CLINICAL STUDY PROTOCOL V130_12 Version 3.0

A Phase III/IV, Stratified, Randomized, Observer Blind, Multicenter Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of a Cell-Based Quadrivalent Subunit Influenza Virus Vaccine Compared to Non-Influenza Comparator Vaccine in Subjects ≥2 years to <18 Years of Age

A Phase III/IV Efficacy Study with QIVc in pediatric Subjects

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PROTOCOL SYNOPSIS

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus UK Ltd	V130_12	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Meningococcal (Groups A, C, Y, W-135) Conjugate Vaccine (Men ACWY)

Title of Study:

A Phase III/IV, Stratified, Randomized, Observer Blind, Multicenter Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of a Cell-Based Quadrivalent Subunit Influenza Virus Vaccine Compared to Non-Influenza Comparator Vaccine in Subjects ≥2 years to <18 Years of Age

Study Period:	**Clinical Phase:**
Approximately 6 to 9 months	Phase III/IV

Background and Rationale:

Influenza A/H1N1, A/H3N2, and B/Victoria and B/Yamagata lineage strains viruses have circulated and caused disease in humans on a global basis since 1977 (Fiore, 2010). Vaccination is the recommended method to prevent influenza. One of the challenges of protecting individuals against influenza is providing a vaccine with an antigenic match against the circulating strains in a given influenza season. Since 1985, two antigenically distinct lineages of influenza B viruses have circulated globally (Rota, 1990) and there is no cross protection between the two lineages (Peltola, 2003, Hu, 2004). As only one B lineage can be selected for inclusion in current trivalent influenza vaccines, there is the risk of a mismatch for the influenza B strain (Belshe, 2010) (Couch, 2007). A quadrivalent vaccine including both lineages of influenza B would minimize the risk of mismatch of a strain of influenza associated with disease in children. QIVc (cell based quadrivalent influenza vaccine) is a four (4) strain inactivated influenza vaccine based on the manufacturing methods of Flucelvax™/Optaflu™, a trivalent inactivated influenza vaccine. In May 2016, QIVc was approved by the FDA, for use in people aged four years and older. As the issue of antibody correlates of protection remains a point of discussion in the interpretation of responses to influenza vaccines in children, the present study is designed to evaluate the absolute efficacy and safety of the QIVc vaccine as compared to a non-influenza comparator vaccine. Supplemental immunogenicity data will be collected to further

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enhance the understanding of immune responses to QIVc vaccination. This study is a regulatory requirement to support the licensure of QIVc for use in children ≥4 years of age in the United States (US). Children ≥2 years of age are enrolled in this study to further evaluate QIVc in a broader age range and to support submissions in various global regions.

The purpose of this study is to demonstrate the efficacy (absolute vaccine efficacy [aVE]), immunogenicity, and safety and tolerability of QIVc compared to non-influenza comparator vaccine in subjects ≥2 years to <18 years of age. If there is more than one season, data from all seasons will be combined.

Efficacy Objectives:

Efficacy will be evaluated in all subjects in relation to cases occurring >14 days after last vaccination and until the end of the influenza season.

Primary Efficacy Objective(s):

To demonstrate absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by first occurrence RT-PCR or culture confirmed influenza, due to any influenza Type A and B strain in subjects ≥2 years to <18 years of age.

In case of successful demonstration (see section 8.2) of the primary efficacy objective:

Co-Primary Efficacy Objective(s):

To demonstrate absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by first occurrence RT-PCR or culture confirmed influenza, due to any influenza Type A and B strain in subjects ≥3 years to <18 years of age.

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Secondary Efficacy Objective(s):

The following objective will be evaluated in the age cohorts: ≥3 years to <9 years of age, ≥2 years to <9 years of age, and ≥ 9 to < 18 years of age:

1. To demonstrate absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by first occurrence RT-PCR or culture confirmed influenza, due to any influenza Type A and B strain.

The following objectives will be evaluated in the age cohorts: ≥3 years to <18 years of age, ≥2 years to <18 years of age, ≥3 years to <9 years of age, ≥2 years to <9 years of age, and ≥ 9 to < 18 years of age:

2. To demonstrate absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by first occurrence RT-PCR influenza, due to any influenza Type A and B strain.

3. To demonstrate absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by first occurrence culture confirmed influenza, due to any influenza Type A and B strain.

4. To demonstrate absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by first occurrence culture confirmed influenza, caused by influenza strains antigenically matched to the strains selected for the seasonal vaccine

Exploratory efficacy objective:

The following objective will be evaluated in the age cohorts: ≥3 years to <18 years of age, and ≥2 years to <18 years of age:

To further characterize the efficacy of QIVc, with specific attention for all-cause mortality, all-cause pneumonia and all-cause otitis media

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Secondary Immunogenicity Objectives:

The following objective will be evaluated in a subset of subjects in the age cohorts: ≥3 years to <9 years of age, and ≥2 years to <9 years of age:

To characterize the immunogenicity of QIVc by haemagglutination inhibition (HI) assay 3 weeks after last vaccination.

Exploratory Immunogenicity Objective:

The following objective will be evaluated in a subset of subjects in the age cohorts: ≥3 years to <9 years of age, and ≥2 years to <9 years of age:

To further characterize the immune response, additional immunogenicity analyses may be conducted using other assays such as microneutralization (MN).

Secondary Safety Objective:

To assess the safety and tolerability of QIVc.

Study Design:

This is a phase III/IV, stratified, randomized, observer blind, multicenter clinical study to evaluate the efficacy, safety and immunogenicity of a cell-based quadrivalent subunit influenza virus vaccine compared to non-influenza comparator vaccine in subjects ≥2 years to <18 years of age.

In this study, a total of 7,692 healthy male and female subjects aged ≥2 years to <18 years of age are planned to be enrolled. Follow-up period of active influenza-like illness (ILI) surveillance is until the end of the influenza season.

After signing of the informed consent by the subject's parent or legal guardian (and where applicable according to local regulations, informed consent (assent) signed by subjects above the specified age) and undergoing review of medical history, physical

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examination, review of prior and concomitant medications/vaccinations, and confirmation of subject eligibility (including pregnancy testing for female subjects of childbearing potential), subjects will be enrolled into the study and randomized via an interactive response technology (IRT) system to receive QIVc or a US licensed non-influenza comparator vaccine. Randomized subjects will be stratified in two age cohorts: ≥2 years to <9 years of age and ≥9 years to <18 years of age. Subjects between ≥2 to <9 years of age will then be further stratified by previous influenza vaccine status as "previously vaccinated" and "not previously vaccinated".

