2 for not previously vaccinated subjects). The study will be conducted in approximately 2502 healthy subjects: 2418 subjects for evaluation of immunogenicity and 84 subjects for evaluation of CMI response.

The study has a treatment period and a follow-up period. For subjects with a previous influenza vaccination history, the treatment period begins at the time of vaccination and ends 28 days after vaccination and will consist of 2 clinical visits and 1 reminder call to complete the Subject Diary Card. The follow up period begins 28 days after vaccination and ends at the time of the study completion visit (180 days after last vaccination). For subjects without or unknown previous influenza vaccination history, the treatment period begins at the time of first vaccination and ends 28 days after the second vaccination and will consist of 3 clinical visits and 2 reminder calls to complete the Subject Diary Card, one after each vaccination. The follow up period begins 28 days after second vaccination and ends at the time of the study completion visit. All subjects, irrespective of previous influenza vaccination history, will receive 1 safety assessment call 90 days after last vaccination during the follow up period and the follow-up period will conclude with a study completion visit (call).

The final analysis of the primary and secondary immunogenicity endpoints will be conducted on cleaned and locked data once all subjects have completed all immunogenicity assessments (end of treatment period, i.e. up to 28 days following the last vaccination dose). At this time, the analysis of all solicited adverse events and of unsolicited adverse events reported during the treatment period will also be conducted. These results will be used to prepare a Clinical Study Report (CSR) with treatment period data. No individual unblinded listings will be generated at this stage.

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus	V130_10	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) US-licensed Egg-Based Quadrivalent Influenza Vaccine (QIV)
A final CSR will present all clinical study data collected up to 180 days following the last vaccination dose, including safety data collected during the follow up period.		
Number of Subjects planned: In this study a total of approximately 2502 healthy subjects will be enrolled: 2418 subjects for evaluation of immunogenicity and 84 subjects for assessment of CMI response. For immunogenicity evaluation approximately 2418 subjects will be enrolled, in order to have approximately 1450 evaluable subjects in the QIVc group and 725 evaluable subjects in the US-licensed QIV group (considering 10% drop-out rate). The subjects will be randomized to 1 of 2 vaccine groups in a ratio of 2:1 (Seqirus QIVc: comparator QIV). Stratification through Interactive Response Technology (IRT) will be used to ensure a balanced distribution among the age groups, at least 30% of subjects should be 6 through 23 months and at least 30% of subjects should be from 24 through 47 months of age. For evaluation of cell-mediated immune (CMI) response, approximately 84 subjects between 24 through 47 months of age will be enrolled in order to have approximately 50 evaluable subjects in the QIVc group and approximately 25 evaluable subjects in the US-licensed QIV group. The subjects will be randomized to 1 of 2 vaccine groups in a ratio of 2:1 (Seqirus QIVc: comparator QIV).		
Study Population and Subject Characteristics: This study will enroll healthy children 6 months through 47 months of age from the United States during one influenza season. The list of inclusion and exclusion criteria is included in protocol Section 4, Selection of Study Population.		

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
Seqirus	V130_10	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) US-licensed Egg-Based Quadrivalent Influenza Vaccine (QIV)

Study Procedures:

Written informed consent must be obtained prior to performing any study-related procedures. The informed consent process may be conducted up to 10 days before day of vaccination (Day 1).

After signing of the informed consent by the subject's parent(s)/legally acceptable representative (LAR) and undergoing review of the reported medical history, physical examination, review of current and prior medications and vaccinations, and confirmation of subject eligibility, subjects will be enrolled into the study.

The study has a treatment period and a follow-up period. The treatment period has scheduled visits planned depending on the subject's influenza vaccination history and age of the subject and ends 28 days after last vaccination. The follow-up period will conclude with a study completion call.

Treatment period:
After vaccination, all subjects will remain under medical supervision and will be monitored for any immediate postvaccination reactions for at least 30 minutes. Local solicited adverse reactions and systemic solicited adverse events will be collected from 30 minutes after vaccination on a Subject Diary Card, and collection will continue for a total of 7 Days. Three (3) days after vaccination parent(s)/LAR(s) will receive a reminder call to complete the Subject Diary Card. Any unsolicited AE and concomitant medication will be collected until 28 days after each vaccine dose.

Blood samples for serology will be collected prior to vaccination (Day 1) and 28 days after last vaccination at scheduled clinic visits for immunogenicity evaluation or to evaluate CMI response.

The collection of body temperature, solicited local adverse reactions, solicited systemic adverse events will continue for a total of 7 days on the Diary Card. Training will be provided for the individual(s) who will perform the measurements of local reactions and

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus	V130_10	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) US-licensed Egg-Based Quadrivalent Influenza Vaccine (QIV)

body temperature (often a parent(s)/LAR(s)), and for those who will enter the information into the Subject Diary Card.

Follow-up period:
During the follow-up period, safety data including adverse events (AEs) leading to withdrawal, New Onset of Chronic Diseases (NOCDs), Serious Adverse Events (SAEs), and all medications used related to these events will be captured at 90 days and 180 days after last vaccination.

Study completion:
The study will conclude with a study completion call 180 days after last vaccination.

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus	V130_10	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) US-licensed Egg-Based Quadrivalent Influenza Vaccine (QIV)

Study Vaccines:

Both QIVc and the US-licensed QIV will be administered intramuscularly (IM), in the anterolateral aspect of the thigh or into the deltoid muscle. For both QIVc and US-licensed QIV, either 1 or 2 doses will be administered depending on each subject's influenza vaccination history. If 2 vaccinations are given, the administration interval will be approximately 28 days.

Study vaccine:

A dose of 0.5 mL of QIVc (Flucelvax Quadrivalent) contains purified 15 µg viral envelope-glycoprotein hemagglutinin (HA) of each of the four (4) influenza strains recommended by WHO for inclusion in the quadrivalent vaccine formulation for the influenza season corresponding to the season of conduct of study.

Comparator vaccine:

Afluria Quadrivalent will be administered as the US-licensed QIV comparator, following dose recommendations described in the US Package Insert (USPI).

Subjects 6 months through 35 months of age will receive 0.25 mL (1 or 2 doses, depending on influenza vaccination history), while subjects 36 months through 47 months of age will receive 0.5 mL (1 or 2 doses, depending on influenza vaccination history).

Immunogenicity Endpoint

Immunogenicity of study vaccines will be evaluated at Day 1 and Day 29 for "previously vaccinated" subjects or Day 1 and Day 57 for "not previously vaccinated" subjects.

Primary Immunogenicity Endpoints

Serum HAI antibody titer against A/H1N1, B/Victoria and B/Yamagata vaccine strains at Day 29/57, using cell-derived target virus:

- Geometric Mean Titer (GMT) by HAI assay
- Seroconversion rate (SCR) defined as the percentage of subjects with either a prevaccination HAI titer <1:10 and a postvaccination HAI titer ≥1:40, or a prevaccination HAI titer ≥1:10 and a ≥4-fold increase in postvaccination HAI titer

Serum neutralizing antibody titer against A/H3N2 vaccine strain at Day 29/57, using cell-derived target virus:

- GMT by MN assay
- SCR defined as the percentage of subjects with either a prevaccination MN titer <1:10 (Lower Limit Of Quantification [LLOQ]) and a postvaccination MN titer ≥1:40 (4*LLOQ), or a prevaccination MN titer ≥1:10 (LLOQ) and a ≥4-fold increase in postvaccination MN titer

Derived Variables:

- The GMT ratio (QIV/QIVc) for each strain
- The inter-group difference in the SCRs (QIV minus QIVc) for each strain

The noninferiority of QIVc compared to US-licensed QIV will be assessed for the eight co-primary endpoints of GMT and SCR for each cell-derived target virus strain included in QIVc as follows:

- The GMT ratio for the A/H1N1 strain (HAI assay)
- The GMT ratio for the A/H3N2 strain (MN assay)
- The GMT ratio for the B Yamagata strain (HAI assay)
- The GMT ratio for the B Victoria strain (HAI assay)
- The difference between the SCRs for the A/H1N1 strain (HAI assay)
- The difference between the SCRs for the A/H3N2 strain (MN assay)
- The difference between the SCRs for the B Yamagata strain (HAI assay)
- The difference between the SCRs for the B Victoria strain (HAI assay)

Secondary Immunogenicity Endpoints:

Humoral immune response in terms of HAI antibodies against A/H1N1, B/Victoria and B/Yamagata strains, using cell- and egg-derived target virus:

- GMT by HAI assay at Days 1 and 29/57

- Geometric Mean Ratio (GMR), defined as the fold increase in serum HAI GMT postvaccination (Day 29/57) compared to prevaccination (Day 1)
- Seropositivity rates (percentages of subjects with HAI titer ≥1:10) at Days 1 and 29/57
- Percentages of subjects with HAI titer ≥1:40 at Days 1 and 29/57
- SCR by HAI assay

Derived variables:

- The GMT ratio (QIV/QIVc) for each strain
- The inter-group difference in the SCRs (QIV minus QIVc) for each strain

Neutralizing antibody titers against A/H3N2 vaccine strains, using cell- and egg-derived target virus:

- GMT by MN assay at Days 1 and 29/57
- GMR, defined as the fold increase in serum MN GMT postvaccination (Day 29/57) compared to prevaccination (Day 1)
- Seropositivity rates (percentages of subjects with MN titer ≥ 1:10 (LLOQ)) at Days 1 and 29/57
- SCR by MN assay

Derived variables:

- The GMT ratio (QIV/QIVc) for A/H3N2 strain
- The inter-group difference in the SCRs (QIV minus QIVc) for A/H3N2 strain

Neutralizing antibody titers against A/H1N1, B/Victoria and B/Yamagata vaccine strains, in a subset of subjects:

- GMT by MN assay at Days 1 and 29/57
- GMR, defined as the fold increase in serum MN GMT postvaccination (Day 29/57) compared to prevaccination (Day 1)
- Seropositivity rates (percentages of subjects with MN titer ≥ 1:10 (LLOQ)) at Days 1 and 29/57
- SCR by MN assay

Derived variables:

- The GMT ratio (QIV/QIVc) for each strain
- The inter-group difference in the SCRs (QIV minus QIVc) for each strain

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
Seqirus	V130_10	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) US-licensed Egg-Based Quadrivalent Influenza Vaccine (QIV)

Secondary Safety Endpoints:

The measures for assessing safety and reactogenicity are as follows:

1. Percentage of subjects with solicited AEs within 7 days after each study vaccination
2. Percentage of subjects with any unsolicited AEs from Day 1 to Day 29 (in previously vaccinated subjects) and from Day 1 to Day 57 (in not previously vaccinated subjects)
3. Percentage of subjects with any SAEs, NOCDs, AEs leading to withdrawal during the entire study period (ie, from Day 1 to Day 181 for previously vaccinated subjects or from Day 1 to Day 209 for not previously vaccinated subjects)

Exploratory Immunogenicity Endpoint(s):

For CMI evaluation, CD4+ T-cell responses will be measured by staining and flow cytometry at baseline (Day 1), and Day 29 (previously vaccinated subjects) or Day 57 (not previously vaccinated subjects), as measured by number of cells expressing interferon gamma (IFN-γ), interleukin 2 (IL-2), tumor necrosis factor alpha (TNF-α), and other markers as may be practical within the available volumes of blood/cells.
In case of additional exploratory immunogenicity analyses, the immune response will be further characterized similar to the analysis of secondary immunogenicity endpoints.

Statistical Analyses

General Statistical Considerations:
In general, summary descriptive statistics of continuous data will be presented as number of observations, mean, standard deviation, median, minimum and maximum. For categorical variables, statistical summaries will include counts and percentages relative to the appropriate population.

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus	V130_10	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) US-licensed Egg-Based Quadrivalent Influenza Vaccine (QIV)
Binary data (ie, percentages of subjects with seroconversion [SC]) will be summarized for each group using unadjusted estimates and will be reported together with two-sided exact 95% CIs (Clopper-Pearson). The difference between the proportions of treatment groups will be determined and the corresponding two-sided 95% CIs calculated by Miettinen-Nurminen method. Safety parameters analysis: descriptive statistic on the number (and percentage) of subjects reporting AEs will be calculated.		

Primary Immunogenicity Analysis:

The noninferiority of QIVc compared to the US-licensed QIV will be assessed by HAI GMT and HAI Seroconversion rates against cell-derived target viruses for A/H1N1, B/Victoria and B/Yamagata strains and by MN GMT and MN seroconversion rates against cell-derived target virus for H3N2 strain. All eight primary hypotheses need to be met in order to demonstrate noninferiority.

Specifically, QIVc will be considered to be noninferior to the US-licensed QIV if, for each of the four strains, the following statistical criteria are met:

***A/H1N1 and B strains*:**

- The upper bound of the two-sided 95% confidence interval (CI) on the ratio of the HAI GMTs does not exceed 1.5. The HAI GMT ratio will be calculated as HAI GMT US-licensed comparator QIV *divided* by HAI GMT QIVc.
- The upper bound of the two-sided 95% CI on the difference between the HAI SCR does not exceed 10%. The HAI SCR difference will be calculated as HAI Seroconversion US-licensed comparator QIV *minus* HAI Seroconversion QIVc. The 95% CI will be computed based on the binomial distribution.

***A/H3N2 strain only*:**

- The upper bound of the two-sided 95% CI on the ratio of the MN GMT does not exceed 1.5. The MN GMT ratio will be calculated as MN GMT US-licensed comparator QIV *divided* by MN GMT QIVc.
- The upper bound of the two-sided 95% CI on the difference between the MN SCRs does not exceed 10%. The MN SCR difference will be calculated as MN Seroconversion US-licensed comparator QIV *minus* MN Seroconversion QIVc. The 95% CI will be computed based on the binomial distribution.

To determine the GMT ratio, a general linear model (GLM) will be fitted on log-transformed postvaccination HAI (or MN) titers and terms for covariates (with further details specified in the protocol and Statistical Analysis Plan [SAP]).

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 4 strains will be analysed separately. The adjusted GMT ratio will be the result for which the noninferiority assessment will be based on.

Secondary Immunogenicity Analysis:
Secondary immunogenicity analyses of GMT, GMRs, seropositivity rates, percentages of subjects with HAI titer ≥ 1:40, SCRs, GMT ratios, and SCR differences will be carried out in a similar fashion as in the primary immunogenicity analyses.

Statistical Considerations for Sample Size Calculations

QIVc will be tested against comparator, ie, US-licensed comparator QIV. The treatment randomization ratio is 2:1 (Seqirus QIVc: Comparator QIV). This study is designed to achieve at least 90% power to demonstrate noninferiority for all of the 8 endpoints: seroconversion rates for 4 strains and GMT ratios for 4 strains using a one-sided alpha of 0.025 for each comparison. No alpha adjustment for multiple endpoints needs to be made.

For comparisons of SCRs, a noninferiority margin of 10% (Comparator QIV-Seqirus QIVc) will be employed. It is assumed that the SCRs for A/ H1N1, B strains, and A/H3N2 based on TIVc are 81%, 69% and 85%, respectively. These estimates are based on the historical data, namely from study V58P16.

It is also assumed that the expected differences between antibody titers (QIVc minus QIV) are consistent with the SCR differences reported as per V58P16, namely 7% for A/H1N1 and 5% for A/H3N2 (based on the MN assay). It is assumed there is no difference between Seqirus QIVc and the comparator QIV for the B strain.

For comparison of GMT ratios, a noninferiority margin of 1.5 (Comparator QIV/ Seqirus QIVc, equivalent to a difference on the log scale of 0.405465108) will be employed. It is assumed that the GMT ratios for A/ H1N1, A/ H3N2, and B strains for QIVc/QIV are 1.49 for the A/H1N1, 1.00 for the A/H3N2 (based on the MN Assay), and 0.84 for the B strains. These GMT ratio estimates are consistent with those observed in study V58P16. It is assumed that the standard deviation of log (titer) is 1.3.

Under these assumptions and with n evaluable = 1450 in the Seqirus QIVc group and 725 in the Comparator QIV the power for 4 GMT ratio endpoints is 94.90 % and the power for 4 SCR endpoints is 99.40%. The overall global power of the 8 endpoints is then 94.90%*99.40% = 94.33%. This provides a total N evaluable = 2175. Allowing for a 10% drop-out, N=2418 subjects will be recruited for immunogencity evaluation.

Approximately 84 additional subjects between 24 through 47 months of age, in order to have approximately 50 evaluable subjects who received QIVc and approximately 25 evaluable subjects who received US-licensed QIV, will be enrolled to assess CMI response. Thus, a total of approximately 2502 subjects will be enrolled in this study.

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus	V130_10	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) US-licensed Egg-Based Quadrivalent Influenza Vaccine (QIV)

Sample size calculations were performed using PASS v12.0.02.

Success Criteria for the Primary Immunogenicity Objectives:

The study is considered successful if all of the 8 co-primary endpoints are achieved.

Further details regarding the analysis of the secondary and exploratory objectives will be fully described in the SAP.

Interim Analysis:

The final analysis of the primary and secondary immunogenicity endpoints will be conducted on cleaned and locked data once all subjects have completed all immunogenicity assessments (end of treatment period, i.e. up to 28 days following the last vaccination dose). At this time, the analysis of all solicited adverse events and of unsolicited adverse events reported during the treatment period will also be conducted. These results will be used to prepare a Clinical Study Report (CSR) with treatment period data. No individual unblinded listings will be generated at this stage.

A final CSR will present all clinical study data collected up to 180 days following the last vaccination dose, including safety data collected during the follow up period.

Data Monitoring Committee:

A Data Monitoring Committee (DMC) will be not utilized for the study.

Table 1-1 Time and Events Table – Previously Vaccinated Subjects

	Treatment Period			Follow-up Period	
	Clinic Visit	Reminder Phone Call	Clinic Visit	Safety Phone Call	Safety Phone Call
Visit Number	V1		V2	V3	V4
Study Day		V1 + 2	V1 + 28	V1 + 90	V1 + 180
Study Day Window	n/a	-1/+1	0 to +7	0 to + 7	0 to + 14
Informed Consent [a]	X [b]				
Medical History	X [b]				
Physical Examination and Clinical signs	X [b, c]		X		
Exclusion/Inclusion Criteria	X [b]				
Randomization	X [b]				
Vaccination	X				
30 Minutes Post Vaccination Assessment	X				
Subject Diary Card Dispensed with Training	X				
Subject Diary Card Reminder Call		X			
Subject Diary Card Reviewed and Collected			X		
Assess all AEs	X		X		
Assess SAEs, NOCDs, AEs leading to withdrawal	X		X	X	X
Assess Relevant Medications/Vaccinations	X		X	X	X
Blood Draw	X [b, d]		X[d]		

Abbreviations: AE = adverse event; n/a = not applicable; NOCD = new onset of chronic disease; SAE = serious adverse event; V = visit.

[a] Confirm consent form(s) signed prior to any procedures. The informed consent process may be conducted earlier, but within 10 days prior to Day 1.

[b] Procedures to be performed prior to vaccination.

[c] Includes measurement of height and weight..

[d] A blood sample will be drawn prevaccination (Day 1) and postvaccination (Day 29) for immunogenicity evaluation or for assessing cell-mediated immunity response.

Table 1-2 Time and Events Table – Not Previously Vaccinated Subjects

	Treatment Period					Follow-up Period	
	Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit	Safety Phone Call	Safety Phone Call
Visit Number	V1		V2		V3	V4	V5
Study Day		V1 + 2	V1 + 28	V2 + 2	V2 + 28	V2 + 90	V2 + 180
Study Day Window	n/a	-1/+1	0 to+7	-1/+1	0 to +7	0 to +7	0 to +14
Informed Consent [a]	X [b]						
Medical History	X [b]						
Physical Examination and Clinical signs	X [b, c]		X		X		
Exclusion/Inclusion Criteria	X [b]		X [b, d]				
Randomization	X [b]						
Vaccination	X		X				
30 Minutes Post Vaccination Assessment	X		X				
Subject Diary Card Dispensed with Training	X		X				
Subject Diary Card Reminder Call		X		X			
Subject Diary Card Reviewed and Collected			X		X		
Assess all AEs	X		X		X		
Assess SAEs, NOCDs, AEs leading to withdrawal	X		X		X	X	X
Assess Relevant Medications/Vaccinations	X		X		X	X	X
Blood Draw	X [b, e]				X [e]		

Abbreviations: AE = adverse event; n/a = not applicable; NOCD = new onset of chronic disease; SAE = serious adverse event; V = visit.

[a] Confirm consent form(s) signed prior to any procedures. The informed consent process may be conducted earlier, but within 10 days prior to Day 1.

[b] Procedures to be performed prior to vaccination.

[c] Includes measurement of height and weight.

[d] Eligibility for subsequent vaccination (see 5.2.2).

[e] A blood sample will be drawn prevaccination (Day 1) and postvaccination (Day 57) for immunogenicity evaluation or for assessing cell-mediated immunity response.

LIST OF ABBREVIATIONS

AE	Adverse Event
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMI	Cell Mediated Immunity
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ESP	External Service Provider
FAS	Full Analysis Set
FDA	Food and Drug Administration
GLM	General Linear Model
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HA	Hemagglutinin
HAI	Hemagglutination Inhibition
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ID	Identification
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IM	Intramuscular
IRB	Institutional Review Board
IRT	Interactive Response Technology
LAR	Legally Acceptable Representative(s)
LLOQ	Lower Limit of Quantification
LSLV	Last Subject Last Visit
MDCK	Madin Darby Canine Kidney
MedDRA	Medical Dictionary for Regulatory Activities
MN	Microneutralization
NA	Neuraminidase
NI	Noninferiority
NOCD	New Onset of Chronic Disease
PFS	Pre-filled Syringes

PPS	Per Protocol Set
QIVc	Cell-derived Quadrivalent Influenza Vaccine
QIV	Quadrivalent Influenza Vaccine
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sBLA	Supplement Biologics License Application
SC	Seroconversion
SCR	Seroconversion Rate
SDA	Source Document Agreement
SOC	System Organ Class
SOP	Standard Operating Procedure
TIV	Trivalent Influenza Vaccine
USPI	US Package Insert
WHO	World Health Organization

LIST OF DEFINITIONS

Any Type A and/or B strain: Defined as any strains included in the vaccine, ie, Type A (A/H1N1 or A/H3N2) and/or Type B

Follow-up period: The follow-up period starts for subjects 28 days after last vaccination and continues up to study completion visit, defined as end of influenza season but at least 180 days after last vaccination date.

End of Study: End of study is defined as the completion of the Last Subject Last Visit (LSLV), i.e, the last subject's Day 181 or Day 209 safety assessment call, or the completion of testing of biological samples to be achieved no later than 8 months after LSLV, whichever is longer

Geometric Mean Titer ratio (GMT ratio): Defined as the geometric mean of the post vaccination (28 days after last vaccination) HAI titer for the US-licensed QIV over the geometric mean of the post vaccination HAI titer for QIVc.

Legally Acceptable Representative (LAR): An individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial (see International Conference on Harmonisation-Good Clinical Practice [ICH-GCP], ICH E6 (R2)).

Lower limit of quantitation (LLOQ) : The lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy.

Not previously influenza vaccinated subject: A subject that has not received 2 or more doses of influenza vaccine prior to the current influenza season, or who does not know the influenza vaccination history.

Previously influenza vaccinated subject: A subject with a known history of at least 2 influenza doses prior to the current influenza season.

Qualified healthcare professional: Any licensed health care professional who is permitted by institutional policy to perform clinical interventions and assessments such as physical examinations, is trained on the study procedure(s) and who is identified within the site signature and delegation log.

Seroconversion Rate (SCR) based on the HAI assay: Seroconversion rate (SCR) defined as the percentage of subjects with either a prevaccination hemagglutinin inhibition (HAI) titer <1:10 and a postvaccination HAI titer ≥1:40, or a prevaccination HAI titer ≥1:10 and a ≥4-fold increase in post vaccination HAI titer.

Seroconversion rates (SCRs) based on the Microneutralization (MN) Assay: SCR is the percentage of subjects with either a prevaccination MN titer <1:10 (LLOQ) and a postvaccination MN titer ≥1:40 (4*LLOQ), or a prevaccination MN titer ≥1:10 (LLOQ) and a ≥4-fold increase in postvaccination MN titer.

Solicited adverse events: Either solicited local adverse reactions or solicited systemic adverse reactions.

Trained healthcare professional: Any health care professional who is permitted by institutional policy, trained to perform delegated tasks, is trained on the study procedure(s) and who is identified within the site signature and delegation log.

Treatment period: Per protocol treatment period begins at the time of vaccination and ends 28 days after last vaccination, which is visit 2 for previously influenza vaccinated subjects and at visit 3 for not-previously influenza vaccinated subjects.

1. BACKGROUND AND RATIONALE

1.1 Background

Influenza is an infectious disease caused by the influenza virus, an orthomyxovirus with two clinically relevant types (Type A and B). The disease is characterized by the abrupt onset of respiratory and systemic symptoms, such as fever, cough, sore throat and rhinitis. It occurs in epidemics throughout the northern and southern hemisphere winter months in temperate climates. Influenza Type A/H1N1, A/H3N2, and Type B/Victoria and B/Yamagata strains have circulated and caused disease in humans on a global basis since 1977 (Fiore et al. 2010), with a high susceptibility to severe influenza in children (Izurieta et al. 2000; Bourgeois et al. 2006). Children <5 years, and particularly those <2 years of age, are at high risk of infection and are a priority for annual seasonal influenza vaccination throughout the world (World Health Organization [WHO] 2012; American Academy of Pediatrics Committee on Infectious Diseases 2016). With vaccination as the recommended method to prevent influenza, both childhood influenza disease burden and community viral transmission could be reduced (Mertz et al. 2016).

One of the challenges of protecting children against influenza is providing a vaccine with an antigenic match against the circulating strains in a given influenza season. Since 1983, two evolutionarily distinct lineages of influenza B viruses have co-circulated in the human population globally (Rota 1990) and influenza B viruses account for roughly 20% of total influenza events in all regions of the world (Ciani et al. 2015). As only one B lineage is selected for inclusion in current trivalent influenza vaccines (TIVs) and there has been no demonstrated cross protection between the two lineages (Peltola et al. 2003; Hu et al. 2004), there is the risk of a mismatch for the influenza B strain (Couch, 2007; Belshe, 2010; Orsi et al. 2018). Since patients infected with influenza B are usually younger than patients infected with influenza A, the effectiveness of vaccination in children seems more dependent on adequate matching (Jayasundara et al. 2014; Ciani et al. 2015; Orsi et al. 2018). To address this, quadrivalent influenza vaccines (QIV) were developed containing B strains from both lineages.

Seqirus' Flucelvax Quadrivalent, is a cell based quadrivalent inactivated subunit influenza vaccine (QIVc) prepared from virus propagated in Madin Darby Canine Kidney (MDCK) cells, and approved by the Food and Drug Administration (FDA) for use in children 4 years and older. QIVc has a formulation with 2 influenza A strains and 2 influenza B strains updated annually as recommended by the WHO for a specific influenza season, and addresses the unmet medical need of better vaccine antigenic matching against co-circulating influenza B strains. A shift from egg- to cell-culture based manufacturing platforms has several advantages, allowing for the possibility to work directly with wild-type viruses, avoiding the generation of egg-adaptive mutations in the HA protein, increasing surge capacity in the event of a pandemic, and providing better manufacturing

control through a closed-system fermentation process (Lambert and Fauci 2010). In addition, cell culture-derived influenza vaccines do not require extensive advanced planning and can, in principle, be vital for responding to the threat of an emerging pandemic.

A marketing authorization for TIVc (Flucelvax) was received from the FDA in the United States (US) in November 2012, for use in subjects of 18 years of age and older. A supplemental Biologics License Application (sBLA) to extend the age indication of TIVc to 4 years and above was submitted to the FDA in November 2014. This was followed, in April 2015, by a Biologics License Application (BLA) submission to obtain marketing authorization of QIVc for the prevention of seasonal influenza in both adult and pediatric subjects (≥4 years of age). In May 2016, QIVc was approved by the FDA for use in people 4 years of age and older.

The goal of the current observer-blind, comparator controlled study in children 6 months through 47 months of age is to demonstrate that vaccination with QIVc elicits an immune response that is not inferior to that of a US-licensed QIV containing the recommended strains for the season. Immunogenicity will be evaluated at Day 1 and Day 29 (previously vaccinated subjects) or Day 1 and Day 57 (not previously vaccinated subjects). For noninferiority assessment, the immunogenicity will be evaluated through measurement of serum HAI antibody titers for all influenza strains, except for A/H3N2. Recent evolutionary changes in A/H3N2 hemagglutinin have resulted in the loss of capacity to agglutinate, and therefore the two A/H3N2 endpoints will be assessed using the MN assay.

1.2 Rationale

The purpose of the study is to demonstrate that vaccination with QIVc elicits an immune response that is not inferior to that of an US-licensed QIV containing the same virus strains, in children 6 months through 47 months of age. This randomized, observer-blind, comparator controlled study of Seqirus' QIVc versus a US-licensed QIV is designed to evaluate both safety and immunogenicity of each of the four influenza strains contained in QIVc, in subjects 6 months through 47 months of age. The data from this study will be used to support the licensure of QIVc for use in children 6 months through 47 months of age.

2. OBJECTIVES

2.1 Primary Immunogenicity Objective

1. To demonstrate that vaccination with QIVc elicits an immune response that is not inferior to that of a US-licensed QIV containing the recommended strains for the season, in subjects 6 months through 47 months of age, as measured by hemagglutination inhibition (HAI) assay for A/H1N1, B/Yamagata and B/Victoria strains and by microneutralization (MN) assay for A/H3N2 strain, using cell-derived target viruses.

2.2 Secondary Immunogenicity Objectives

1. To describe the immunogenicity of QIVc and US-licensed QIV by HAI assay for A/H1N1, B/Victoria, and B/Yamagata strains, and by MN assay for A/H3N2 strain, using egg-derived target viruses.

2. To describe the immunogenicity of QIVc and US-licensed QIV by HAI assay for A/H1N1, B/Victoria, and B/Yamagata strains, and by MN assay for A/H3N2 strain, using cell-derived target viruses.

3. To describe the immunogenicity of QIVc and US-licensed QIV by MN assay for A/H1N1, B/Victoria, and B/Yamagata strains, in a subset of subjects

2.3 Secondary Safety Objectives

1. To evaluate the safety and reactogenicity of QIVc and US-licensed QIV

2.4 Exploratory Immunogenicity Objectives

1. To evaluate the homologous cell-mediated immunity (CMI) response, prevaccination and postvaccination, in a small population of subjects.

2. To further describe the immune response to vaccination, additional immunogenicity analyses may be conducted such as HAI assay for A/H3N2 using cell- and egg-derived target virus.

3. STUDY DESIGN

3.1 Overview of Study Design

This multicenter phase 3 clinical study is a randomized, observer-blind, comparator controlled, multicenter study of QIVc versus US-licensed QIV in children 6 months through 47 months of age. Study vaccine administration will be a single dose, or 2 doses 28 days apart, depending on the influenza vaccination history of the subject.

The study will be conducted in approximately 2502 healthy male and female subjects 6 months through 47 months of age: 2418 subjects for immunogenicity evaluation and 84 subjects for evaluation of CMI. Stratification through IRT will be used to ensure a balanced distribution among the age groups, at least 30% of subjects should be 6 through 23 months and at least 30% of subjects should be from 24 through 47 months of age.

After signing of the informed consent by the subject's parent(s)/LAR(s) and undergoing review of medical history, physical examination, review of prior and concomitant medications/vaccinations, and confirmation of subject eligibility, subjects will be enrolled into the study and randomized via an IRT system to receive QIVc or US-licensed QIV in a 2:1 ratio.

The study has a treatment period and a follow-up period. For subjects with a previous influenza vaccination history, the treatment period begins at the time of vaccination and ends 28 days after vaccination and will consist of 2 clinical visits and 1 reminder call to complete the Subject Diary Card. The follow up period begins 28 days after vaccination and ends at the time of study completion visit. For subjects without or unknown previous influenza vaccination history, the treatment period begins at the time of first vaccination and ends 28 days after the second vaccination and will consist of 3 clinical visits and 2 reminder calls to complete the Subject Diary Card, one after each vaccination. The follow-up period begins 28 days after second vaccination and ends at the study completion visit. All subjects, irrespective of previous influenza vaccination history, will receive 1 safety assessment call 90 days after last vaccination during the follow up period and the follow-up period will conclude with a study completion visit (call).

Subjects will provide a serological specimen via a blood draw before vaccination on Day 1 and 28 days after last vaccination. Previously vaccinated subjects will provide a serological specimen on Day 1 and Day 29 (vaccination on Day 1), while not previously vaccinated subjects will provide a serological specimen on Day 1 and Day 57 (vaccination at Day 1 and Day 29). The serological specimen on the day of vaccination will be obtained before vaccination. For the majority of subjects (approximately 2418), immunogenicity will be measured by HAI and MN assays from the serological specimen. In a small group of approximately 84 subjects, evaluation of CMI response will be performed instead of the immunogenicity evaluation.

Currently available influenza vaccines are not licensed below the age of 6 months. This protocol will exclude any subjects who have received influenza vaccine in the past 6 months. Therefore, all eligible subjects below 12 months of age will be considered as not previously vaccinated against influenza for study enrollment.

The final analysis of the primary and secondary immunogenicity endpoints will be conducted on cleaned and locked data once all subjects have completed all immunogenicity assessments (end of treatment period, i.e. up to 28 days following the last vaccination dose). At this time, the analysis of all solicited adverse events and of unsolicited adverse events reported during the treatment period will also be conducted. These results will be used to prepare a Clinical Study Report (CSR) with treatment period data. No individual unblinded listings will be generated at this stage.
A final CSR will present all clinical study data collected up to 180 days following the last vaccination dose, including safety data collected during the follow up period.