"Previously vaccinated" subjects are defined as any child 9 years of age and older, and any child under the age of 9 years who has received 2 or more doses of seasonal influenza vaccine before or during the last influenza season. The two previous doses need not have been given during the same season or consecutive seasons. "not previously vaccinated" subjects are defined as any child under the age of 9 years who did not receive 2 or more doses of seasonal influenza vaccine before or during the last influenza season and any child under the age of 9 years with unknown influenza vaccination history.

Subjects ≥2 to <9 years of age who are "not previously vaccinated" will receive two (2) vaccinations separated by approximately 28 days. Subjects ≥2 to <9 years of age who are "previously vaccinated" and subjects ≥9 to <18 years of age will receive one (1) vaccination. A subset of subjects will be selected to participate in an assessment of immunogenicity, balanced by vaccination status and assigned vaccination allocation (see below, number of subjects planned). Solicited adverse events will be collected for all subjects.

After randomization, all subjects will receive a dose of 0.5 mL of study vaccine to which they were assigned (QIVc or non-influenza comparator vaccine) on Day 1, administered intramuscularly in the deltoid muscle, preferably of the non-dominant arm. For those subjects who are "not previously vaccinated" a second dose will be given on Day 29, as presented below:

Subjects	QIVc Group	Comparator Group
"previously vaccinated" ≥2 years to <9 years of age, and ≥9 years to <18 years of age	Day 1: QIVc	Day 1: Men ACWY
"not previously vaccinated" ≥2 years to <9 years of age	Day1: QIVc Day 29: QIVc	Day 1: Men ACWY Day 29: Saline

Saline is administered for blinding purposes. To maintain the observer-blind design of the study, the roles and responsibilities of "blinded" and "unblinded" team members will be defined. After vaccination, safety assessments and study related procedures and monitoring thereof must be performed by "blinded" team members.

After each vaccination, all subjects will remain under medical supervision at the study site for at least 30 minutes to be monitored and evaluated for adverse events (AEs). The parent/legal guardian or a designated person (e.g., caregiver) will be instructed on the measurement of local and systemic solicited adverse events, including body temperature (preferably oral), and on the completion of the Subject Diary cards. A Subject Diary will be used to describe solicited local and systemic adverse events that may occur post-vaccination from Day 1 through Day 7 (all subjects) and Day 29 through Day 35 ("not previously vaccinated" subjects). Any adverse event and concomitant medication use after vaccination will be collected from Day 1 to Day 22 during the Day 22 clinic visit ("previously vaccinated" subjects) and from Day 1 to Day 50, during the Day 29 and Day 50 clinic visit ("not "previously vaccinated" subjects). Information collected at these visits will be documented in the subject's source records and captured in the electronic Case Report Form (eCRF). All subjects will also receive an ILI booklet on Day 1, and they (or the parent/legal guardian or a designated person) will be instructed to measure their body temperature using the thermometer provided, starting from onset day of protocol defined ILI to the day they come in to the clinic for the Nasopharyngeal (NP) swab collection. The ILI booklet will be returned at the time of their NP visit.

During the remaining follow-up phase of the study (up to Day 181 for "previously vaccinated" subjects or Day 209 for "not previously vaccinated" subjects, or until the end of influenza season, whichever is longer), safety data including adverse events leading to withdrawal, New Onset of Chronic Diseases (NOCDs), Serious Adverse Events (SAEs), ILIs and all medications use related to these events will be captured via safety phone calls as described in the time and events table.

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As the nature of safety data reporting differs in younger and older pediatric populations, solicited adverse events reflected on the diary card will be age appropriate in each of two (2) age groups: subjects ≥2 to <6 years of age and subjects ≥6 to <18 years of age.

For each "previously vaccinated" subject, two visits (Day 1, Day 22), one reminder telephone call after vaccination to remind the parents/legal guardians to complete the diary card (Day 3) and two safety follow-up telephone calls (Day 91 and Day 181, or end of season, whichever is longer) are planned. Influenza surveillance will be performed weekly and during planned visits, during influenza season.

For each "not previously vaccinated" subject, three visits (Day 1, Day 29, Day 50), two reminder telephone calls after each vaccination to remind the subject and/or the parents/legal guardians to complete the diary card (Days 3, Day 31), and two safety follow-up telephone calls (Day 120 and Day 209) are planned. Influenza surveillance will be performed weekly and during planned visits, during influenza season.

In addition, all subjects may have additional unscheduled visits if they meet pre-defined study criteria for the unscheduled visit.

A subset of the ≥2 to <9 years of age cohort will have blood drawn before each vaccination and at 3 weeks after last vaccination (resulting in 2 blood draws per subject in "previously vaccinated" subjects, and 3 blood draws per subject in "not previously vaccinated" subjects). Blood drawn in these subsets will be evaluated for antibody responses as measured by immunogenicity.

Weekly active influenza contacts for ILI will be conducted from Day 1 until the end of influenza season, or until early discontinuation.

Subjects who show clinical signs of influenza (see ILI case definition) will have an unscheduled visit in order to have a nasopharyngeal (NP) swab (or oropharyngeal swab if collection of NP swab is not feasible) collected for evaluation of the presence of influenza virus, and a safety follow-up call 30 days after ILI onset to determine if subsequent medically-attended adverse events occurred and concomitant medication

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associated with these events were used. The NP swab should be collected as soon as possible, preferably within 3 days, but up to 6 days following the onset of protocol defined ILI symptoms. In case ILI symptoms are present during a scheduled clinic visit, then the NP swab may be collected at this visit. NP swabs will be evaluated by RT-PCR and culture at a central laboratory, followed by characterization of the influenza strains as "vaccine strains" versus other influenza strains. RT-PCR and culture confirmed influenza cases will be evaluated within specific timeframes of first and second study vaccination.

Total length of subject participation is 180 days after last vaccination, or until the end of influenza season, whichever is longer.