Details of the study procedures and assessments are provided in Section 5, Study Procedures and Section 7, Assessments, respectively.

3.2 Study Period

Each subject should expect to participate in the study for 180 days after last vaccination (approximately 6 to 7 months).

3.3 Blinding Procedures

3.3.1 Blinding Methods

The trial is designed as an observer-blind study. During the treatment period of the study designated unblinded nurse(s), physician(s), or other qualified health care professional will be responsible for administering the study vaccine to the subjects. They will be instructed not to reveal the identity of the study vaccines either to the subject's parent(s)/LAR(s) or the investigative site personnel (ie, investigator and study nurse) involved in the conduct of the trial, except in an emergency. The designated unblinded nurse(s) or physician(s) will not take part in evaluating the subject(s) for safety or collect study data after the vaccinations. Vaccines will be assigned administered through an IRT system. Neither the subject's parent(s)/LAR(s) or any of the investigative staff who are involved in the treatments or clinical evaluation of the subject will be aware of the vaccine administered. Vaccine administration should be shielded from the subject's parent(s)/legal guardian(s) and blinded study personnel. The unblinded personnel should not be involved in data collection such as safety assessments and/or physical assessment and should not access the blinded data entry fields. In case of an emergency, the

Investigator can disclose the subject's assigned vaccine. The information can be retrieved from the IRT system either via web or phone (a 24/7 backup service).

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

Investigators, Seqirus study team members, and all External Service Providers (ESPs) who are directly involved in the conduct of the trial or in the analysis of the study results, or have contact with study centers, will remain blinded to the treatment codes until the final database lock at the end of the study. Only biostatisticians conducting the statistical analysis for the treatment period, will have access to the individual treatment codes. No unblinded individual subject level information will be shared with Seqirus and ESP personnel conducting the study until the final database lock. Seqirus study team members preparing the draft CSR with treatment period data will remain blinded to the individual treatment codes.

3.3.2 Planned Unblinding Procedures

The relevant portions of the clinical database will be cleaned and locked after collection of safety and immunogenicity data has been completed for all subjects during the treatment period of the study, i.e. up to 28 days following the last vaccination dose (final treatment period data). Only personnel of the ESP and Seqirus conducting the statistical analysis will have access to the individual treatment codes. This information will not be shared with Seqirus and ESP personnel conducting the study until the follow up safety data has been locked for final analysis. Seqirus study team members preparing the CSR with treatment period data will remain blinded to the individual treatment codes. The results will not be shared with investigators and other site staff.

Safety follow up data will be locked when all subjects have completed all clinical data collected up to 180 days following the last vaccination dose (end of study). The Seqirus Benefit Risk Physician responsible for Sponsor's assessment of adverse events during the follow up phase will remain blinded at individual and group level through the follow up period, until final database lock at study completion. A final clinical study report will present all clinical study data collected up to 180 days following the last vaccination dose, including safety follow up data.

3.4 Data Collection

3.4.1 Data Collected from Subjects

The following data will be collected from each subject over the duration of their study participation:

- Informed Consent
- Demographic Information (see Section 5.1.2, Screening).
- Physical Examination Information (see Section 5.1.2, Screening).
- Adverse Events (see Section 7.1, Safety Assessment).
- Relevant Medical History (see Section 5.1.2, Screening).
- Influenza Vaccination History
- Relevant Concomitant Medications (see Section 5.1.2, Screening and Section 6.5, Prior and concomitant Medications and Vaccines).
- All Vaccination History (see Section 5.1.2, Screening).

All data collected must only be identified using the Seqirus Subject ID, as described in Section 5.1.4, Randomization.

3.4.2 Tools Used for Data Collection

Electronic Data Capture (EDC) system and a paper Subject Diary Card(s) will be used to collect data for this study.

Subject Diary Card

Subjects' parent(s)/LAR will be given a paper diary at their Day 1 clinic visit to complete. The paper diary, hereafter referred to as the Subject Diary Card, should be completed by the subjects' parent(s)/LAR. The Subject Diary Card will be the only source document allowed for solicited local adverse reactions and systemic adverse events (including body temperature measurements), starting after the initial 30-minute postvaccination period, and continuing for a total of 7 Days.

At the Day 29 clinic visit ("previously vaccinated" subjects) or at the Day 29 and Day 57 clinic visit ("not previously vaccinated" subjects) subjects' parent(s)/LAR are to return

the completed Subject Diary Card and the site staff should review the information entered with them. The following additional rules apply to documentation of safety information collected in the Subject Diary Card:

1. No corrections or additions to the information recorded by the subjects' parent(s)/LAR will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the Subject Diary Card must be described as missing in the eCRF.

The following additional rules apply to documentation of Subject Diary Card information collected in the eCRFs:

1. The site must enter all readable entries in the Subject Diary Card into the eCRF, including those values that may be biologically implausible (eg, body temperature: 1000°F).
2. Any illegible or implausible data should be reviewed with the subject's parent(s)/ legally acceptable representative(s). If an underlying solicited or unsolicited adverse event is described on review with the subject's parent(s)/LAR, this should be described in the source document and reported as an unsolicited adverse event in the Adverse Event eCRF (eg, if the subject's parent(s)/LAR(s)above confirms body temperature of 100°F on the day in which body temperature 1000°F was written into the Subject Diary Card, the temperature of 100°F should be recorded in the Adverse Event eCRF and documented in source).
3. Any newly described safety information (including a solicited adverse event) must not be written into the Subject Diary Card and must be described in the study file as a verbally reported adverse event. Any adverse event reported in this fashion must be described as an unsolicited adverse event and therefore entered on the Adverse Event eCRF.

Case Report Forms

This study utilizes electronic Case Report Forms (eCRFs) to collect study-related data from each subject. A trained health care professional is required to enter subject data in the eCRFs in English based on the medical information available in each subject's source record.

Data should be entered into the eCRF in a timely fashion following each subject's clinic visit, study procedure, or phone call. Each subject's Case Report Form (CRF) casebook will be compared with the subject's source records by a Seqirus-approved study monitor (or designee) over the duration of the study in order to ensure data collection accuracy.

3.5 Collection of Clinical Specimens

The following clinical specimens are required to be collected from each subject in this study:

- Blood at the Day 1 and the Day 29 clinic visit (previously vaccinated subjects) or at the Day 1 and Day 57 clinic visits (not previously vaccinated subjects).

Processing of each specimen should be completed by a trained health care professional and in accordance with the study-specific Clinical Specimen Laboratory Manual. Testing of clinical specimens will be performed by a Seqirus designated laboratory. For additional details, see the study-specific Clinical Specimen Laboratory Manual.

Blood Specimen

The total amount of blood collected over the study period per subject will be approximately 16 mL. Approximately 8 mL sample of blood will be drawn from all subjects at Days 1 and 29 (previously vaccinated subjects), or at Days 1 and 57 (not previously vaccinated subjects). In this study, the blood volume will be approximately 8 mL at each time point. See Section 7, Assessments for additional details.

Blood specimen will be analyzed for immunogenicity evaluation (HAI and MN analyses in approximately 2418 subjects) or for assessing CMI response (in approximately 84 subjects from pre-selected sites based on demonstrated capability to process samples for this testing). All 8 mL of the collected blood specimen will be used for HAI and MN analyses in the immunogenicity group. For the CMI response group, approximately 5 mL of the collected blood sample will be used to measure CMI response. Approximately 3 mL of the blood specimen provided in the CMI group will be used to measure immunogenicity. The intention of assessing immunogenicity in the CMI group is to descriptively compare antibody responses between the 2 groups of subjects.

3.6 Stopping/Pausing Guidelines

There are no predetermined stopping rules in this study. Subjects may be withdrawn from the study according to investigator discretion as described in Section 3.8, Premature Withdrawal from Study.

The Sponsor can halt the study at any time. If the study is halted, the Sponsor will promptly notify the health authorities and investigators, who will promptly inform the parent(s)/LAR of study subjects and Institutional Review Board(s) (IRBs) as per local regulations. Further enrollment will only occur after written authorization is provided by the Sponsor in consultation with the health authorities and IRB(s), as appropriate.

3.7 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will not be utilized for the study.

3.8 Premature Withdrawal From Study

A subject may withdraw at any time, or be dropped from the study at the discretion of the Investigator should any untoward effects occur and/or for safety reasons. In addition, a subject may be withdrawn by the Investigator or the Sponsor if he/she violates the study protocol and/or related procedures. The Investigator or study coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an adverse event.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The Investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal. If a subject's parent(s)/LAR(s) wants to withdraw the subject from the study before all doses are administered or prior to the last planned study visit, the subject's parent(s)/LAR(s) will be asked to be followed for safety for the duration of the study. When a subject is withdrawn from the study, the procedures described in Section 5.5.1, Early Termination Visit should be completed whenever possible.

The reasons for premature withdrawal from the study include adverse event, death, withdrawal of consent, lost to follow-up, other, and protocol deviation. These reasons are described in greater detail below.

Adverse Event

For any subject withdrawn from study participation prior to the planned Study Completion Call, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the Adverse Event eCRF page by indicating "Withdrawn from study due to AE." Any ongoing AEs at the time of study withdrawal must be followed until resolution or stabilization.

Subjects who develop an SAE judged to be possibly or probably related to the study vaccine, including hypersensitivity reactions, should not receive subsequent vaccination.

If a medically-attended adverse event occurred, the event should also be reported on the Adverse Event eCRF page (see Section 7.1, Safety Assessment).

Death

For any subject withdrawn from study participation due to death, this should be noted on the Study Completion eCRF and the associated SAE that led to the death must be reported on the SAE page.

Withdrawal of consent

The subject's parent(s)/LAR(s) can withdraw consent for participation in the study at any time without penalty or loss of benefit to which the subject is otherwise entitled. Reason for early termination should be deemed as "withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (ie, reason other than AE). If the subject's parent(s)/LAR intends to withdraw consent from the study, the Investigator should clarify if the subject will withdraw completely from the study or if the subject will continue study participation for safety. If the subject requests complete withdrawal from the study, no further study interventions or data collection will be performed with the subject.

In the US, if a subject's parent(s)/LAR withdraws consent but does not revoke the Health Insurance Portability and Accountability Act (HIPAA) authorization, the Sponsor will have full access to the subject's medical records, including termination visit information. If a subject's parent(s)/ LAR revokes only the HIPAA authorization, the Sponsor will have full access to all of the subject's medical records prior to the date and time of written revocation.

Lost to Follow-Up

For subjects who fail to show up for planned visits (clinic or telephone calls), study staff are encouraged to make at least 3 documented attempts to contact the subject's parent(s)/LAR(s) by telephone and at least 1 documented written attempt to contact the subject's parent(s)/LAR(s) to encourage the completion of study completion procedures. These efforts to contact the subject should be recorded in the source document. The termination date for the subject to be captured on the study completion eCRF page is the date of the last successful contact (clinic visit or telephone) with the subject's parent(s)/LARs.

Other

Examples for subjects withdrawn from the study due to other reasons can include: Sponsor decision to terminate the study, subject meeting a pre-specified withdrawal

criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the Study Completion CRF page and any ongoing AE's at the time of study withdrawal must be followed until resolution/stabilization.

Study Terminated by Sponsor

If the clinical study is prematurely terminated by the Sponsor, the Investigator is to promptly inform the study subjects and IRB and should assure appropriate therapy and follow up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be returned to the Sponsor.

Protocol Deviation

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. In general, subjects associated with protocol deviations may remain in the study unless continuation in the study jeopardizes the subject's health, safety, or rights.

Investigators will apply due diligence to avoid protocol deviations. Under no circumstances should the Investigator contact Seqirus or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the Investigator feels a change to the protocol would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Seqirus and approved by the IRB, it cannot be implemented.

3.9 End of Study

Most clinical trials intended to support the efficacy/immunogenicity and safety of an Investigational Product proceed to full completion of planned sample size accrual.

Evaluation of the primary and secondary immunogenicity objectives requires the testing of biological samples from the study subjects, which can only be completed after all samples are collected. The last samples for the analysis of the primary and secondary immunogenicity objectives will be taken at Day 29 or Day 57. For the purpose of this protocol, end of study is defined as the completion of the Last Subject Last Visit (LSLV), ie, the last subject's Day 181 or Day 209 safety assessment call, or the completion of testing of biological samples to be achieved no later than 8 months after LSLV, whichever is longer.

4. SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

In order to participate in this study, all subjects must meet ALL of the inclusion criteria described:

1. Individuals 6 through 47 months of age on the day of informed consent.
2. Individuals whose parent(s)/ LAR(s) have voluntarily given written informed consent after the nature of the study has been explained according to local regulatory requirements, prior to study entry.
3. Individuals who can comply with study procedures, including follow-up[1].
4. Individual who is in generally good health as per the Investigator's medical judgement.

Prior to receipt of second study vaccination, subjects must be re-evaluated to confirm that they are eligible for subsequent vaccination. If subjects do not meet criteria 3 and/or 4 of the original inclusion criteria listed above, they should not receive additional vaccinations.

4.2 Exclusion Criteria

Each subject must not have:

1. Acute (severe) febrile illness (see Section 4.3 Criteria for Delay of Vaccination).
2. History of any anaphylaxis, serious vaccine reactions or hypersensitivity, including allergic reactions, to any component of vaccine or medical equipment whose use is foreseen in this study.
3. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws. These may include known bleeding disorders, or treatment with anticoagulants in the 3 weeks preceding vaccination.
4. A known history of Guillain-Barre Syndrome or other demyelinating diseases such as encephalomyelitis and transverse myelitis.

[1] A subject and parent(s)/legally acceptable representative(s) are considered to be compliant if the Investigator judges that the subject will complete the Subject Diary Card, return for all the follow-up visits, be available for telephone calls, as scheduled in the study.

5. Abnormal function of the immune system resulting from clinical conditions, which include:
    a. Known or suspected congenital or acquired immunodeficiency.
    b. Systemic administration of corticosteroids (PO/IV/IM) at any dose for more than 14 days, within 90 days prior to informed consent. Topical, inhaled and intranasal corticosteroids are permitted. Intermittent use (1 dose in 30 days) of intra-articular corticosteroids is also permitted.
    c. Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent.
6. Received immunoglobulins or any blood products within 180 days prior to informed consent.
7. Received an investigational or non-registered medicinal product within 30 days prior to informed consent, or intend to participate in another clinical trial during the study.
8. Study personnel, family and household members of study personnel should not participate.
9. Any other clinical condition that, in the opinion of the investigator, might interfere with the results of the study or pose additional risk to the subject due to participation in the study.
10. Received influenza vaccination or has had documented influenza disease in the last 6 months prior to informed consent.
11. Received any other vaccines than influenza vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to study vaccination or who are planning to receive any vaccine within 28 days after study vaccination.

Prior to receipt of second study vaccination, subjects must be evaluated to confirm that they are eligible for subsequent vaccination. If subjects meet any of the original exclusion criteria listed above or experienced severe tolerability issues after first study vaccination, they should not receive additional vaccinations. However, these subjects should be encouraged to continue study participation. This review of eligibility should be documented in the source document and the reason for not administrating a scheduled study vaccine should be documented in the eCRF.

4.3 Criteria for Delay of Vaccination

There may be instances when individuals meet all eligibility criteria for vaccination yet have a transient clinical circumstance which warrant delay of vaccination (ie, body temperature elevation ≥38.0°C / ≥100.4°F) within 3 days prior to intended study

vaccination, or use of antipyretics and/or analgesic medications within 24 hours prior to vaccination. Under such circumstances, a subject may be considered eligible for study enrollment after the above defined window for delay has passed and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible. In these instances, missing the visit window is not considered a protocol deviation.

5. STUDY PROCEDURES

The sections that follow provide an overview of the procedures that are to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either clinic visits or safety assessment call, as specified in Table 5-1 below and in the Time and Events Tables (Table 1-1 and Table 1-2).

Table 5-1 Study Procedures

Visit Category	Procedures
Prevaccination Clinic Visit(s)	Section 5.1, Prevaccination Clinic Visits / Day 1 Prevaccination describes procedures to be followed prior to study vaccination: informed consent, screening, enrollment, and randomization
Vaccination Clinic Visit(s)	Section 5.2, Vaccination Clinic Visit(s) describes procedures to be followed during each clinic visit involving vaccination: vaccination, postvaccination procedures, and postvaccination reminders
Postvaccination Visit(s)	Section 5.3, Postvaccination Visits describes follow-up clinic visits and safety assessment calls
Unscheduled Visit(s)	Section 5.4, Unscheduled Visit(s) describes possible procedures to be followed at an unscheduled clinic visit
Study completion Visit	Section 5.5, Study Completion Visit describes procedures to be followed at the last study visit for a subject (may include early termination visit)

5.1 Prevaccination Clinic Visits / Day 1 Prevaccination

This section describes the procedures that must be performed for each potential subject prior to vaccination, including obtaining informed consent, screening, enrollment and randomization.

5.1.1 Informed Consent

"Informed consent" is the voluntary agreement of an individual or their parent(s)/LAR to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual's parent(s)/LAR must have sufficient knowledge and understanding of the nature of the proposed research, the anticipated risks and potential benefits, and the requirements of the research to be able to make an informed decision.

Informed consent of the parent(s)/LAR following IRB guidance **must** be obtained before conducting any study-specific procedures (ie, all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source document in addition to maintaining a signed and dated version of the informed consent. Additional specifics regarding the informed consent processes are located in Section 13.2, Informed Consent Procedures.

If the parent(s)/LAR are unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature. An "impartial witness" is defined as a person who is independent from study conduct, who cannot be unfairly influenced by those involved with the study, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form (ICF) and any other written information supplied to the subject. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject's parent(s)/LAR(s) and after the subject's parent(s)/LAR(s) has verbally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject's parent(s)/LAR(s) and that informed consent was freely given by the subject's parent(s)/ LAR.

The informed consent process may be conducted within 10 days prior to Day 1.

5.1.2 Screening

After an individual's parent(s)/LAR has consented for the individual to participate in the study and informed consent is signed, sites will manually assign subjects a unique Screening Number. The subject's unique Screening Number will be documented in the Screening and Enrollment Log. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in Section 4, Selection of Study Population, and evaluated during this screening procedure.

Screening procedures will include the following:

1. Demographic data will be collected from the subject, including: date of birth, sex, race, ethnicity, height and weight.

2. The subject's prior influenza vaccination history will be obtained and recorded ("previously vaccinated" or "not previously vaccinated"). The Investigator will request a vaccination card or other documentation of previous vaccination history from the subject's parent(s)/LAR. If available, the card or other documentation will

be copied and placed in the subject's file to serve as source documentation. If documentation of vaccination history is not available, subject's parent(s)/LAR(s) verbal recall of prior vaccination will be recognized as sufficient medical history; this attempt and information must be captured in the source documentation. If the subject's parent(s)/LAR(s) is unable to recall previous vaccination status, then they should be considered "not previously vaccinated."

3. Relevant medical history will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for study participation and previous and ongoing illnesses or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an adverse event that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem.

4. Perform a review of organ systems by interview that queries the subject or subject's parent(s)/LAR(s) as to any complaints the subject has experienced across each organ system. This will be performed before enrollment and used to guide physical examination. The general physical examination is to be performed by a qualified health care professional. Corresponding information is documented in the subject's source documents.

5. If applicable, prior and concomitant medications or vaccinations taken up to 1 month prior to start of study should be collected (refer to Section 6.5, Prior and Concomitant Medications and Vaccines for further details).

6. Collection of clinical signs is to be performed: weight, height and body temperature. If body temperature is ≥ 38.0°C / ≥ 100.4°F at the time of screening, vaccination must be postponed until 3 days after the fever has resolved (see Section 4.3, Criteria for Delay of Vaccination).

7. The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source document and Concomitant Medications CRF. The use of antipyretics/analgesics within 24 hours prior to vaccine administration is a reason to delay study vaccination (see Section 4.3 Criteria for Delay of Vaccination, and Section 6.5, Prior and Concomitant Medications and Vaccines).

8. Prior to vaccination, blood will be drawn from all subjects (Section 5.1.5, Blood Draw).

Measurement and recording of clinical signs, height, weight, and body temperature may be conducted by a trained health care professional (see List of Definitions).

A general physical examination is to be performed by a qualified health care professional (see List of Definitions).

The data described above will be written in the source document and entered in eCRF (see Section 9.1, Source Documentation). Should the physical assessment reveal any abnormal values or events, these must be documented as part of medical history.

In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. The reason for screen failure must be documented in the Screening and Enrollment Log. If the individual is determined to be eligible for the study, he/she will be enrolled into the study.

5.1.3 Enrollment

After signing the informed consent form and review of eligibility criteria, if an individual is determined to be eligible for study participation, the investigator or delegate will enroll the subject and enter subject information and stratification information into the Interactive Response Technology (IRT) system.

5.1.4 Randomization

Enrolled subjects will be randomized in the IRT system by a 2:1 ratio and automatically assigned a unique Subject ID. Subjects participating in the CMI group (approximately 84 subjects) will be enrolled in a limited number of sites through sequential allocation (in principle, subjects in which CMI will be evaluated will be enrolled first). The Subject ID will be the subject's unique identification (ID) number for all eCRFs and associated study documentation that will be used for duration of the study. After randomization, the Screening Number ceases to be used and remains in the Screening and Enrollment Log only. The list of randomization assignments is produced by the EDC/IRT service provider.

Stratification through IRT will be used to ensure a balanced distribution among the age groups, at least 30% of subjects should be 6 through 23 months and at least 30% of subjects should be from 24 through 47 months of age.

For A/H1N1, B/Victoria, and B/Yamagata strains, immunogenicity of QIVc and US-licensed QIV will be evaluated by MN assay in a 20% subset of subjects. After blood specimens have been collected a randomly selected subset (20%) of these samples will be analyzed. Detailed information regarding the randomization procedures associated with the selection of the samples to be analyzed can be found in the Statistical Analysis Plan (SAP).

If for any reason, after signing the Informed Consent Form (ICF), the subject who is eligible and enrolled fails to be randomized, this is called a randomization failure. The reason for all randomization failures should be recorded in the Screening and Enrollment Log and in the source document as specified in the Source Document Agreement (SDA). The information on subjects who are randomization failures should be kept distinct from subjects who are screen failures, as described in Section 5.1.2, Screening.

If for any reason, after randomization the subject fails to undergo treatment, this is an Early Termination and the reason should be recorded in source document as specified in the SDA. The information on these Early Termination subjects should be kept distinct in the source documentation from randomization failures.

5.1.5 Blood draw

After randomization, but prior to vaccination, all subjects will have approximately 8 mL of blood drawn for immunogenicity evaluation or to assess CMI response. Since there are 2 blood draws per subject, the total blood volume drawn per subject in this study is approximately 16 mL. Details regarding the volume of blood and testing to be performed are in Section 3.5. (see Section 3.5, Collection of Clinical Specimens). These data will be written in the source document (see Section 9.1, Source Documentation) and must be documented in the eCRF.

5.2 Vaccination Clinic Visit(s)

Please refer to the Time and Events Tables (Table 1-1 and Table 1-2). Vaccination will be performed on Day 1 (all subjects) and Day 29 ("not previously vaccinated" subjects) using the vaccine identified by the assigned Pack ID.

After completing the prevaccination procedures as described in Section 5.1, Vaccination Clinic Visit – Day 1 Prevaccination Procedures, the vaccine will be administered to the subject according to the procedures described in Section 6.3, Vaccine Preparation and Administration, observing the blinding procedures described in Section 3.3, Blinding Procedures.

Prior to administration of the study vaccination, it needs to be confirmed that the subject is eligible for vaccination and does not meet any criteria for exclusion or delaying study vaccination as described in Section 4, Selection of Study Population.

5.2.1 Day 1 Postvaccination Procedures (All Subjects)

The following postvaccination procedures will be performed:

1. Training should be directed at the individual(s) who will perform the measurements of local reactions and body temperature, and those who will enter the information into the subject diary card. This individual may not be the subject's parent(s)/LAR(s), but if a person other than the subject's parent(s)/LAR(s) enters information into the subject diary card, this person's identity must be documented in the study file and this person must receive training on the diary card. Training of the subject's parent(s)/LAR(s) on how to measure an injection site reaction should be performed while the subject is under observation after vaccination.

   Subject Diary Card instruction must include the following:

   1. The subject's parent(s)/LAR(s) must understand that timely completion of the Subject Diary Card on a daily basis is a critical component to study participation. The subject's parent(s)/LAR(s) should also be instructed to write clearly and to complete the Subject Diary Card in pen. Any corrections to the Subject Diary Card that are performed by the person completing the Subject Diary Card should include a single strikethrough line with a brief explanation for any change. **No changes can be made to the Subject Diary Card after it is returned to the clinic.**
   2. Starting on the day of vaccination, the subject's parent(s)/LAR(s) will check in the evening for specific types of reactions at the injection site (solicited local adverse reactions), any specific generalized symptoms (solicited systemic adverse events), body temperature any other symptoms or change in the subject's health status, and any medications/vaccinations taken (excluding vitamins and minerals). These solicited adverse events and body temperature will be recorded in the "six hours" location on the Subject Diary Card.
   3. Body temperature measurement is to be performed using the thermometer provided by the site. In children younger than 36 months of age, measurement of temperature rectally is preferred. Oral, axillary or tympanic membrane routes may be used in older children. If the subject appears unusually hot or cold during the day, the subject's parent(s)/LAR(s) should check body temperature. If the subject has fever, the highest body temperature observed that day should be recorded on the Subject Diary Card. The measurement of solicited local adverse reactions is to be performed using the ruler provided by the site.
   4. The collection of body temperature, solicited local adverse reactions, solicited systemic adverse events on the Subject Diary Card will continue for a total of 7 days.

2. After vaccination, the subject will be observed for at least 30 minutes including observation for local and systemic adverse events, unsolicited AEs, and body temperature measurement. Please take the opportunity to remind the subject's parent(s)/LAR(s) how to measure solicited adverse events and body temperature as part of this observation

period. Record all safety data collected in the source documents. **The 30-minute observation data must be recorded in the source documents only; not in the Subject Diary Card.**

3. Schedule the next study activities, reminder telephone call, and clinic visit, with the subject's parent(s)/LAR(s).
4. Remind the subject's parent(s)/LAR(s) to complete the Subject Diary Card daily and to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization.

5.2.2 Day 29 Prevaccination Procedures ("not previously vaccinated" subjects)

The following procedures should be carried out at the clinic visit on Day 29 before the vaccination is performed:

1. At the clinic visit, the Subject Diary Card will be reviewed. Please see Section 3.4.2, Tools Used for Data Collection for additional guidance on Subject Diary Card review.

   The qualified health care professional will interview the subject's parent(s)/LAR(s) to obtain information relating to unsolicited AEs including SAEs, AEs leading to study or vaccine withdrawal, NOCDs, associated concomitant medications and all vaccinations (see Section 6.5, Prior and Concomitant Medications and Vaccines). All safety information described by the subject's parent(s)/LAR(s) must be written down in the source documents.

2. Perform a review of organ systems by interview that queries the subject's parent(s)/LAR(s) as to any complaints the subject has experienced across each organ system. This will be used to guide the physical examination. Corresponding information is documented the subject's source documents.
3. Take body temperature. In children younger than 36 months of age, measurement of temperature rectally is preferred. Oral, axillary or tympanic membrane routes may be used in older children. If the body temperature is ≥38.0°C / ≥100.4°F, vaccination must be postponed until 3 days after the fever has resolved. Vaccination is also postponed for any clinically significant active infection based on investigator's clinical judgment (see Section 4.3, Criteria for Delay of Vaccination).
4. The use of any analgesics (oral, topical, etc.) and/or antipyretics within 24 hours prior to vaccination is a reason to delay vaccination (see Section 6.5, Prior and Concomitant Medications and Vaccines). Use of these medications can decrease the immune response to the vaccination. Verify that the subject has not applied topical analgesic/anesthetic to the anticipated injection site within the past 24 hours, as application of

analgesic/anesthetic patch/cream may interfere with the ability to interpret local reactions after vaccination. If topical analgesic/anesthetic has been applied to the area to be injected, the opposite limb that has not been treated with analgesic/anesthetic may be injected. If subject took oral antipyretics and/or analgesic medications within 24 hours prior to vaccination, document this and the reason for their use (prophylaxis versus treatment) in the subject's source record and eCRF.

Prior to receipt of second study vaccination ("not previously vaccinated" children), subjects must be evaluated to confirm that they are eligible for subsequent vaccination. If subjects meet any of the original exclusion criteria (except for those listed under Section 4.2, Exclusion Criteria) or meet any of the criteria listed under Section 4.3, Criteria for Delay of Vaccination, they should not receive additional vaccinations. This reassessment of eligibility should be documented in source documents; if the subjects is found not eligible for the second vaccination, the reason for not administering scheduled vaccine should be documented in eCRF.

5.2.3 Day 29 Postvaccination Procedures ("not previously vaccinated" subjects)

After confirming subject continues to meet study eligibility criteria by completing procedures outlined in Section 5.2.2, Day 29 Prevaccination Procedures (not previously vaccinated subjects) above, perform vaccination of the subject according to the assigned study vaccine and according to the procedures described in Section 6, Treatment of Subjects.

The following postvaccination procedures should be carried out on Day 29:

1. Careful re-training, if necessary, of the subject's parent(s)/LAR(s) on how to measure local reactions and body temperature, how to complete and how often to complete the Subject Diary Card is crucial. Reference Section 5.2.1, Day 1 Postvaccination Procedures (All Subjects) for Subject Diary Card instruction. Any re-training must be recorded in the source documents.
2. After vaccination, the subject will be observed for at least 30 minutes including observation for local and systemic adverse events, AEs, and body temperature measurement. Please take the opportunity to remind the subject's parent(s)/LAR(s) how to measure solicited adverse events and body temperature as part of this observation period. Record all safety data collected in the source documents. **The 30-minute observation data must be recorded in the source documents only; not in the Subject Diary Card.**
3. Schedule/review the next study activities, reminder telephone calls, and clinic visit, with the subject's parent(s)/LAR.

Remind the subject's parent(s)/LAR(s) to complete the Subject Diary Card daily and to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization.

5.2.4 Postvaccination Reminders

Reminder calls or alerts are not intended to be an interview for collection of safety data. If the subject's parent(s)/LAR(s) wishes to describe safety information, this information should only be collected by a healthcare professional at the site, and the safety data described must be written down in the subject's medical chart.

Subject Diary Card Reminder Calls
Subject Diary Card reminder calls will be performed on Day 3 (all subjects) and Day 31 ("not previously vaccinated" subjects). The purpose of this call is to remind the subject's parent(s)/LAR(s) about completion of the Subject Diary Card. The call follows the Subject Diary Card Reminder Telephone Call Script provided to the site. The subject's parent(s)/LAR(s) should be reminded to contact the site to discuss medical questions.

5.3 Postvaccination Visits

Postvaccination visits (clinic visit or safety assessment call) will be performed on Days 29, 91 and 181. ("previously vaccinated" subjects) or on Days 57, 119 and 209 ("not previously vaccinated" subjects). In the event that a scheduled or unscheduled visit or call coincides, procedures may be combined.

5.3.1 Postvaccination Clinic Visits

The following procedures will be performed on Day 29 for "previously vaccinated" subjects and on Day 57 for "not previously vaccinated" subjects:

1. At the clinic visit, the Subject Diary Card will be reviewed. Please see Section 3.4.2, Tools used for Data Collection for additional guidance on Subject Diary Card review. If any other adverse events are reported, this should be discussed with a qualified health care professional.

   The subject's parent(s)/LAR will be interviewed to determine if any unsolicited adverse events (including medically attended AEs, SAEs and AEs leading to study or vaccine withdrawal) occurred and if any concomitant medications or vaccines were taken/received in the time since the last clinic visit. The qualified health care professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Adverse events

reported by the subject's parent(s)/LAR at this follow-up clinic visit must be recorded in the subject's source document and on an Adverse Events eCRF, as specified in Section 7.1, Safety Assessment.

2. Perform a review of organ systems by interview that queries the subject's parent(s)/LAR(s) as to any complaints the subject has experienced across each organ system. This will be used to guide the physical examination. Corresponding information is documented in the subject's source documents.

3. Blood will be drawn (approximately 8 mL) from all subjects for serology testing. Details regarding the volume of blood and testing to be performed are in Section 3.5, Collection of Clinical Specimens.

4. Schedule safety telephone calls on Days 91 and 181 for "previously vaccinated" subjects and on Days 119 and 209 for "not previously vaccinated" subjects.

Remind the subject's parent(s)/LAR(s) to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

5.3.2 Safety assessment calls

Safety assessment calls will be performed on Days 91 and 181 (previously vaccinated subjects) or Days 119 and 209 (not previously vaccinated subjects).

Safety assessment calls are calls made to the subject's parent(s)/ LAR by a qualified healthcare professional designated on the site log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject's parent(s)/LAR(s) will be interviewed according to the script. Safety assessment calls performed on Days 91 and 181 (previously vaccinated subjects) or Days 119 and 209 (not previously vaccinated subjects) will collect information relating to a subset of unsolicited adverse events including SAEs, NOCDs, AEs leading to withdrawal, and concomitant medications or vaccinations associated with those events. All safety information described by the subject's parent(s)/LAR(s) must be written down in a designated location within the source document and not written on the script used for the telephone call.