Laboratory confirmed influenza cases will be reviewed on a regular basis (blinded review). After the majority of cases for the second season have been collected, and after observing at least 50% of planned events meeting the co-primary endpoint, an interim analysis for efficacy and futility will be performed by a Data Monitoring Committee (DMC). Stopping rules for futility and efficacy and any additional details regarding the DMC will be defined in the SAP and in the DMC Charter, including how the interim analysis will assess the primary objective. These two influenza seasons are defined as the first 2 influenza seasons after study start but no later than through April 2018, guided by influenza seasonality and peak season in Northern Hemisphere.

As the circulation of influenza viruses is seasonal and the rates of influenza are difficult to predict, this study is group sequentially designed with one or more interim analyses planned over the course of the study. The goal of Interim Analyses is, first, to minimize the risk of not being able to take a significant test decision after the end of the study, and second, to be able to stop the study for early evidence of efficacy or for futility after observing at least 191 of planned lab-confirmed influenza cases.

If the number of influenza cases is less or equal to 190 (minimum number of cases to indicate efficacy or futility), no interim analysis for efficacy and futility will be done and the study will be extended to an additional influenza season.

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If the number of influenza cases in the cohort ≥3 years to <18 years of age is greater or equal to 191 but less than 381 an interim analysis for efficacy and futility with an appropriate adjustment of the type I error will be conducted by a DMC, to decide if study objectives have been reached or the study may be extended to an additional season. The need for further interim analyses and further extensions will be assessed by the DMC. If it is determined that the study objectives have been reached, enrolment will be halted.

If the number of influenza cases in the cohort ≥3 years to <18 years of age is greater or equal to 381 (targeted number of cases to be able to evaluate the co-primary objective) the study will be unblinded and the final analysis will be performed.

A final clinical study report will present all efficacy, immunogenicity and safety data collected from the treatment period through to the end of follow-up period (180 days following the last vaccination dose, or until the end of influenza season, whichever is longer).

Number of Subjects planned:

Assuming an approximate 10% drop out rate, minimally 7,692 male and female subjects ≥2 years and <18 years of age are planned to be enrolled. Subjects will be randomized in a 1:1 ratio to receive QIVc (n=3,846) or non-influenza comparator vaccine (n=3,846). Approximate numbers of subjects planned for enrollment in the age groups are presented below.

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Table 1. Approximate Number of Subjects Planned for Enrollment

Age cohort	**≥2 to <9 years of age**		**≥9 to <18 years of age**	**Total**
Vaccine	**"not previously vaccinated" Subjects**	**"Previously Vaccinated" Subjects**		
QIVc	1,022 to 1,430	614 to 1,022	1,803	3,846
Men ACWY	1,022 to 1,430	614 to 1,022	1,803	3,846
Total	2,044 to 2,860	1,228 to 2,044	3,606	7,692

A subset of subjects will be required to provide a blood sample and immunogenicity assessments will be conducted. The subset will comprise of maximally 444 subjects in the ≥2 to <9 years of age cohort for the second season and for the third season, resulting in approximately of 400 evaluable subjects per season: approximately 200 evaluable subjects in the QIVc group (100 in "not previously vaccinated" subjects and 100 "previously vaccinated" subjects) and approximately 200 evaluable subjects in the non-influenza comparator vaccine group (100 "not previously vaccinated" subjects and 100 "previously vaccinated" subjects) per season. For every subsequent season, the number of subjects enrolled into the immunogenicity subset is maximized at 222 subjects per season (111 from the active arm and 111 from the non-influenza comparator arm) resulting in approximately 200 evaluable subjects per following season. The subset will be selected via randomization at the time of enrolment.

Study Population and Subject Characteristics:

This study will enroll healthy male and female subjects ≥ 2 years to < 18 years old.

The list of inclusion and exclusion criteria is included in protocol Section 4, Selection of Study Population.

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Study procedures:

All subjects enrolled in this study will receive a single vaccination with either QIVc or a non-influenza comparator vaccine ("previously vaccinated" subjects), or two administrations, approximately 28 days apart ("not previously vaccinated" subjects). Until the end of the influenza season, subjects or subject's parent/legal guardian will be asked to notify study personnel as soon as possible at the onset of ILI symptoms, so that an unscheduled visit to retrieve nasopharyngeal (NP) swab samples, can occur (preferably within 3, but up to 6, days). All subjects or subject's parent/legal guardian will also receive an ILI booklet on Day 1, and will be instructed to measure their body temperature using the thermometer provided starting from onset day of protocol defined ILI to the day of NP swab collection. After NP swab collection, subjects will receive a new ILI booklet. The ILI booklet will be returned at the time of their NP clinic visit.

On Day 1, a complete physical examination will be conducted for all enrolled subjects. On Day 22 ("previously vaccinated" subjects) or Day 29 and Day 50 ("not previously vaccinated" subjects) a symptom directed physical examination will be performed by a trained health care professional in addition to evaluating safety for all subjects. During the Follow-up Period, all subjects will participate in two (2) safety phone calls on Days 91 and 181, or the end of influenza season, whichever is longer ("previously vaccinated" subjects), or Days 120 and 209, or the end of influenza season, whichever is longer ("not previously vaccinated" subjects). Subjects will also receive weekly phone calls to assess for ILI symptoms during the active ILI surveillance period, defined as the period until the end of the influenza season.

Subjects experiencing an ILI will have (1) a clinic or home visit to collect a nasopharyngeal (NP) swab as soon as possible, preferably within 3 days, and up to 6, days following onset of protocol defined ILI symptoms, and (2) a safety follow-up call 30 days after ILI onset to determine if subsequent medically-attended adverse events occurred and concomitant medication associated with these events were used. The use of anti-viral medications will not be permitted before the NP swab, but will be allowed after a NP swab has been obtained, and documented as concomitant medications. Nasopharyngeal swabs will be processed for viral culture and RT-PCR confirmation.

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Culture positive samples will undergo antigenic characterization. Subjects participating in the immunogenicity subset will have blood samples collected at their Days 1 and 22 clinic visit (for "previously vaccinated" subjects), or Days 1, 29 and 50 clinic visit (for "not previously vaccinated" subjects).

Subjects will be asked to return their completed Subject Diary at their Day 22 clinic visit ("previously vaccinated" subjects), or Day 29 and Day 50 clinic visit ("not previously vaccinated" subjects).