The subject's parent(s)/LAR(s) will be asked as to whether the subject was hospitalized or was evaluated at an emergency room for any illness since the site's last contact with the subject. If an SAE has been identified by the site staff during the interview which has not previously been reported by the subject's parent(s)/LAR, this SAE will be reported by the site within 24 hours to Seqirus or delegate. Any additional relevant medical history will be reported to Seqirus or delegate and recorded as needed.

The subject's parent(s)/LAR(s) will receive a reminder of the next planned study activity, if applicable. The subject's parent(s)/LAR(s) will be reminded to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit or to a visit to/by a doctor or is otherwise of concern.

5.4 Unscheduled Visit(s)

An unscheduled study visit may be performed as necessary for further evaluation of safety information that is described on the telephone that is to be investigated further at any time during the study.

5.5 Study Completion Visit

Study completion will occur 180 days after last vaccination. For all subjects, the termination visit is a telephone call performed by a qualified health care professional.

The study completion visit will coincide with the safety call on Day 181 (previously vaccinated subjects) or Day 209 (not previously vaccinated subjects). The date of completion is the date of the last contact (telephone call) in which the subject's health status was assessed or, in cases where the subject's parent(s)/LAR(s) does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the Study Completion CRF page. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see Section 5.5.1, Early Termination Visit.

At the Study Completion Visit, the following procedures will be performed:

- Interview the subject's parent(s)/LAR(s) to obtain information regarding potential SAEs, NOCDs, and AEs leading to withdrawal and the medication to treat these
- Ask the subject's parent(s)/LAR(s) as to whether the subject was hospitalized or was evaluated at an emergency room for any illness since the site's last contact with the subject. If an SAE has been identified by the site staff during the interview and has not previously been reported by the subject's parent(s)/LAR(s), this SAE must be reported by the site within 24 hours to Seqirus or delegate. Record any additional relevant medical history as needed.

The site will review with the subject's parent(s)/LAR(s) the plan of when information relating to the subject's participation in the study may be available (eg, study results). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject's parent(s)/LAR(s) chooses to share this information.

The site will complete the study completion eCRF page and this will mark the completion of the subject's participation in the study.

5.5.1 Early Termination Visit

When a subject is withdrawn from treatment or withdraws from the study, the Investigator will notify the Sponsor and, when possible, will perform the procedures listed below. The reason(s) for the early termination will be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were randomized but not treated.

At the clinic visit or during the telephone call, the same procedures will be performed as during the study completion visit, see Section 5.5, Study Completion Visit, if possible.

In addition, the following procedures will be performed:

- Collect and review Subject Diary Card, if applicable.
- Review the subject's safety data (if collection of these was in progress at the time of study completion).

The site will review with the subject's parent(s)/LAR(s) the plan of when information relating to the subject's participation in the study may be available (eg, study results, treatment assignments). It will also be discussed how information relating to the subject's participation in the study will be shared with the subject's healthcare provider, if the subject/subject's parent(s)/LAR(s) chooses to share this information.

The site will complete the termination eCRF page and this will mark the completion of the subject's participation in the study.

6. TREATMENT OF SUBJECTS

All vaccines associated with this study are to be stored separately from other vaccines and medications in a secure location under appropriate storage conditions with temperature monitoring. **All vaccines associated with this study must be checked for expiration date prior to use. Expired vaccines must not be administered to subjects.**

6.1 Study Vaccine(s)

The term 'study vaccine' refers to those vaccines provided by the Sponsor or delegate, which will be evaluated as part of the study objectives. The study vaccines specific to this study are described below.

QIVc

An approximately 0.5 mL dose of QIVc (cell-derived seasonal quadrivalent influenza vaccine) contains nominally 15 μg of hemagglutinin (HA) of each of the 2 influenza type A strains and each of the 2 influenza type B strains for a total of 60 μg of HA in the vaccine. The strain composition will be that recommended by the WHO, Center for Biologics Evaluation and Research (CBER), and Committee for Medicinal Products for Human Use (CHMP) for quadrivalent influenza vaccines contemporaneous to the timing of the study. The full composition of the vaccine is reported in Table 6.1-1.

Table 6.1-1 QIVc Vaccine Composition

Names of Ingredients	Quantity per Dose* (0.5 mL/D; ose)	Function
Active Ingredients Hemagglutinin (HA) and Neuraminidase (NA) antigens from the influenza virus strains recommended by the WHO / CBER/ CHMP for the respective season Strain A1 Strain A2 Strain B1 Strain B2	≥ 15µg HA (per strain)	Influenza Vaccine
Other Ingredients		
Buffer M (PBS) pH 7.2 sodium chloride potassium chloride magnesium chloride hexahydrate disodium phosphate dihydrate **potassium dihydrogen phosphate** **Water for injection**	[redacted] **Up to 0.5 mL**	Isotonic aid Isotonic acid Stabilizer Buffer **Buffer** **diluent**

Abbreviations: CBER = Center for Biologics Evaluation and Research; CHMP = Committee for Medicinal Products for Human Use; HA = hemagglutinin; mg = milligrams; mL = milliliters; µg = micrograms; NA = neuraminidase; QIVc = cell-based quadrivalent influenza vaccination; WHO = World Health Organization

* the quantities indicated in this table reflect the amount in a 0.5 mL dose.

** each dose of Flucelvax Quadrivalent may contain residual amounts of β-propiolactone (<0.5 µg), cetyltrimethlyammonium bromide (≤18 µg), polysorbate 80 (≤1500 µg), MDCK cell protein (≤8.4 µg), protein other than HA (≤240 µg), MDCK cell DNA (≤10 ng), which are used in the manufacturing process. The 0.5 mL pre-filled syringes (PFS) contain no preservative or antibiotics.

US-licensed QIV comparator vaccine:

Afluria Quadrivalent® inactivated influenza virus vaccine

Afluria Quadrivalent® will be used as a US-licensed QIV comparator vaccine. Afluria Quadrivalent® is an inactivated influenza virus vaccine for intramuscular injection. Afluria Quadrivalent® is supplied in a 0.25 mL and a 0.5 mL pre-filled syringe (PFS). For children 6 months through 35 months of age, 0.25 mL dose of vaccine will be administered. For children 36 months through 47 months of age, 0.5 mL will be administered.

For a comprehensive review of Afluria Quadrivalent® please refer to the United States Product Information (USPI) supplied by Seqirus or delegate; this document should be reviewed by the Investigators prior to initiating the study.

6.2 Non-Study Vaccines

Not applicable.

6.3 Vaccine Preparation and Administration

The investigator or designee will be responsible for oversight of the administration of vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site. Expired vaccines must not be administered.

QIVc will be provided in pre-filled syringes (PFS), with an injectable volume of approximately 0.5 mL. Afluria Quadrivalent is supplied as a 0.25 mL and a 0.5 mL PFS. The full volume contained in the PFS is to be administered.

Standard immunization practices are to be observed and care should be taken to administer the injection intramuscularly into the anterolateral region of the thigh (for subjects 6 through 11 months, in general) or in the deltoid region (for subjects ≥12 months, in general).

Detailed vaccine preparation and administration instructions will be provided to investigators prior to study start.

It is recommended that 25 gauge, 25 mm (1 inch) of length needle is used for the vaccine administration.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:
Prior to vaccination, subjects must be determined to be eligible for study vaccination and it must be clinically appropriate in the judgment of the investigator to vaccinate. Eligibility for vaccination prior to first study vaccine administration is determined by evaluating the entry criteria outlined in protocol Sections 4.1, Inclusion Criteria and 4.2, Exclusion Criteria.

Eligibility for subsequent study vaccination is determined by following the criteria outlined in Section 4.3, Criteria for Delay of Vaccination.

The study vaccines should not be administered to individuals with known hypersensitivity to any component of these vaccines.

Standard immunization practices are to be observed and care should be taken to administer the injection: Intramuscularly into the anterolateral region of the thigh (for subjects 6 through 11 months, in general) or in the deltoid region (for subjects ≥12 months, in general). Before administering a vaccine, the vaccination site is to be disinfected with a skin disinfectant (eg, 70% alcohol). Allow the skin to dry. **DO NOT inject intravascularly or intragluteally**.

As with all injectable vaccines, trained medical personnel and appropriate medical treatment should be readily available in case of anaphylactic reactions following vaccine administration. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis must be available.

6.4 Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was not reconstituted as instructed or administered by a different route from the intended route of administration. An overdose of study vaccine (whether accidental or intentional) is defined when a dosage higher than the recommended dosage (as per the QIVc dosing regimen referred to in Section 6.1, Study Vaccine(s) or as per the package insert of Afluria Quadrivalent®) is administered.

Any vaccine administration error or overdose of study vaccine detailed in this protocol must be reported as an adverse event, and if the vaccine administration error or overdose is associated with a SAE, it must be reported as such within 24 hours to the Sponsor.

6.5 Prior and Concomitant Medications and Vaccines

All medications, vaccines and blood products taken or received by the subject within 1 month prior to the start of the study are to be recorded on the Prior and Concomitant Medications eCRF.

In addition, the following are considered prior medications for this protocol: all medication/vaccines described in the inclusion and exclusion criteria of this protocol including:

a) Influenza vaccination in the last 12 months.
b) Systemic administration of corticosteroids (PO/IV/IM) within 90 days prior to informed consent.
c) Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent.

d) Received immunoglobulins or any blood products within 180 days prior to informed consent.

The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source document and Concomitant Medications CRF. The use of antipyretics/analgesics within 24 hours prior to vaccine administration is a reason to delay study vaccination (see Section 4.3, Criteria for Delay of Vaccination).

Medications taken for prophylaxis are those intended to prevent the onset of symptoms. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

Concomitant medications include all medications (including vaccines with the exception of vitamins, minerals and alternative medicines) taken by/administered to the subject at and after enrollment continuing up to the end of the treatment period and must be documented on the Concomitant Medications eCRF. During the follow-up period, all vaccinations should be documented and only those concomitant medications are documented on the Concomitant Medications eCRF if associated with an SAE, NOCDs, or AE leading to study withdrawal.

When recording concomitant medications/vaccines, they should be checked against the study entry and continuation criteria in Section 4, Selection of Study Population to ensure that the subject should be enrolled/continue in the study.

A non-study influenza vaccination(s) is considered a protocol deviation if received during the study and may result in the subject being excluded from the Per Protocol Set (PPS)

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following:

- Supply the study vaccine(s).
- Appropriate labeling of all study vaccines in compliance with the legal requirements of each country where the study is to be performed.
- Appropriate storage and distribution of study vaccines.

The Investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including:
  - Confirmation that the vaccines were received in good condition and in the right amount.
  - Confirmation to the Sponsor that temperature range during shipment from the Sponsor to the Investigator's designated storage location in the correct range (2°C to 8°C / 36°F to 46°F).
  - Report any temperature deviation and do not use vaccines until further confirmation by the Sponsor or delegate that the vaccines are authorized for use.
- Proper storage of the study vaccines, including:
  - Storage in a secure, locked, temperature-controlled location.
  - Proper storage according to the instructions specified on the labels and in the Pharmacy Manual.
  - Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.
- Appropriate management of the study vaccines, including:
  - Non-use of vaccines in case of temperature deviation, prior to receipt of authorization for use from the Sponsor or delegate.
  - Use only in accordance with the approved protocol.
  - Proper handling, including confirmation that the vaccine has not expired prior to administration.
  - Appropriate documentation of administration of vaccines to study subjects including:
    - Date, dosage, batch/lot numbers, expiration dates, unique identifying numbers assigned to subjects and study vaccines, and time of vaccine administration. This information will be maintained in an accountability log that will be reviewed by the site monitor.
    - Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as maintaining records of which and how many vaccines were received, which vaccines were administered to subjects, which vaccines were destroyed at the site, and which vaccines were returned to the Sponsor, as applicable.

- Proper adherence to the local institutional policy with respect to destruction of study vaccines.
- Complete record keeping of study vaccine use, wastage, return or destruction, including documentation of:
  - Copy of the site's procedure for destruction of hazardous material.
  - Number of doses destroyed, date of destruction, destruction code (if available), method of destruction, and name of individual performing destruction.

Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the Sponsor provides written authorization for use. In the event that the use cannot be authorized, the Sponsor will make every effort to replace the vaccine supply. All vaccines used in conjunction with this protocol must be stored separately from normal hospital/practice stocks to prevent unintentional use of study vaccines outside of the clinical study setting.

Monitoring of vaccine accountability will be performed by the study monitor during site visits and at the completion of the study.

At the conclusion of the study, and as appropriate during the course of the study, the Investigator must ensure that all unused study vaccines, packaging and supplementary labels are destroyed locally (upon approval from Sponsor) or returned to the Sponsor.

7. ASSESSMENTS.

7.1 Safety Assessment

The measures of safety used in this study are routine clinical procedures. They include a close vigilance for, and stringent reporting of, selected local and systemic adverse events routinely monitored in vaccine clinical studies as indicators of reactogenicity.

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product at any dose that does not necessarily have to have a causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

The period of observation for AEs extends from the time the subject's parent(s)/LAR(s) signs informed consent until he or she completes the specified safety follow-up period Day 181 (for previously vaccinated subjects) or Day 209 (for not previously vaccinated subjects). AEs occurring after the informed consent form is signed but prior to receiving study vaccine/product will be documented as an AE and recorded within source document. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from "treatment emergent" AEs (AEs occurring after administration of the first study vaccine).

Adverse events are collected as either solicited or unsolicited adverse events. Solicited events are derived from organized data collection systems, such as the Subject Diary Card(s) or interviews.

7.1.1 Solicited Adverse Events

The term "reactogenicity" refers to solicited signs and symptoms ("solicited adverse events") occurring in the hours and days following a vaccination, to be collected by the subject's parent(s)/LAR(s) for a period of 7 days, using a pre-defined Subject Diary Card.

Each solicited adverse reaction and/or event is to be assessed and entered into the Subject Diary Card (see Section 3.4.2, Tools used for Data Collection for more details). Each adverse event is to be assessed by the sponsor according a defined severity grading scale (further details are provided in the SAP). The following solicited adverse events are included in the Subject Diary Card.

Solicited local adverse reactions
Injection site:

- Induration (hardness), in mm
- Erythema (redness), in mm
- Ecchymosis (bruising), in mm
- Tenderness, grading:
    - 0=None
    - 1=no interference with daily activity
    - 2=interferes with daily activity
    - 3=prevents daily activity

Solicited systemic adverse events

- Change of eating habits
    - 0= None
    - 1= Eating less than normal for 1 - 2 feeds / meals
    - 2= Missed 1 or 2 feeds / meals
    - 3= Missed more than 2 feeds / meals
- Sleepiness, grading:
    - 0=None
    - 1=shows an increased drowsiness
    - 2=sleeps through feeds / meals
    - 3=sleeps most of the time and it is hard to arouse him/ her
- Vomiting (throwing up)
    - 0= None
    - 1= 1 - 2 times in 24 hours
    - 2= 3 - 5 times in 24 hours
    - 3= 6 or more times in 24 hours or requires intravenous hydration
- Diarrhea (loose stools)
    - 0= Fewer than 2 loose stools in 24 hours
    - 1= 2-3 loose stools in 24 hours
    - 2= 4-5 loose stools in 24 hours
    - 3= 6 or more loose stools in 24 hours or requires intravenous hydration
- Irritability
    - 0= None
    - 1= Requires more cuddling and is less playful than usual
    - 2= More difficult to settle
    - 3= Unable to console

- Shivering
  - 0= None
  - 1= Present but does not interfere with daily activity
  - 2= Interferes with daily activity
  - 3= Prevents daily activity

Other solicited adverse events-related variables

- Fever derived from measured body temperature (defined as ≥ 38.0°C/≥ 100.4°F). Measurement of temperature with a digital thermometer is preferred. In children younger than 36 months of age, measurement of temperature rectally is preferred. Oral, axillary or tympanic membrane routes may be used in older children.

The study staff must review the data entered into the Subject Diary Card as described in Section 3.4.2, Tools Used for Data Collection and Section 5.3.1, Postvaccination Visits. All solicited local reactions and solicited systemic adverse events are considered causally related to vaccination.

Note: Any solicited adverse event that meets any of the following criteria must be entered into subjects' source document (see Section 9.1, Source Documentation) and also as an adverse event on the Adverse Event eCRF:

- Solicited local or systemic adverse event leading to the subject withdrawing from the study or the subject being withdrawn from the study by the Investigator (adverse event leading to withdrawal, see Section 7.1.3, Evaluation of Adverse Events).
- Solicited local or systemic adverse event that otherwise meets the definition of a serious adverse event (see Section 7.1.4, Serious Adverse Events).
- If a solicited local reaction or solicited systemic adverse event continues beyond day 7 after vaccination, it will also be recorded as an unsolicited AE on the Adverse Event eCRF.

7.1.2 Unsolicited Adverse Events

All unsolicited adverse events need to be collected during the treatment period, which is from informed consent to Day 29 for subjects with a history of previous influenza vaccination, or to Day 57 for subjects with an unknown or without an influenza vaccination history. During the follow-up period, from Day 29 or Day 57 respectively depending on previous influenza vaccination history up to the study completion visit, only those unsolicited adverse events that are either NOCD, lead to withdrawal or are Serious Adverse Events, need to be reported on the Adverse Events eCRF.