If a subject withdraws from the study, they will be asked to undergo a final assessment for safety.

Study Vaccines:

Study Vaccine: QIVc

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

Comparator Vaccine:

A dose of 0.5 mL of meningococcal (Groups A, C, Y, W-135) Conjugate Vaccine (Men ACWY) will be administered as non-influenza comparator vaccine.

Efficacy Endpoints:

Primary and Co-Primary Efficacy Endpoint:

The primary and co-primary efficacy endpoint is the time from the last study vaccination to the onset of the first occurrence confirmed influenza by either RT-PCR-

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confirmed or culture-confirmed (time to event analyses), due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season

Secondary Efficacy Endpoint:

The efficacy endpoint for secondary objective 1 is the time from the last study vaccination to the onset of the first occurrence confirmed influenza by either RT-PCR-confirmed or culture-confirmed (time to event analyses), due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season.

The efficacy endpoint for secondary objective 2 is the time from the last study vaccination to the onset of the first-occurrence confirmed influenza by RT-PCR-confirmed (time to event analyses), due to any influenza Type A or B strain regardless of antigen match to the strains selected for the seasonal vaccine, (occurring at >14 days after the last vaccination and until the end of the influenza season).

The efficacy endpoint for secondary objective 3 is time from the last study vaccination to the onset of the first-occurrence confirmed influenza by culture-confirmed (time to event analyses), due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, (occurring at >14 days after the last vaccination and until the end of the influenza season)

The efficacy endpoint for secondary objective 4 is the time from the last study vaccination to the onset of the first-occurrence confirmed influenza by culture-confirmed (time to event analyses), due to influenza Type A or B strain antigenic matched to the strains selected for the seasonal vaccine, (occurring at >14 days after the last vaccination and until the end of the influenza season).

An ILI Case is defined as follows (The Centers for Disease Control and Prevention (CDC) criteria ILI is modified for young children for the purposes of this study to

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include additional symptoms): fever of ≥100.0°F / ≥37.8°C along with any of the following: cough, sore throat, nasal congestion, or rhinorrhea.

An influenza case is defined as RT-PCR-confirmed or culture-confirmed influenza in a subject who meets the CDC criteria for ILI modified for young children. RT-PCR or culture confirmed case definition will be used for the primary and co-primary efficacy objective. The RT-PCR or culture-confirmed case definition will be used for secondary objective 1, the RT-PCR-confirmed case definition will be used for secondary objective 2, and the culture-confirmed case definition will be used for secondary efficacy objectives 3 and 4.

Secondary Safety Endpoint(s):

The measures for assessing safety and tolerability are as follows:

1. Percentage of subjects with solicited AEs will be assessed for 7 days following vaccination at Day 1 ("previously vaccinated" subjects) or Day 1 and Day 29, ("not previously vaccinated" subjects) in the QIVc group and the non-influenza comparator vaccine group.

2. Percentage of subjects with all unsolicited AEs will be assessed from Day 1 to Day 22 for "previously vaccinated" subjects or Day 1 to Day 50 for "not previously vaccinated" subjects in the QIVc group and in non-influenza comparator vaccine group.

3. Percentage of subjects with SAEs, AEs leading to withdrawal from vaccination and/or the study, ILIs, NOCDs reported during the subject's entire participation in the study, i.e. from Day 1 to Day 181 (for "previously vaccinated" subjects) or to Day 209 (for "not previously vaccinated" subjects), and all medications associated with these events.

4). Percentage of subjects with medically-attended adverse events within 30 days after the first occurrence ILI.

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Secondary Immunogenicity Endpoints (immunogenicity subset):

For the immunogenicity analysis, the measures for immunogenicity as determined by serum HI antibody titers for Day 1 (all subjects in immunogenicity subset), Day 22 (all "previously vaccinated" subjects receiving a single vaccine dose) or Days 29 and 50 (all "not previously vaccinated" subjects receiving 2 doses) for all four influenza strains are as follows:

- Geometric mean HI titers (GMTs).
- Seroconversion rates (SCR): Percentage of subjects with either a pre-vaccination titer < 1:10 and a post-vaccination titer ≥ 1:40 or a pre-vaccination titer ≥ 1:10 and a ≥ 4-fold increase in post-vaccination titer
- Geometric mean ratio (GMR): The geometric mean of the fold increase of post-vaccination HI titer over the pre-vaccination HI titer
- Percentage of subjects with HI titer ≥ 1:40.

Exploratory Efficacy Endpoint(s):

The measures for exploring efficacy include all-cause mortality, all-cause pneumonia and all-cause otitis media.

Exploratory Immunogenicity Endpoint(s):

In case of additional immunogenicity analyses, such as MN, the immune response will be characterized in a similar manner as described in the 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

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relative to the appropriate population. Two-sided 95% confidence intervals will be provided for descriptive statistics, as warranted. The 95% CI for percentages will be exact CIs based upon the binomial distribution.

Primary Efficacy Objectives:

The primary objective of the study is to demonstrate the absolute vaccine efficacy (aVE) of QIVc versus a non-influenza comparator vaccine against influenza A/B infection in subjects ≥2 years to <18 years of age

The primary measure of efficacy is the estimate of absolute vaccine efficacy (aVE): the vaccine efficacy of QIVc relative to the non-influenza comparator vaccine for preventing first-occurrence influenza-confirmed disease by either RT-PCR-confirmed or culture-confirmed influenza strains contained in QIVc and the non-influenza comparator, regardless of antigenic match.

Absolute vaccine efficacy will only be assessed for laboratory confirmed influenza cases by either RT-PCR-confirmed or culture-confirmed) with illness occurring at >14 days after the last vaccination and until end of the influenza season, since clinical protection is not immediate with vaccination.

Absolute Vaccine efficacy (aVE) against first occurrence laboratory-confirmed influenza cases will be defined as the relative reduction in influenza infection rate in the QIVc group to the non-influenza comparator vaccine group, namely VE = 1 – (QIVc hazard rate / non-influenza comparator vaccine hazard rate).

Time-to-event methodology based on a proportional hazard model will be used for all efficacy analyses. Vaccine Efficacy (VE) against first or only confirmed influenza cases will be determined using a standard formula: VE = 1 - HR where HR is the hazard ratio for influenza confirmed (by either RT-PCR-confirmed or culture-confirmed) ILI in the QIVc group versus the non-influenza comparator group.

The absolute efficacy will be tested according to the following null (H_0) and alternative

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(H_1) hypotheses:

$$H_0: 1 - HR = VE \leq 0.2 \quad \text{versus} \quad H_1: 1 - HR = VE > 0.2,$$

where HR is a hazard ratio of QIVc versus non-influenza comparator and VE is vaccine efficacy. The primary objective will be achieved if the lower limit of the two-sided confidence interval of VE estimate, with at least 95% coverage in a multiple sequential hypothesis testing, exceeds 0.2 in subjects ≥2 years to <18 years of age.

In case an interim analysis will be performed the 95% CI will be adjusted accordingly.

Further details of statistical methods and analyses will be specified in the Statistical Analysis Plan (SAP).

Co-Primary Efficacy Objective

The co-primary objective of the study is to demonstrate that the absolute vaccine efficacy (aVE) of QIVc versus a non-influenza comparator vaccine against influenza A/B infection in subjects ≥3 years to <18 age of years is significantly > 30%.

The co-primary objective will only be demonstrated in case of successful demonstration of the primary efficacy objective (i.e. in hierarchical testing procedure only after demonstration of absolute vaccine efficacy of QIVc in subjects ≥2 years to <18 years of age).

If the lower limit of the confidence interval of the VE is greater than 30%, then the efficacy of QIVc in preventing RT-PCR confirmed influenza A and or B in children ≥3 to <18 years of age will be demonstrated.

Further details of statistical methods and analyses will be specified in the Statistical Analysis Plan (SAP).

Secondary Objectives

Efficacy:

The efficacy endpoint for secondary efficacy objective 1 is the proportion (hazard) of first-occurrence RT-PCR-confirmed or culture-confirmed influenza (occurring at >14 days and until end of influenza season) in subjects who received QIVc vs. non-influenza comparator vaccine. This endpoint will be evaluated for any influenza A and B strain, regardless of antigenic match.

The efficacy endpoint for secondary efficacy objective 2 is the proportion (hazard) of first occurrence RT-PCR-confirmed influenza (occurring at >14 days after last vaccination and until end of influenza season) who received QIVc vs. non-influenza comparator vaccine. This endpoint will be evaluated for any influenza A and B strain, regardless of antigenic match.

The efficacy endpoint for secondary objective 3 is the proportion (hazard) of first-occurrence culture-confirmed influenza (occurring at >14 days after last vaccination and until end of influenza season) who received QIVc vs. non-influenza comparator vaccine. This endpoint will be evaluated for any influenza A and B strain, regardless of antigenic match.

The efficacy endpoint for secondary efficacy objective 4 is the proportion (hazard) of first-occurrence culture-confirmed influenza (occurring at >14 days after the last vaccination and until end of influenza season) who received QIVc vs. non-influenza comparator vaccine. This endpoint will be evaluated for strains antigenically matched to the strains selected for the seasonal vaccine.

Similarly, as for the primary efficacy objective, hazard ratio will be calculated to test for vaccine efficacy for the secondary efficacy objectives. Further details of statistical methods and analyses will be specified in the Statistical Analysis Plan (SAP).

Immunogenicity:

The vaccine immunogenicity objective will be assessed in a subset of subjects with a maximum of 400 evaluable subjects per season, 200 from the QIVc group and 200 from the non-influenza vaccine comparator group.
Immunogenicity endpoints of seroconversion, GMT, GMR and the proportion of subjects with a post-vaccination HI titer of ≥40 will be assessed in an immunogenicity subset of study subjects.

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus UK Ltd	V130_12	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Meningococcal (Groups A, C, Y, W-135) Conjugate Vaccine (Men ACWY)

Seroconversion is defined as a post-vaccination HI titer ≥ 1:40 for subjects with a pre-vaccination HI titer < 1:10 or a minimum four-fold rise in post-vaccination HI antibody titer for subjects with a pre-vaccination titer ≥ 1:10.

Safety:

Secondary objectives include assessing the safety and tolerability of QIVc. The analyses of the safety endpoints will be descriptive.

Further details of statistical methods and analyses will be specified in the Statistical Analysis Plan (SAP).

Exploratory objectives:

Efficacy:

Efficacy of QIVc will be further characterized with specific attention for all-cause mortality, all-cause pneumonia and all-cause otitis media. The analyses of the exploratory efficacy endpoints will be descriptive.

Further details of statistical methods and analyses will be specified in the Statistical Analysis Plan (SAP).

Success Criteria:

The study is successful if the primary efficacy objective is achieved.

Success Criteria for the Primary and Co-Primary Objective:

Vaccine Efficacy (VE) and its CI will be calculated for the RT-PCR or culture confirmed influenza A and B disease presenting as influenza like illness (ILI).

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
Seqirus UK Ltd	V130_12	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Meningococcal (Groups A, C, Y, W-135) Conjugate Vaccine (Men ACWY)

Criteria for evaluation Primary Objective: If the lower limit (LL) of the two-sided 95% confidence interval (CI) of VE is greater than 20%, then the efficacy of QIVc in preventing laboratory confirmed influenza A and or B disease in subjects ≥2 years to <18 years of age will be demonstrated.

Criteria for evaluation: Co-Primary Objective: If the lower limit (LL) of the two-sided 95% confidence interval (CI) of VE is greater than 30%, then the efficacy of QIVc in preventing laboratory confirmed influenza A and or B disease in subjects ≥3 years to <18 years of age will be demonstrated.

Sample Size and Power Calculation for Primary Efficacy Objective:

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

Primary Efficacy Objective ≥2 years to <18 years of age

Estimated sample size to arrive at 298 events, is 4,814 evaluable subjects (or 2,407 evaluable subjects per treatment group), assuming attack rate in non-influenza comparator vaccine subjects of 8%, vaccine efficacy of 45%, and the risk of infection contained entirely within period covered by follow-up. Accounting for early dropout and uncertainty about the assumed parameters, 5,349 subjects are planned to be enrolled to demonstrate that the lower limit of the two-sided 95% CI for the VE is greater than 20% for the primary endpoint assessment with approximately 90% power.