An unsolicited adverse event is an adverse event that was not solicited using a Subject Diary Card and that was spontaneously communicated by a subject's parent(s)/LAR(s) who has signed the informed consent form.

Potential unsolicited AE's may be medically-attended (defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider), or were of concern to the subject's parent(s)/LAR. In case of such events, subject's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report the event(s). Unsolicited AE may also be reported during postvaccination clinic visits or safety assessment phone calls. The detailed information about the reported unsolicited AE's will be collected by a qualified health care professional during the interview and will be documented in the subject's source records. Depending on the timing and nature of the event, the AE should be reported in the AE eCRF (see Section 7.1.3, Evaluation of Adverse Events to Section 7.1.5, Methods of Recording Adverse Events and Serious Adverse Events).

An unsolicited AE may be considered a worsening of symptoms or illnesses reported in the Medical History eCRF (see Section 5.1.2, Screening).

7.1.3 Evaluation of Adverse Events

Every effort should be made by the Investigator to evaluate safety information reported by a subject for an underlying diagnosis and to capture this diagnosis as the event in the AE page. In other words, the practice of reporting only symptoms (e.g., "cough" or "ear pain") are better reported according to the underlying cause (e.g., "asthma exacerbation" or "otitis media").

The severity of events reported on the Adverse Events eCRF will be determined by the investigator as:

Mild:	transient with no limitation in normal daily activity.
Moderate:	some limitation in normal daily activity.
Severe:	unable to perform normal daily activity.

The relationship of the study treatment to an AE will be determined by the Investigator based on the following definitions:

1. Not Related

The AE is not related to an investigational vaccine if there is evidence that clearly indicates an alternative explanation. If the subject has not received the vaccine, the timing

of the exposure to the vaccine and the onset of the AE are not reasonably related in time, or other facts, evidence or arguments exist that reasonably suggest an alternative explanation, then the AE is not related.

2. Related

   a. Possibly Related

The administration of the investigational vaccine and AE are considered reasonably related in time and the AE could be explained by exposure to the investigational vaccine or by other causes.

   b. Probably Related

Exposure to the investigational vaccine and AE are reasonably related in time and no alternative explanation has been identified.

The relationship of the study treatment to an unsolicited AE will be determined by the investigator.

Note: solicited AEs will not be evaluated for relationship to study treatment, as solicited events are by default considered as related to study vaccine in this study. Grading for severity of solicited local and systemic AEs is described in the SAP.

Adverse events will also be evaluated by the investigator for the co-existence of any of the other following conditions:

- "Medically-attended adverse event": an adverse event requiring hospitalization, or emergency room visit, or visit to/by a health care provider.
- NOCDs: an adverse event that represents a new diagnosis of a chronic medical condition that was not present or suspected in a subject prior to study enrollment.
- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.

If solicited or unsolicited adverse events have been reported and the subject's parent(s)/LAR(s)indicated that the symptoms required medical attendance or were of concern, the subject's parent(s)/LAR(s) must be contacted for further information.

When the subject's parent(s)/LAR(s) is contacted for any of these reasons, the contact must be documented in the subject's source documentation.

All AEs, regardless of severity, will be monitored until resolution or until the investigator assesses them as chronic or stable. All subjects experiencing AEs - whether considered associated with the use of the study vaccine or not - must be monitored until symptoms

subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. The investigator's assessment of ongoing Adverse Events at the time of each subject's last visit should be documented in the subject's source document.

7.1.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose results in one or more of the following:

- Death.
- Is life-threatening (ie, the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe.
- Required or prolonged hospitalization.
- Persistent or significant disability/incapacity (ie, the event causes a substantial disruption of a person's ability to conduct normal life functions).
- Congenital anomaly/or birth defect.
- An important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above.

Adverse events which do not fall into these categories are defined as non-serious.

It should be noted that a severe adverse event need not be serious in nature and that a serious adverse event need not, by definition, be severe.

Serious adverse events will be captured on the Adverse Events eCRF. All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are determined to be possibly or probably related to the study vaccine should be reported to the Sponsor as related/suspected events.

The relationship of the study treatment to an SAE will be determined by the investigator based on the following definitions:

1. Related/suspected

The SAE is judged by the investigator to be possibly or probably related to the study vaccine on the AE CRF page (see Section 7.1.3, Evaluation of Adverse Events).

2. Not Related

The SAE is not related if exposure to the study vaccine has not occurred, **or** the occurrence of the SAE is not reasonably related in time, **or** the SAE is considered unlikely to be related to use of the study vaccine, i.e. there are no facts (evidence) or arguments to suggest a causal relationship.

The relationship of the study vaccine to an SAE will be determined by the investigator.

In addition, SAEs will be evaluated by the Sponsor or designee for "expectedness." An unexpected AE is one that is not listed in the current Summary of Product Characteristics or the Investigator's Brochure (IB) or an event that is by nature more specific or more severe than a listed event.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the Medical History CRF. If the onset of an event occurred before the subject entered the study (eg, any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical study or was necessary due to a worsening of the pre-existing condition.

7.1.4.1 Adverse Events of Special Interest

Not applicable.

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

Findings regarding Adverse Events must be reported on an Adverse Event /SAE CRF, as specified in Section 7.1.1, Solicited adverse events. All findings in subjects experiencing AEs must be reported also in the subject's source document.

All SAEs which occur during the course of the study, whether considered to be associated with the study vaccination or not, must be reported within the EDC system **within 24 hours of the site becoming aware of the event** to Seqirus or its designee. Specific instructions and contact details for collecting and reporting SAEs to Seqirus will be provided to the investigator.

All SAEs are also to be documented on the Adverse Events CRF. Any medication or other therapeutic measures used to treat the AE will be recorded on the appropriate CRF(s) in addition to the outcome of the AE.

After receipt of the initial report, representatives of Seqirus or its designee will contact the investigator if it is necessary to obtain further information for assessment of the event.

All SAEs must be reported by the investigator to his/her corresponding IRB in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the Sponsor.

Seqirus or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (also known as SUSARs) to the regulatory authority(ies) and the IRB. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to Seqirus or its designee, the Sponsor or designee will communicate the information to the investigator and the Sponsor or designee will be responsible for submitting this information to the IRB and other relevant authorities.

7.1.5.1 Post-Study Events

Any SAE that occurs outside of the protocol-specified follow-up period and is considered to be caused by the study vaccine must be reported to Seqirus or its designee. These SAEs will be processed by Seqirus or its designee as during the course of the study, until 180 days after study completion. Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the investigator.

7.1.6 Pregnancies

Not applicable.

7.1.7 Safety Laboratory Measurements

No scheduled safety laboratory measurements are planned for this study.

7.2 Efficacy Assessment

Not applicable.

7.3 Immunogenicity Assessment

The measure of immunogenicity used in this study are standard, ie, widely accepted and generally recognized as reliable, accurate, and relevant (able to describe the quality and extent of the immune response).

The immunogenicity analyses will evaluate immunogenicity of QIVc measured by the HAI and microneutralization assay by titrating antibodies against the influenza strains

homologous to the seasonal vaccine in the immunogenicity group of subjects (see Section 2.1, Primary Immunogenicity Objective, Section 2.2, Secondary Immunogenicity Objectives, and Table 7.3-1). The homologous cell-mediated immunity (CMI) response will be evaluated in the CMI group of subjects as an exploratory immunogenicity objective. In case of additional exploratory immunogenicity analyses, the immune response will be further characterized similar to the analysis of secondary immunogenicity endpoints.

The time points for the evaluation of antibody responses after vaccination will help to inform how a subject responds to the QIVc vaccine compared to the influenza comparator vaccine at Day 1 (baseline) and 29 (previously vaccinated subjects) or at Day 1 (baseline), and Day 57 (not previously vaccinated subjects) for peak antibody responses to the strains selected for the seasonal vaccine are typically observed after 4 weeks of vaccination. Blood will be drawn for evaluation of CMI at Day 1 and Day 29 (previously vaccinated subjects) or at Day 1 and Day 57 (not previously vaccinated subjects).

HAI antibody responses will be evaluated for A/H1N1 and both B strains, and neutralizing antibody responses will be evaluated for the A/H3N2 strain in the immunogenicity group of subjects (primary immunogencity evaluation). Recent evolutionary changes in A/H3N2 hemagglutinin have resulted in the loss of capacity to agglutinate, and therefore the two A/H3N2 endpoints will be assessed using the MN assay. Cell-derived target virus data will be used for the primary immunogenicity analysis in both assays.

For the secondary immunogenicity evaluation, HAI antibody responses will be evaluated in the immunogenicity group of subjects for A/H1N1 and both B strains, and neutralizing antibody responses will be evaluated for A/H3N2 strains, using egg- and cell-derived target virus in both assays.

Table 7.3-1 Percentage of Subjects in the Immunogenicity Group Evaluation of Cell- and Egg-Derived Target Virus

Strain	Assay	Cell-derived Target Virus	Egg-derived Target Virus
A/H1N1	HAI assay	100%[1]	100%[2]
A/H3N2	MN assay	100%[1]	100%[2]
B/Vic	HAI assay	100%[1]	100%[2]
B/Yam	HAI assay	100%[1]	100%[2]

Abbreviations: HAI = hemagglutination inhibition; MN = microneutralization;
[1] covered by primary objective
[2] covered by secondary objective

Neutralizing antibody responses against A/H1N1 and both B strains will be evaluated in a subset of subjects (20% of total number of subjects enrolled for immunogenicity). Cell-derived target viruses will be used for secondary immunogenicity evaluation of neutralizing antibody responses.

Serology tests conducted for the primary immunogenicity evaluation will be prioritized over tests conducted for the secondary immunogenicity evaluation, which will be prioritized over exploratory immunogenicity testing, as presented in Table 7.3-2.

Testing will be conducted by Seqirus or designated laboratory in a blinded manner towards the treatment arm.

Table 7.3-2 Priority Ranking of Serology Testing in Study V130_10

Strain	Assay	Reagents Source	Priority Rank
A/H1N1	HAI	Cell-derived reagents	1
A/H3N2	MN	Cell-derived reagents	
B/Yamagata	HAI	Cell-derived reagents	
B/Victoria	HAI	Cell-derived reagents	
A/H1N1	HAI	Egg-derived reagents	2
A/H3N2	MN	Egg-derived reagents	
B/Yamagata	HAI	Egg-derived reagents	
B/Victoria	HAI	Egg-derived reagents	
A/H1N1 (subset only)	MN	Cell-derived reagents	3
B/Yamagata (subset only)	MN	Cell-derived reagents	
B/Victoria (subset only)	MN	Cell-derived reagents	
Exploratory testing – A/H3N2	HAI	Cell-derived reagents	4
Exploratory testing – A/H3N2	HAI	Egg-derived reagents	

Abbreviations: HAI = hemagglutination inhibition; MN = microneutralization

8. STATISTICAL CONSIDERATIONS

A complete description of the statistical analyses and methods will be available in the Statistical Analysis Plan, which will be finalized before the database is locked for the treatment period data.

8.1 Endpoints

8.1.1 Primary Endpoint(s).

8.1.1.1 Primary Safety Endpoints

Not applicable.

8.1.1.2 Primary Efficacy Endpoints

Not applicable.

8.1.1.3 Co-Primary Immunogenicity Endpoints

Serum HAI antibody titer against A/H1N1, B/Victoria and B/Yamagata vaccine strains at Day 29/57, using cell-derived target virus:

- Geometric Mean Titer (GMT) by HAI assay
- Seroconversion rate (SCR) defined as the percentage of subjects with either a prevaccination HAI titer <1:10 and a postvaccination HAI titer ≥1:40, or a prevaccination HAI titer ≥1:10 and a ≥4-fold increase in post vaccination HAI titer

Serum neutralizing antibody titer against A/H3N2 vaccine strain at Day 29/57, using cell-derived target virus:

- GMT by MN assay
- SCR defined as the percentage of subjects with either a prevaccination MN titer <1:10 and a postvaccination MN titer ≥1:40 or a prevaccination MN titer ≥1:10 and a ≥4-fold increase in post vaccination MN titer

Derived Variables:

- The GMT ratio (QIV/QIVc) for each strain
- The inter-group difference in the SCRs (QIV minus QIVc) for each strain

The noninferiority of QIVc compared to US-licensed QIV will be assessed for the eight co-primary endpoints of geometric mean titer (GMT) and seroconversion rate (SCR) for each cell-derived target virus strain included in QIVc as follows:

- The GMT ratio for the A/H1N1 strain (HAI assay)
- The GMT ratio for the A/H3N2 strain (MN assay)
- The GMT ratio for the B Yamagata strain (HAI assay)
- The GMT ratio for the B Victoria strain (HAI assay)
- The difference between the SCRs for the A/H1N1 strain (HAI assay)
- The difference between the SCRs for the A/H3N2 strain (MN assay)
- The difference between the SCRs for the B Yamagata strain (HAI assay)
- The difference between the SCRs for the B Victoria strain (HAI assay)

8.1.2 Secondary Endpoints

8.1.2.1 Secondary Safety Endpoints

The measures for assessing safety and reactogenicity are as follows:

1. Percentage of subjects with solicited AEs within 7 days after each study vaccination
2. Percentage of subjects with any unsolicited AEs from Day 1 to Day 29 (in previously vaccinated subjects) and from Day 1 to Day 57 (in not previously vaccinated subjects)
3. Percentage of subjects with any SAEs, NOCDs, AEs leading to withdrawal during the entire study period (ie, from Day 1 to Day 181 for previously vaccinated subjects or from Day 1 to Day 209 for not previously vaccinated subjects).

8.1.2.2 Secondary Efficacy Endpoints

Not applicable.

8.1.2.3 Secondary Immunogenicity Endpoints

Humoral immune response in terms of HAI antibodies against A/H1N1, B/Victoria and B/Yamagata strains, using cell- and egg-derived target virus:

- GMT by HAI assay at Days 1 and 29/57
- Geometric Mean Ratio (GMR), defined as the fold increase in serum HAI GMT postvaccination (Day 29/57) compared to prevaccination (Day 1)
- Seropositivity rates (percentages of subjects with HAI titer ≥1:10) at Days 1 and 29/57

- Percentages of subjects with HAI titer ≥1:40 at Days 1 and 29/57
- SCR by HAI assay

Derived variables:

- The GMT ratio (QIV/QIVc) for each strain
- The inter-group difference in the SCRs (QIV minus QIVc) for each strain

Neutralizing antibody titers against A/H3N2 vaccine strains, using cell- and egg-derived target virus:

- GMT by MN assay at Days 1 and 29/57
- GMR, defined as the fold increase in serum MN GMT postvaccination (Day 29/57) compared to prevaccination (Day 1)
- Seropositivity rates (percentages of subjects with MN titer ≥ 1:10 (LLOQ)) at Days 1 and 29/57
- SCR by MN assay, where SCR for MN is defined as the percentage of subjects with either a prevaccination MN titer <1:10 and a postvaccination MN titer ≥1:40, or a prevaccination MN titer ≥1:10 (LLOQ)) and a ≥4-fold increase in post vaccination MN titer

Derived variables:

- The GMT ratio (QIV/QIVc) for each strain
- The inter-group difference in the SCRs (QIV minus QIVc) for each strain

Neutralizing antibody titers against A/H1N1, B/Victoria and B/Yamagata vaccine strains, in a subset of subjects:

- GMT by MN assay at Days 1 and 29/57
- GMR, defined as the fold increase in serum MN GMT postvaccination (Day 29/57) compared to prevaccination (Day 1)
- Seropositivity rates (percentages of subjects with MN titer ≥1:10 (LLOQ)) at Days 1 and 29/57
- SCR by MN assay

Derived variables:

- The GMT ratio (QIV/QIVc) for each strain
- The inter-group difference in the SCRs (QIV minus QIVc) for each strain

8.1.3 Exploratory Endpoints

8.1.3.1 Exploratory Safety Endpoints

Not applicable.

8.1.3.2 Exploratory Efficacy Endpoints

Not applicable.

8.1.3.3 Exploratory Immunogenicity Endpoints

The CMI responses to vaccination are considered exploratory endpoints in the study. CD4+ T-cell responses will be measured by staining and flow cytometry at baseline (Day 1), and Day 29 (previously vaccinated subjects) or at baseline (Day 1) and Day 57 (not previously vaccinated subjects), in approximately 84 subjects (2:1 ratio, 56 subjects in QIVc and 28 subjects in licensed QIV group） as measured by numbers of cells expressing interferon gamma (IFN-γ), interleukin 2 (IL-2), tumor necrosis factor alpha (TNF-α), and other markers as may be practical within the available volumes of blood/cells (further detailed in the lab manual).

In case of additional exploratory immunogenicity analyses, the immune response will be further characterized similar to the analysis of secondary immunogenicity endpoints.

The analysis of the exploratory endpoints will be fully described in the SAP.

8.2 Success Criteria

The study is considered successful if all the 8 co-primary endpoints are achieved.

8.2.1 Success Criteria for Primary Objective(s)

8.2.1.1 Success Criteria for Primary Safety Objective(s)

Not applicable.

8.2.1.2 Success Criteria for Primary Efficacy Objective(s)

Not applicable.

8.2.1.3 Success Criteria for Primary Immunogenicity Objective(s)

The noninferiority of QIVc compared to the US-licensed QIV will be assessed by the 8 co-primary endpoints of GMT and SCR for the A/H1N1, A/H3N2 and the B strains. Definitions for noninferiority based on endpoints measured by hemagglutination inhibition assay (HAI) are derived from the FDA Guidance on seasonal inactivated influenza vaccines (*Guidance for Industry Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines 2007*). A modified definition will be applied to assessment of the endpoint based on the MN assay. Specifically, Seqirus QIVc will be

considered to be non-inferior to the US-licensed QIV if, for each of the four strains, the following statistical criteria are met:

***A/H1N1 and B strains*:**

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

***A/H3N2 strain only*:**

- The upper bound of the two-sided 95% confidence interval (CI) on the ratio of the MN GMT does not exceed 1.5. The MN GMT ratio will be calculated as MN GMT US-licensed comparator QIV *divided* by MN GMT QIVc.
- 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 QIVc). The 95% CI will be computed based on the binomial distribution

No adjustment for type I error for multiplicity will be made.

8.2.2 Success Criteria for Secondary Objective(s)

8.2.2.1 Success Criteria for Secondary Safety Objective(s)

Not applicable.

8.2.2.2 Success Criteria for Secondary Efficacy Objective(s)

Not applicable.

8.2.2.3 Success Criteria for Secondary Immunogenicity Objective(s)

Not applicable.

8.3 Analysis Sets

There will be 4 analysis populations defined for the study analyses.

8.3.1 All Enrolled Set

All screened subjects who provide informed consent, receive subject ID, and provide demographic and/or baseline screening information, regardless of the subject's randomization and treatment status in the study.

8.3.2 Full Analysis Set

All subjects in the All Enrolled Set who are randomized and receive a study vaccination. The Full Analysis Set (FAS) will be used to produce summaries and listings of subject characteristics.

8.3.3 Safety Set

The Safety Set 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 safety set will be used to produce summaries and listings of all safety data.

8.3.4 Evaluable Set – Immunogenicity Analysis

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

- receive vaccine on Day 1
- provide serology specimens which yield valid serology assay results from both Day 1 and Day 29 (Previously vaccinated subjects) or Day 1 and Day 57 (Not previously vaccinated subjects)
- do not experience a laboratory-confirmed influenza illness between Day 1, Day 29, and Day 57
- do not receive any prohibited medication during the study that is medically assessed to potentially impact immunogenicity results

8.3.5 Per Protocol Set

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

The Per Protocol Set will be the primary population of interest for the primary/secondary immunogenicity analysis and a supporting analysis will be performed using the Evaluable Set. Membership of the PPS will be determined prior to unblinding the study.

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 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 finalized and prior to unblinding.

Examples for subjects excluded due to other reasons than protocol deviations are subjects who withdrew informed consent.

In case of misrandomization with regard to treatment arm, the subject is excluded from the PPS.

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

8.3.6 Subgroups

The immunogenicity analysis will be performed by stratifying for the following subgroups:

- Subjects with a prevaccination HAI titer < 1:10 and prevaccination HAI titer ≥ 1:10
- Subjects with a prevaccination MN titer < LLOQ and prevaccination MN titer ≥ LLOQ
- Subjects with and without recent seasonal influenza vaccine (defined as influenza vaccine within the past 12 months).
- Subjects "previously vaccinated" and "not previously vaccinated."
- Subjects will be additionally analyzed by age, center, gender, race and ethnicity.

Safety analyses will also be performed by age groups and time periods as detailed in the SAP.

8.3.7 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. Clinical study report (CSR)-reportable (major) protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoints, which will be specified in the Protocol Deviation Specifications to this study protocol. In some cases, exclusion of data may be due to a reason other than a protocol deviation, e.g. early termination.

8.4 Statistical Analysis Plan

A complete description of the statistical analyses and methods will be available in the Statistical Analysis Plan (SAP), which will be finalized prior to unblinding.

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, median, minimum and maximum) for age, height, weight, BMI, and comorbidity score at enrollment will be calculated overall and by vaccine groups.

Distributions of subjects by sex, ethnic origin (race, ethnicity), and previous vaccination status will be summarized overall, and by vaccine group.

8.4.1.1 Concomitant Medications

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

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

If a start date for a medication 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.

Medications will be coded using the WHO Drug dictionary.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

Not applicable.

8.4.2.1.1 Analysis of Extent of Exposure

Not applicable.

8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

Not applicable.

8.4.2.1.3 Analysis of Unsolicited Adverse Events

Not applicable.

8.4.2.1.4 Analysis of Safety Laboratory Values

Not applicable.

8.4.2.2 Analysis of Primary Efficacy Objective(s)

8.4.2.2.1 Statistical Hypothesis

Not applicable.

8.4.2.2.2 Analysis Sets

Not applicable.

8.4.2.2.3 Statistical Methods

Not applicable.

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

The primary immunogenicity objective is:

1. To demonstrate that vaccination with QIVc elicits an immune response that is not inferior to that of an US-licensed QIV containing the recommended strains for the season, in subjects 6 months through 47 months of age, as measured by hemagglutination inhibition (HAI) assay for A/H1N1, B/Yamagata and B/Victoria strains and by microneutralization (MN) assay for A/H3N2 strain, using cell-derived target viruses.

8.4.2.3.1 Statistical Hypothesis

Noninferiority of QIVc to US-licensed QIV

The noninferiority of QIVc compared to the US-licensed QIV will be assessed by the 8 co-primary endpoints of GMT and SCR for the A/H1N1, A/H3N2 and the B strains. Definitions for noninferiority based on endpoints measured by HAI are derived from the FDA Guidance on seasonal inactivated influenza vaccines (*Guidance for Industry Clinical Data Needed to Support Licensure of Seasonal Inactivated Influenza Vaccines 2007*). A modified definition will be applied to assessment of the endpoint based on the MN assay. Specifically, Seqirus QIVc will be considered to be noninferior to the US-licensed QIV if, for each of the four strains, the following statistical criteria are met:

***A/H1N1 and B strains*:**

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

***A/H3N2 strain only*:**

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

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

- H0: Ri > 1.5, for any strain
- Ha: Ri ≤ 1.5, for any strain, and
- H0: Di > 10, for any strain
- Ha: Di ≤ 10, for all strain

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

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

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

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

No adjustment will be made for multiple comparisons.

8.4.2.3.2 Analysis Sets

The Per Protocol Set will be used for the primary immunogenicity analysis and a supporting analysis will be performed using the Evaluable Set, as noted in Section 8.3.4. Evaluable Set – Immunogenicity Analysis. 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 between the Per-Protocol Population and the Evaluable Population.

8.4.2.3.3 Statistical Methods

All statistical analyses for HAI (or MN) titers will be performed on the logarithmically transformed (base 10) values. Individual HAI titers below the detection limit (<10) will be set to half of that limit (5). Individual MN titers below the lower limit of quantification (LLOQ), will be set to half of that limit (1/2* LLOQ).

Co-primary immunogenicity endpoints of GMT and SCR for each virus strain contained in the vaccine will be assessed in subjects 6 Months through 47 Months of Age overall.

Primary analysis will be performed in subjects 6 Months through 47 Months of Age for the Per-Protocol Set. The difference in SCRs will be presented with exact 95% (CIs). Each of the four strains will be analyzed separately.

To determine the GMT ratio (adjusted analysis) a general linear model (GLM) will be fitted on log transformed (base ten) postvaccination HAI (or MN) titers as the outcome variable and terms for covariates: vaccine treatment, prevaccination HAI (or MN) titer, age stratum, gender, vaccination history, age-by-vaccine interaction and study site. The complete set of covariates that may be used in the model to calculate the adjusted GMT will be specified in the SAP.

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 analyzed separately. The adjusted GMT ratio will be the result for which the noninferiority assessment of the HAI (or MN) GMT co-primary endpoint will be based on.

The statistical models might be reduced in case they fail to converge. Further details will be provided in the Statistical Analysis Plan.

The complete set of covariates that may be used in the model to calculate the adjusted GMT ratio will include treatment group (2 treatments), age sub-group, gender (male or female), influenza vaccination received prior year (Y or N), prevaccination mean GMT titer (value) and investigator site (site identifier)

The GLM specification is:

*Adjusted Analysis GMT Model: Log-transformed Postvaccination HAI (or MN) Titer = Vaccine + Age Strata + Gender + Vaccination History [y/n] + Log-transformed Prevaccination HAI (or MN) Titer + Site + 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 postvaccination GMT only will also be presented.

Binary data (ie, percentages of subjects with seroconversion and with titer ≥1:40) will be summarized for each group using unadjusted estimates and will be reported together with two-sided exact 95% CIs. No multiplicity adjustment to the CI levels will be implemented.

If all 8 co-primary endpoints fulfilled noninferiority criteria then overall noninferiority of QIV compared to the US-licensed comparator QIV was to be concluded.

Handling of Missing Values for Immunogenicity Data

For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), ie, not informative. Therefore, the immunogenicity and key secondary analyses will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used. Further details of the statistical methods will be provided in the SAP.

8.4.3 Analysis of Secondary Objective(s)

8.4.3.1 Analysis of Secondary Safety Objective(s)

8.4.3.1.1 Analysis of Extent of Exposure

The number of subjects actually receiving the vaccinations will be summarized by vaccine group.

8.4.3.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

All solicited adverse events will be summarized according to defined severity grading scales.

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

Postvaccination solicited adverse events reported for 7 days after each vaccination and will be summarized for the intervals day 1 to 3, day 4 to 7, day 1 to 7 by maximal severity and by vaccine group, excluding the 30-minute measurement, which will be summarized separately. Injection-site erythema, ecchymosis, and induration will be summarized according to categories based on linear measurements: Type I: none (0 mm), any (1 to <10 mm, 10 to 25 mm, 26 to 50 mm, >50 mm); Type II: Grade 0 (<10 mm), any (10 to 25 mm, 26 to 50 mm, >50 mm) (see SAP for further details).

Injection site tenderness and systemic adverse events (except fever) occurring up to 7 days after each vaccination will be summarized according to "mild", "moderate" or "severe" categorization. For the definition of severity grades see Section 7.1.3, Evaluation of Adverse Events of the protocol and SAP.

Each solicited local and systemic adverse event will also be further summarized as "none" versus "any." "Any" will include reactions with a diameter of at least 1 mm.

Implausible measurements (for further definition see SAP) will be left out of the analysis.

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

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

8.4.3.1.3 Analysis of Unsolicited Adverse Events

This analysis applies to all adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in AE CRF, with a start date on or after the date of first vaccination. AE starting prior to the first vaccination will only be listed.

The original verbatim terms used by investigators to identify AEs in the CRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The AEs will then be grouped by MedDRA preferred terms into frequency tables according to system organ class (SOC). All reported AEs, as well as AEs judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group and by interval of study observation (Day 1 to Day 29, Day 29 to Day 181 in "previously vaccinated" subjects and Day 1 to Day 57, Day 57 to Day 209 in "not previously vaccinated" subjects). When an AE occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories:

- SAE
- NOCDs
- Adverse events that are possibly or probably related to vaccine
- Adverse event leading to withdrawal or early termination
- Adverse event resulting in death
- Adverse events leading to a medically-attended visit during the treatment period

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

8.4.3.1.4 Statistical Hypotheses

Not applicable.

8.4.3.1.5 Analysis Sets

Not applicable.

8.4.3.1.6 Statistical Methods

Not applicable.

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

8.4.3.2.1 Statistical Hypothesis

Not applicable.

8.4.3.2.2 Analysis Sets

Not applicable.

8.4.3.2.3 Statistical Methods

Not applicable.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

Characterization of immunogenicity of QIVc

The measures for immunogenicity will be determined by HAI and MN assay for Day 1 and Days 29/57 (depending on influenza vaccination history). HAI will be evaluated in all

subjects, tested against A/H1N1 and both B strains. MN will also be evaluated in all subjects, tested against A/H3N2 strain.

Humoral immune response in terms of HAI antibodies against A/H1N1, B/Victoria and B/Yamagata strains, using cell- and egg-derived target virus:

- GMT by HAI assay at Days 1 and 29/57
- Geometric Mean Ratio (GMR), defined as the fold increase in serum HAI GMTs postvaccination (Day 29/57) compared to prevaccination (Day 1)
- Seropositivity rates (percentages of subjects with HAI titer ≥1:10) at Days 1 and 29/57
- Percentages of subjects with HAI titer ≥1:40 at Days 1 and 29/57
- SCR by HAI assay

Derived variables:

- The GMT ratio (QIV/QIVc) for each strain
- The inter-group difference in the SCRs (QIV minus QIVc) for each strain

Neutralizing antibody titers against A/H3N2 vaccine strains, using cell- and egg-derived target virus:

- GMT by MN assay at Days 1 and 29/57
- GMR, defined as the fold increase in serum MN GMT postvaccination (Day 29/57) compared to prevaccination (Day 1)
- Seropositivity rates (percentages of subjects with MN titer ≥1:10 (LLOQ)) at Days 1 and 29/57
- SCR by MN assay

Derived variables:

- The GMT ratio (QIV/QIVc) for each strain
- The inter-group difference in the SCRs (QIV minus QIVc) for each strain

Neutralizing antibody titers against A/H1N1, B/Victoria and B/Yamagata vaccine strains, in a subset of subjects:

- GMT by MN assay at Days 1 and 29/57
- GMR, defined as the fold increase in serum MN GMT postvaccination (Day 29/57) compared to prevaccination (Day 1)
- Seropositivity rates (percentages of subjects with MN titer ≥1:10 (LLOQ)) at Days 1 and 29/57;
- SCR by MN assay

Derived variables:

- The GMT ratio (QIV/QIVc) for each strain

- The inter-group difference in the SCRs (QIV minus QIVc) for each strain

8.4.3.3.1 Statistical Hypotheses

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

8.4.3.3.2 Statistical Methods

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

Binary data (i.e. percentages of subjects with seroconversion and with titer ≥ 1:40) will be summarized for each group using crude estimates and will be reported together with 2-sided exact 95% CIs. No multiplicity adjustment to the CI levels will be implemented.

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

Further details of the statistical methods will be provided in the SAP.

8.4.4 Analysis of Exploratory Objectives

8.4.4.1 Analysis of Exploratory Safety Objectives

Not applicable.

8.4.4.2 Analysis of Exploratory Efficacy Objectives

Not applicable.

8.4.4.3 Analysis of Exploratory Immunogenicity Objectives

Exploratory immunogenicity endpoints of homologous CMI responses will be summarized using descriptive statistics by treatment group.

In case of additional exploratory immunogenicity analyses, the immune response will be further characterized similar to the analysis of secondary immunogenicity endpoints.

8.5 Sample Size and Power Considerations

QIVc will be tested against comparator, i.e. US-licensed comparator QIV. The treatment randomization ratio is 2:1 (Seqirus QIVc: Comparator QIV). This study is designed to achieve at least 90% power to demonstrate noninferiority for all of the 8 endpoints: seroconversion rates for 4 strains and GMT for 4 strains using a one-sided alpha of 0.025 for each comparison. No alpha adjustment for multiple endpoints will be made.

For comparisons of SCR a noninferiority margin of 10% (Comparator QIV-Seqirus QIVc) will be employed. It is assumed that the SCRs for A/H1N1 , B strains and A/H3N2 based on TIVc are 81%, 69% and 85% respectively. These estimates are based on the estimated SCR rates of historical data, namely from study V58P16.

It is also assumed that the expected difference between antibody titers (QIV minus QIVc) is consistent with the SCR differences reported as per V58P16, namely 7% for A/H1N1 and 5% for A/H3N2 (based on the MN assay).

It is assumed there is no difference between Seqirus QIVc and the comparator QIV for the B/strain.

For comparison of GMT ratio a noninferiority margin of 1.5 (Comparator QIV/ Seqirus QIVc, equivalent to a difference on the log scale of 0.405465108) will be employed for the assessment of the A/H1N1, A/H3N2 and B strains. It is assumed that the GMT ratio's for A/H1N1, A/H3N2 and B strains for QIVc are 1.49 for the A/H1N1, 1.00 for the A/H3N2 (based on the MN Assay) and 0.84 for the B-strain. These GMT ratio estimates are consistent to those observed from protocol V58P16. It is assumed that the standard deviation of log (titer) is 1.3 across all strains.