Co-primary Efficacy Objective *≥3 years to <18 years of age*

Assuming a true vaccine efficacy of 50% it was calculated that approximately 381 observed confirmed ILI cases would be needed to demonstrate that the lower limit of the two-sided 95% CI for the VE is greater than 30% with approximately 90% power.

Estimated sample size to arrive at 381 events, is 6,350 evaluable subjects (or 3,175 evaluable subjects per treatment group), assuming attack rate in non-influenza comparator vaccine subjects of 8%, assumed vaccine efficacy of 50%, VE is greater than 30%, and the risk of infection contained entirely within period covered by follow-up. Accounting for early dropout and uncertainty about the assumed parameters, minimally 7,056 subjects are planned to be enrolled to demonstrate that the lower limit of the two-sided 95% CI for the VE is greater than 30%.

Table 2 summarizes the power calculations assumptions and the number of events required to meet primary and co-primary endpoint.

Table 2 Power calculation for Primary and Co-Primary Endpoints

Age group	VE Success Criteria	Assumed Vaccine Efficacy	Influenza attack rate in comparator group	Power	Minimal total evaluable subjects per Treatment Group	Minimal enrolled subjects needed per Treatment group*	Minimal total Number Enrolled*	Minimal total Number of ILIs to demonstrate LL e 95% CI for VE is >30% or 20%
≥2 years to <18 years of age	20%	45%	8%	>90%	2,407	2,674	5,349	298
≥3 years to <18 years of age	30%	50%	8%	>90%	3,175	3,528	7,056	381

*accounted for early dropout and uncertainty

A provision for triggering a new cohort of subjects is also included, and is based on either attainment of an inadequate total number laboratory confirmed influenza case in both seasons, or paired with the outcome of an interim analysis (noted below).

Nasopharyngeal swab samples will be analyzed in batches and the number of laboratory confirmed influenza cases will be reviewed on a regular basis (blinded review). Following the end of the second influenza season, and after observing at least 50% of planned events meeting the co-primary endpoint, an interim analysis for efficacy and futility will be performed by a Data Monitoring Committee (DMC). Stopping rules for futility and efficacy and any additional details regarding the interim analysis will be specified in the DMC Charter and in the SAP.

For this analysis a restricted unblinding will be done, i.e. only external DMC members and Contract Research Organization (CRO) employees executing it will receive access

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
Seqirus UK Ltd	V130_12	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Meningococcal (Groups A, C, Y, W-135) Conjugate Vaccine (Men ACWY)

to the randomization codes and unblinded data for the purpose of preparing the interim analyses.

Strata such as age group and history of previous vaccination will be accounted for in the final analysis as strata in proportional hazard's model. The use of strata in such context does not affect sample size calculation.

To account for the sample size requirements to demonstrate that the lower limit of the two-sided 95% CI for the VE is greater than 30% in ≥3 to <18 years old (co-primary objective) and the contributable 2 year plus enrolment for the co-primary objective , the total sample size is estimated to be minimally 7,692 subjects. While minimum enrolment for the 2+ age cohort will not be pre-defined a maximum of 635 subjects (=7,692 – 7,056) in this age group can be enrolled to maintain a power >90% for the co-primary endpoint. Thus, in total minimally 7,692 subjects are planned be enrolled over the entire age distribution of ≥2 to <18 years of age.

Sample Size for Secondary Immunogenicity Objectives (Immunogenicity Subset):

The assessment of immunogenicity within the immunogenicity subset (subjects ≥2 years to <9 years of age) is descriptive. The number of subjects enrolled is maximized at 400 evaluable subjects per season for the second season and for the third season. With a 1:1 allocation, approximately 200 (evaluable) subjects would be from the active arm and 200 (evaluable) subject would be from the non-influenza active comparator arm. Assuming a 10% drop out rate approximately 444 subjects will be enrolled per season. For the subsequent seasons (fourth, fifth, etc. season) the number of subjects enrolled into the immunogenicity subset is maximized at 222 subjects per season (111 from the active arm and 111 from the non-influenza comparator arm), resulting in approximately 200 evaluable subjects.

Sample Size for Safety:

With a Safety Population of 2,674 evaluable subjects in the safety set of QIVc, AEs with population rates of 1 in 1,000 have a 93.1% probability of being detected.

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
Seqirus UK Ltd	V130_12	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Meningococcal (Groups A, C, Y, W-135) Conjugate Vaccine (Men ACWY)

Events with population rates of 1 in 893 have a 95% chance of being observed with n=2,674) Events with population rates of 1 in 2,000 have a 73.7% chance of being observed with n=2,674

Sample size calculations were performed using PASS v12.0.2.

Interim Analysis:

As the circulation of influenza viruses is seasonal and the event rates of influenza are difficult to predict, this study is group sequentially designed, with a case count-driven interim analysis. The goal of the Interim Analyses is, first, to minimize the risk of not being able to take a significant test decision after the end of the study, and second, to be able to stop the study for early evidence of efficacy or for futility after observing at least 50% of planned ILI cases meeting the co-primary endpoint.

Primary Efficacy Analysis:
The number of laboratory confirmed influenza cases will be reviewed on a regular basis. After the majority of cases for the second season have been collected, and after observing at least 50% of planned events meeting the co-primary endpoint, an interim analysis for efficacy and futility will be performed by a DMC. The two influenza seasons are defined as the first 2 influenza seasons after study start but no later than through April 2018, guided by influenza seasonality and peak season in Northern Hemisphere.

- If the number of influenza cases is less or equal to 190, no interim analysis for efficacy and futility will be done and the study will be extended because the probability to make a conclusion for efficacy is too low.

- If the number of influenza cases is greater or equal to 191 but less than 381, an interim analysis for efficacy and futility with an appropriate adjustment of the type I error (as detailed in SAP) will be conducted by a DMC, to decide if study objectives have been reached or the study may be extended. The need for further interim analyses and further extensions will be decided by DMC.

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus UK Ltd	V130_12	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Meningococcal (Groups A, C, Y, W-135) Conjugate Vaccine (Men ACWY)

- If the number of influenza cases is greater or equal to 381 (targeted number of cases to be able to evaluate the co-primary objective) the study will be unblinded and the final analysis will be performed by the Sponsor.