Under these assumptions and with n evaluable = 1450 in the Seqirus QIVc group and 725 in the Comparator QIV the power for 4 GMT ratio endpoints is 94.90% and the power for 4 SCR endpoints is 99.40%. The overall global power of the 8 endpoints is then 94.90%*99.40% = 94.33%. This provides a total N evaluable = 2175. Allowing for a 10% drop-out, 2418 subjects will be recruited for immunogencity assessment. Approximately 84 additional subjects between 24 through 47 months of age will be enrolled to study CMI response, in order to have approximately 50 and 25 evaluable subjects in the QIVc

and Comparator QIV groups, respectively. Thus, approximately 2502 subjects will be enrolled in this study.

Sample size calculations were performed using PASS v12.0.02.

Table 8.5-1 summarizes the list of all co-primary endpoints with strains, the planned noninferiority margin and underlying assumptions used for the sample size computations.

Table 8.5-1 Summary of Assumptions Used for Sample Size Calculations

NI comparison	**A/H1N1**	**A/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	**81%**	**85%**	**69%**
Power for SCR comparison tests for each strain (%)	**100%**	**100%**	**99.7%**
Global Power for 4 SCR Endpoints	**99.40%**		
Noninferiority Margin for the GMT ratio	1.5	1.5	1.5
Common Standard Deviation of $\log_e$(titer)	1.3	1.3	1.3
Power for GMT ratio tests for each strain (%)	100%	100%	97.42%
Global Power for 4 GMT ratio Endpoints	**94.90%**		
Global Power for 8 Co-primary Endpoints	**94.33%**		

Abbreviations: GMT = geometric mean titer; NI = noninferiority; SCR = serconversion rate.
Sample size calculations were performed using PASS v12.0.02.

8.6 Interim Analysis

No interim analysis is planned for this study. The final analysis of the primary and secondary immunogenicity endpoints will be conducted on cleaned and locked data once all subjects have completed all immunogenicity assessments (end of treatment period, i.e. up to 28 days following the last vaccination dose). At this time, the analysis of all solicited adverse events and of unsolicited adverse events reported during the treatment period will also be conducted. These results will be used to prepare a Clinical Study Report (CSR) with treatment period data. No individual unblinded listings will be generated at this stage.

This analysis constitutes the final analyses of the primary and secondary immunogenicity endpoints and therefore preserves the integrity of the clinical study results.

9. SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

In order to ensure consistency across sites, study monitoring and auditing will be standardized and performed in accordance with the Sponsor's or delegated contract research organization's (CRO) standard operating procedures (SOPs) and applicable regulatory requirements (e.g., FDA, EMA, and ICH guidelines).

Prior to enrollment of the first study subject, Seqirus or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices and all electronic systems. CRFs supplied by the Sponsor must be completed for each enrolled subject (see Section 8.3.1, All Enrolled Set for definition of enrolled subject). Documentation of screened but not enrolled subjects must be maintained at the site and made available for review by the site monitor. Data and documents will be checked by the Sponsor and/or monitor.

9.1 Source Documentation

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The kinds of documents that will serve as source documents will be agreed between Sponsor or delegate and investigator and designees and specified in the SDA prior to subject enrollment.

In addition, source documentation **must** include all of the following: subject identification (on each page), eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of adverse events, documentation of prior/concomitant medication/vaccines, study vaccine receipt/dispensing/return records, study vaccine administration information, any data collected by a telephone conversation with the subject's parent(s)/LAR(s) and date of completion and reason.

The subject's parent(s)/LAR(s) must also allow access to the subject's medical records if available. Each subject's parent(s)/LAR(s) must be informed of this prior to the start of the study and consent for access to medical records may be required in accordance with local regulations.

All safety data reported by subject's parent(s)/LAR(s) must be written down in source documents prior to entry of the data into eCRFs. If there are multiple sources of information (e.g., Subject Diary Card, verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an adverse event, these sources must be identified in the source documents and discrepancies between sources clarified. The

ultimate diagnosis must be justified and written in the source documents, and this diagnosis must be captured in the Adverse Event eCRF.

The Subject Diary Card source data is hosted by an ESP engaged for this study, on behalf of the study investigators. Each investigator will be provided with a certified archive copy of all diary data relating to subjects at that site and must confirm it is readable.

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to enrollment of the first study subject, Seqirus or its designee (e.g., a CRO) will develop a Clinical Monitoring Plan to specify how centralized and/or on-site monitoring, including clinical specimen reconciliation, will be performed for the study. Study progress will be monitored by Seqirus or its designee as frequently as necessary to ensure:

- that the rights and well-being of human subjects are protected
- the reported study data are accurate, complete, and verifiable from the source documents and
- the conduct of the study is in compliance with the current approved protocol/amendment(s), GCP and applicable regulatory requirements

Contact details for the Seqirus team or its designee involved in study monitoring will be provided to the investigator. Study data recorded on CRFs will be verified by checking the CRF entries against source documents in order to ensure data completeness and accuracy as required by study protocol.

Data verification may also be performed through a centralized review of data (e.g., checking for outliers or other anomalies). Additional documents such as the investigator site file, pharmacy records, and informed consent documentation must also be available for review if requested. Arrangements for monitoring visits will be made in advance in accordance with the monitoring plan, except in case of emergency.

The investigator and/or site staff must make source documents of subjects enrolled in this study available for inspection by Seqirus or its representative at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (eg, FDA, EMA and others) and/or IRBs. The investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

10. DATA MANAGEMENT

10.1 Data Entry and Management

In this study, all clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, and physical assessments), safety data, and immunogenicity data will be entered onto electronic case report forms (eCRFs) in a timely fashion by the investigator and/or the investigator's dedicated site staff. Data is entered in eCRF using a secure EDC system and stored on a secure server, which is compliant with Title 21 Part 11 policies of the Code of Federal Regulations (FDA, 1997). The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor or its designated CRO prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the CRFs to verify their accuracy.

Access to the EDC system for data entry or review will require training and distinct individual access code assignments to those site staff members who will be entering study data and those involved in study oversight who may review study data. Data are collected within the EDC system, to which the Sponsor and site monitors have "read only" access.

10.2 Data Clarification

As part of the conduct of the trial, the Sponsor may have questions about the data entered by the site, referred to as queries. The monitors and the Sponsor or its designated CRO are the only parties that can generate a query. All corrections and clarifications will be entered into the EDC system and will be identified by the person entering the information, the reason for the change, as well as the time of the changes made. If changes are made to a previously and electronically signed CRF, the investigator must confirm and endorse the changes.

10.3 Data Protection

Seqirus and its delegate respects the subjects' rights to privacy and will ensure the confidentiality of their medical information in accordance with all applicable laws and regulations.

The Sponsor as Data Controller according to the General Data Protection Regulation ("GDPR") on the protection of individuals with regard to the processing of personal data and on the free movement of such data confirms herewith compliance to GDPR in all stages of Data Management.

11. RECORD RETENTION

Investigators must retain all study records required by Seqirus and by the applicable regulations in a secure and safe facility. The investigator must consult a Seqirus representative before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files.

The sponsor specific essential documents should be retained until at least 2-years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2-years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor (ICH E6 (R2)).

"Essential documents" are defined as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable national regulatory or institutional requirements. (ICH E6 (R2)).

The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed (ICH E6 (R2)).

The principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing. These laboratory samples will be securely stored for future testing at a global Seqirus or Seqirus controlled/contracted facility for up to 15 years and then destroyed, for purposes to conduct additional analyses needed related to the study, or ultimately for future analysis to further understand the immune response to the vaccine or to influenza disease. Only laboratory staff performing the testing will have access to these samples. By signing the ICF, the subject's parent(s)/LAR(s) agrees that samples will be retained for use limited to additional analyses related to this study. If the parent(s)/LAR also agrees to have the subject's samples stored for future testing after the study is completed, this can be indicated on the ICF.

12. USE OF INFORMATION AND PUBLICATION

Seqirus ensures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov, and in compliance with current regulations.

Seqirus also ensures that key results of this clinical study will be posted in a publicly accessible database within the required time-frame from the end of study as defined in Section 3.9, End of Study.

In accordance with standard editorial, ethical practices and current guidelines of Good Publication Practice (Graf, 2009), Seqirus will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement prior to the start of the study. The coordinating investigator will also sign the clinical study report on behalf of the principal investigators (CPMP/EWP/2747/00). Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Seqirus personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Seqirus personnel.

Seqirus must be notified of any intent to publish data collected from the study and prior approval from Seqirus must be obtained prior to submission for publication.

13. ETHICAL CONSIDERATIONS

13.1 Regulatory and Ethical Compliance

The study will be conducted in compliance with the protocol, GCP and applicable regulatory requirement(s).

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations: including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, ICH E6 (R2), and Japanese Ministry of Health, Labor, and Welfare, Seqirus codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Parliament Council 2001, US Code of Federal Regulations, ICH 1997).

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after the subject's parent(s)/LAR(s) provide written informed consent, as described in Section 5.1.1, Informed Consent. Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subject's parent(s)/LAR(s) reviewed and approved by the IRB. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject or LAR of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject's parent(s)/LAR(s). The subject's parent(s)/LAR must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject's parent(s)/LAR **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted up to 10 days prior to vaccination on Day 1. If the subject's parent(s)/LAR is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

Prior to the start of the study, Seqirus will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Seqirus before submission to the IRB and a copy of the approved version must be provided to the Seqirus monitor after IRB approval.

13.3 Responsibilities of the Investigator and IRB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB before study start. Properly constituted IRB/EC is defined in the integrated addendum to ICH E6: ICH Guideline for Good Clinical Practice E6(R2). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to Seqirus before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Seqirus monitors, auditors, Seqirus Clinical Quality Assurance representatives, designated agents of Seqirus, IRBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Seqirus immediately that this request has been made.

The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period.
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period.
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions
- Ensuring that qualified healthcare professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event related to the study.
- If permission to do so is given by the subject's parent(s)/LAR, ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (eg, change in monitor(s), change of telephone number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the IRB for review and approval/favorable opinion,
(b) to the Sponsor for agreement and, if required,
(c) to the regulatory authority(ies).

13.4 Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (eg, change of telephone number(s), logistical changes). Protocol amendments must be approved by Seqirus, health authorities where required, and the IRB. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB approval. Notwithstanding, the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Seqirus should be notified of this action, the IRB at the study site, and, if required by local regulations, the relevant health authority) should be informed within 10 working days.

14. REFERENCE LIST

American Academy of Pediatrics Committee on Infectious Diseases. (2016) Recommendations for Prevention and Control of Influenza in Children, 2016–2017. Pediatrics; 138: e20162527.

Belshe RB. (2010) The need for quadrivalent vaccine against seasonal influenza. Vaccine; 28: D45-53.

Bourgeois FT, Valim C, Wei JC, et al. (2006) Influenza and other respiratory virus-related emergency department visits among young children. Pediatrics; 118(1): e1-8.

Ciani S, Huang QS, Ciblak MA, et al. (2015) Epidemiological and virological characteristics of influenza B: results of the Global Influenza B Study. Influenza and Other Respiratory Viruses; 9(Suppl. 1): 3–12.

Code of Federal Regulations (1997): Food and Drug Administration, U.S. Department of Health and Human Services: Title 21, Part 11: Electronic Records Electronic Signatures. Federal Register 62: 13464

Committee for Medicinal Products for Human Use (CHMP). Note for Guidance on Coordinating Investigator Signature of Clinical Study Reports CPMP/EWP/2747/00 [internet]. London: EMA; 2001. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003656.pdf

Couch RB. (2007) Background and presentation of possible vaccine options. Presented at: Food and Drug Administration, Center for Biologics Evaluation and Research, Vaccines and Related Biological Products Advisory Committee Meeting; February 27-28, 2007; Washington, DC.

European Parliament Council (2001): Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001. Official Journal of the European Communities. L 121/34-44

Fiore AE, Uyeki TM, Broder K, et al. (2010) Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep; 59: 1-62.

Graf C, Battisti WP, Bridges D (2009). Good publication practice for communicating company Sponsored medical research: the GPP2 guidelines. BMJ; 339: b4330

Hu JJ, Kao CL, Lee PI, et al. (2004) Clinical features of influenza A and B in children and association with myositis. J Microbiol Immunol Infect; 37: 95–8.

International Conference on Harmonisation (ICH) (1997) ICH Harmonised Tripartite ICH Guideline for Good Clinical Practices E6 (R2). Federal Register, 62 (90): 25691-25709

Izurieta HS, Thompson WW, Kramarz P, et al. (2000) Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Engl J Med; 342: 232-9.

Jayasundara K, Soobiah C, Thommes E, et al. (2014) Natural attack rate of influenza in unvaccinated children and adults: a meta-regression analysis. BMC Infectious Diseases; 14: 670.

Lambert LC, Fauci AS. (2010) Influenza Vaccines for the Future. N Engl J Med; 363: 2036-44.

Mertz D, Fadel SA, Lam P, et al. (2016) Herd effect from influenza vaccination in non-healthcare settings: a systematic review of randomised controlled trials and observational studies. Euro Surveill; 21: pii=30378.

Orsi A, Colomba GME, Pojero F, et al. (2018) Trends of influenza B during the 2010-2016 seasons in two regions of north and south Italy: the impact of the vaccine mismatch on influenza immunisation strategy. Hum Vaccin Immunother; 14: 523-31.

Peltola V, Ziegler T, Ruuskanen O, et al. (2003) Influenza A and B virus infections in children. Clin Infect Dis; 36: 299–305.

Rota PA. Co-circulation of two distinct evolutionary lineages of influenza type B virus since 1983. Virology 1990; 175: 59-68.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (CBER) (2009): Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (CBER) (2007): Guidance for Industry. Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines.

World Health Organization (WHO). (2012) Weekly Epidemiologic Record; 87: 461-76.

59th World Medical Association General Assembly (October 2008) Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Seoul, Korea.

CLINICAL STUDY PROTOCOL AMENDMENT

Study Number: V130_10

Protocol Title: A Phase 3, Randomized, Observer-Blind, Multicenter, Noninferiority Study to Evaluate Safety and Immunogenicity of a Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) and a United States-licensed Quadrivalent Subunit Influenza Virus Vaccine (QIV) in Healthy Subjects 6 Months Through 47 Months

Amendment Number 3

Revised Protocol version 4.0 issued on 09 DEC 19

The present amendment reflects changes to Protocol version 3 issued on 17 MAY 19

DESCRIPTION OF CHANGE(S) AND RATIONALE:

Study V130_10 has been designed to demonstrate that vaccination with QIVc elicits an immune response that is not inferior to that of an US-licensed QIV in children 6 months through 47 months of age. QIVc is currently approved by the Food and Drug Administration (FDA) for use in children 4 years and older. The data from this study will be used to support the licensure of QIVc for use in children 6 months through 47 months of age. In order to allow for timely submission of this sBLA it was decided to accelerate the V130_10 Clinical Study Report. The final analysis of the primary and secondary immunogenicity endpoints will be conducted once all subjects have completed all immunogenicity assessments (end of treatment period, i.e. up to 28 days following the last vaccination dose). At this time, the analysis of all solicited adverse events and of unsolicited adverse events reported during the treatment period will also be conducted.

This document describes the changes to the V130_10 Study Protocol Version 3.0 that are associated with the above described analysis of data collected during the treatment period.

CHANGE	LOCATION(S) OF CHANGE	RATIONALE FOR CHANGE
The synopsis and study protocol text contain wording explaining that the final analysis of the primary and secondary immunogenicity endpoints will be conducted once all subjects have completed all immunogenicity assessments (end of treatment period). At this time, the analysis of all solicited adverse events and of unsolicited adverse events reported during the treatment period will also be conducted.	Synopsis, Protocol Section 3.1 (Overview of Study Design), Section 8.6 (Interim Analysis)	Acceleration of Clinical Study Report is required for timely sBLA submission to extend the approved age range in the USA from the current 4 years and above to 6 months and above.

CHANGE	LOCATION(S) OF CHANGE	RATIONALE FOR CHANGE
Procedures describing Database Lock and Unblinding of Randomization Code for the Analysis were added to the protocol text.	Protocol Section 3.3.1 (Blinding Methods), 3.3.2 (Planned Unblinding Procedures) of the Study Protocol	Procedures for Database Lock and Unblinding at the end of the treatment period were described because of final analysis of the safety and immunogenicity data collected during the treatment period.
Screening procedures include collection of prior and concomitant medications or vaccinations taken up to 1 month prior to start of study	Section 5.1.2 (Screening)	Correction of typographical error. In version 3.0 of the protocol a 2 months period was erroneously mentioned.
ESP term (External Service Providers) was added to Protocol and List of abbreviations. End of Study definition was added to the List of Definitions	Protocol List of Abbreviations, List of Definitions, Section 9.1 (Source Documentation), Section 3.3.1 (Blinding Methods), Section 3.3.2 (Planned Unblinding Procedures)	The term vendor was replaced by ESP (External Service Provider) consistent with standard list of abbreviations. End of Study was defined in Section 3.9 of version 3.0 of the protocol but was not mentioned in the List of Definitions.