Stopping rules for futility and efficacy and any additional details regarding the interim analysis will be specified in the DMC Charter and SAP.

Data Monitoring Committee:

A DMC will be utilized for the study (evaluation of efficacy and safety data for interim analysis). Additional details regarding the review of the data by the DMC will be contained in the DMC charter and section 3.7 of the protocol.

Table 3: Time and Events Table – "previously vaccinated" Subjects (One Dose Regimen) - Treatment Period

	Visit Type	Clinic Visit	Reminder Phone Call	Clinic Visit
	Study Day	**1**	**3**	**22**
	Visit Window (Days)	**N/A**	**+/- 1**	**-1 to +4**
	Visit Number	**1**		**2**
Study Event	**References**			
Study Treatment				
Vaccination	Section 5.2	X		
Screening and Safety				
Informed Consent [a]	Section 5.1.1	X [b]		
Medical History	Sections 5.1.2	X [b]		
Physical Exam	Sections 5.1.2 and 5.3.1	X [b, c]		X
Pregnancy Test [d]	Sections 5.1.2 and 5.3.1	X [b]		
Exclusion/Inclusion Criteria	Section 4.0	X [b]		
Randomization	Section 5.1.4	X [b]		
30 Minutes Post Injection Assessment	Section 5.2.1	X		
Subject Diary Dispensed with Training	Section 5.2.1	X		
Subject Diary Reminder Call	Section 5.2.4		X	
Subject Diary Reviewed and Collected	Section 5.3.1			X
Assess all AEs	Sections 7.1	X		X
Assess SAEs	Section 7.1.4	X		X

	Visit Type	Clinic Visit	Reminder Phone Call	Clinic Visit
	Study Day	**1**	**3**	**22**
	Visit Window (Days)	**N/A**	**+/- 1**	**-1 to +4**
	Visit Number	**1**		**2**
Study Event	**References**			
Assess for NOCDs, AEs leading to withdrawal, ILI	Section 7.1.3	X		X
Assess Relevant Medications/ Vaccinations	Sections 5.1.2, 5.3.1 and 6.5	X [b]		X
Efficacy				
ILI Instruction Sheet Dispensed	Section 5.2.1	X		
ILI Booklet Dispensed with Instructions	Section 5.2.1	X		
Message/ Phone Call to Assess ILI	Section 5.3.3		X [e]	
Immunogenicity				
Serology Blood Draw [f]	Section 3.5	X [b]		X

		Visit Type	Clinic Visit	Reminder Phone Call	Clinic Visit
		Study Day	1	3	22
		Visit Window (Days)	N/A	+/- 1	-1 to +4
		Visit Number	1		2
Study Event	**References**				

Notes:

[a] Confirm consent form(s) signed prior to any procedures and document timing in source documents. 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] For female subjects of childbearing potential

[e] Message/ phone call surveillance for primary protocol-defined ILI to be performed on a weekly basis from Study Day 1 until end of influenza season .

[f] Only applies to subjects selected for participation in the immunogenicity subset

Table 4: Time and Events Table – "previously vaccinated" Subjects (One Dose Regimen) - Follow-up Period

		Visit Type	Safety Phone Call	Safety Phone Call
		Study Day	91	181 or End of influenza season [a]
		Visit Window (Days)	+/- 3	- 7 to +14
		Visit Number	3	4
Study Event	**References**			
Safety				
Physical Exam	Sections 5.1.2 and 5.3.1			

	Visit Type	Safety Phone Call	Safety Phone Call
	Study Day	91	181 or End of influenza season [a]
	Visit Window (Days)	+/- 3	- 7 to +14
	Visit Number	3	4
Study Event	**References**		
Assess SAEs	Section 7.1.4	X	X
Assess for NOCDs, AEs leading to withdrawal, ILI	Section 7.1.3	X	X
Assess Relevant Medications/ Vaccinations	Sections 5.1.2 and 6.5	X	X
Efficacy			
Message/ Phone Call to Assess ILI	Section 5.3.3	X [b]	
Study Completion Procedures			
Study Termination [c]	Section 5.5		X

Notes:

[a] whichever is longer

[b] Message/ phone call surveillance for primary protocol-defined ILI to be performed on a weekly basis from Study Day 1 until end of influenza season, .

[c] Subjects who terminate the study early are recommended to complete certain study-related procedures. See section 5.5, Study Termination Visit for further details.

Table 5: Time and Events Table – "not previously vaccinated" Subjects (Two Dose Regimen) - Treatment Period

	Visit Type	Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit
	Study Day	**1**	**3**	**29**	**31**	**50**
	Visit Window (Days)	**N/A**	**+/- 1**	**+/- 3**	**+/- 1**	**-1 to +4**
	Visit Number	**1**		**2**		**3**
Study Event	**References**					
Study Treatment						
Vaccination	Section 5.2	X		X		
Screening and Safety						
Informed Consent[a]	Section 5.1.1	X [b]				
Medical History	Sections 5.1.2	X [b]				
Physical Exam	Sections 5.1.2, 5.2.2 and 5.3.1	X [b, c]		X [b]		X
Pregnancy Test [d]	Sections 5.1.2, 5.2.2 and 5.3.1	X [b]		X [b]		
Exclusion/Inclusion Criteria	Section 4.0	X [b]				
Randomization	Section 5.1.4	X [b]				
30 Minutes Post Injection Assessment	Sections 5.2.1 and 5.2.3	X		X		
Subject Diary Dispensed with Training	Section 5.2.1	X				
Subject Diary Reminder Call	Section 5.2.4		X		X	
Subject Diary Reviewed and Collected	Section 5.3.1 and 5.2.2			X [b]		X
Assess all AEs	Section 7.1	X		X [b]		X
Assess SAEs	Section 7.1.4	X		X [b]		X

	Visit Type	Clinic Visit	Reminder Phone Call	Clinic Visit	Reminder Phone Call	Clinic Visit
	Study Day	**1**	**3**	**29**	**31**	**50**
	Visit Window (Days)	**N/A**	**+/- 1**	**+/- 3**	**+/- 1**	**-1 to +4**
	Visit Number	**1**		**2**		**3**
Study Event	**References**					
Assess for NOCDs, AEs leading to withdrawal, ILI	Section 7.1.3	X		X [b]		X
Assess Relevant Medications/Vaccinations	Sections 5.1.2, 5.2.2, 5.3.1 and 6.5	X [b]		X [b]		X
Efficacy						
ILI Instruction Sheet Dispensed	Section 5.2.1	X				
ILI Booklet Dispensed with Instructions	Section 5.2.1	X				
Message/ Phone Call to Assess ILI	Section 5.3.3	X [e]				
Immunogenicity						
Serology Blood Draw [f]	Section 3.5	X [b]		X [b]		X

Notes:

[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] For female subjects of childbearing potential
[e] Message/ phone call surveillance for primary protocol-defined ILI to be performed on a weekly basis from Study Day 1 and until end of influenza season.
[f] Only applies to subjects selected for participation in the immunogenicity subset

Table 6: Time and Events Table – "not previously vaccinated" Subjects (Two Dose Regimen) - Follow-up Period

	Visit Type	Safety Phone Call	Safety Phone Call
	Study Day	120	209 or End of influenza season [a]
	Visit Window (Days)	+/- 3	-7 to +14
	Visit Number	4	5
Study Event	**References**		
Safety			
Physical Exam	Sections 5.1.2, 5.2.2 and 5.3.1		
Assess SAEs	Section 7.1.4	X	X
Assess for NOCDs, AEs leading to withdrawal, ILI	Section 7.1.3	X	X
Assess Relevant Medications/ Vaccinations	Sections 5.1.2, 5.2.2, 5.3.1 and 6.5	X	X
Efficacy			
Message/ Phone Call to Assess ILI	Section 5.3.3	X[b]	
Study Completion Procedures			
Study Termination [c]	Section 5.5		X

Notes:
[a] whichever is longer.
[b] Message / phone call surveillance for primary protocol-defined ILI to be performed on a weekly basis from Study Day 1 and until end of influenza season,.
[c] Subjects who terminate the study early are recommended to complete certain study-related procedures. See section 5.5, Study Termination Visit for further details.

Table 7: Time and Events Table – ILI Visit Schedule

	Visit Type	**Clinic Visit**	**ILI Follow-up Safety Call**
	ILI Day[a]	**1-4**	**31**
	Visit Window (Days)	**+3**	**+7**
	Visit Number	**n/a**	**n/a**
Study Event	**References**		
NP Swab Specimen Collection	Section 5.4	X	
Assess ILI symptoms and Relevant Medications	Section 5.4	X	X
Assess for Medically-Attended Adverse Events	Section 5.4	X	X
Assess Relevant Medications	Section 5.4	X	
Physical Exam	Section 5.4	X	
ILI Booklet Reviewed and Collected	Section 5.4	X	

LIST OF ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
BLA	Biologics License Application
BMI	Body Mass Index
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ER	Event Rate
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HA	Hemagglutinin
HI	Haemagglutination Inhibition
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ID	Identification
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
DMC	Data Monitoring Committee
ILI	Influenza-Like Illness
IM	Intramuscular
IRB	Institutional Review Board
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
Men ACWY	Meningococcal (Groups A, C, Y, W-135) Conjugate Vaccine
MN	Microneutralization
NA	Neuraminidase
NOCD	New Onset of Chronic Disease

NP	Nasopharyngeal
NH	Northern Hemisphere
PCR	Polymerase Chain Reaction
PFS	Pre-filled Syringes
PP	Per Protocol
PPS	Per Protocol Set
PRO	Patient Reported Outcome
PV	Pharmacovigilance
QIVc	Cell-derived Quadrivalent Influenza Vaccine
QIV	Quadrivalent Influenza Vaccine
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sBLA	Supplement Biologics License Application
SC	Seroconversion
SDA	Source Data Agreement
SH	Southern Hemisphere
SOC	System Organ Class
SOP	Standard Operating Procedure
TIV	Trivalent Influenza Vaccine
VRBPAC	Vaccines and Related Biological Products Advisory Committee
VSAE	Vaccine Serious Adverse Events
WHO	World Health Organization

DEFINITIONS

End of influenza season: The end of the influenza season will be defined as the end of June for Northern Hemisphere (NH) influenza seasons and end of December for Southern Hemisphere (SH) influenza seasons. For tropical countries, with no typical NH or SH influenza season, the season is defined by the use of the strains in the vaccine formulation (i.e. strains as recommended for the NH or the SH influenza season) and the timing of vaccination.

End of study: Evaluation of the primary and secondary efficacy objectives requires the testing of biological samples from the study subjects, which can only be completed after all samples are collected. Nasopharyngeal swabs may be collected up to end of influenza season. For the purpose of this protocol, end of study is defined as the completion of the testing of such biological samples, to be achieved no later than 8 months after LSLV.

Influenza case: An ILI associated with RT-PCR or culture confirmed influenza.

Influenza-like illness (ILI) onset: The first day on which a subject fulfils the criteria for protocol-defined ILI.

Medically-attended Adverse Event: Defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider.

Study definition of Influenza-like illness (ILI): Fever of ≥37.8°C (100°F) and at least one of the following: cough, sore throat, nasal congestion, or rhinorrhea.

Qualified healthcare professional: Any licensed health care professional who is permitted by institutional policy to perform clinical interventions and assessments such as physical examinations and who is identified within the Study Staff Signature Log.

Trained healthcare professional: Any health care professional who is permitted by institutional policy and trained to perform delegated tasks and who is identified within the Study Staff Signature Log.

1. BACKGROUND AND RATIONALE

1.1 Background

Influenza has long been a major health concern in the world with an annual attack rate estimated at 5-10% in adults and 20-30% in children (World Health Organization, 2012). Every year, several hundred million people become infected with influenza globally resulting in 250,000 to 500,000 deaths. Ninety (90) million of these cases and 28,000 to 111,500 deaths occur in children younger than 5 yrs of age (Nair et al., 2011). Influenza is accountable for as many as 20% excess hospitalizations in young children, and the increased morbidity has an economic impact (Neuzil KM et al., 2000). The average yearly direct medical costs of emergency room visits and hospitalization of children less than 5 yrs old in the US ranged from $44 million to $512 million in a study that evaluated influenza-associated medical costs during influenza seasons 2000/2001 to 2003/2004 (Fairbrother et al., 2010). Missed work days to care for sick children add to the economic burden of childhood influenza. In addition, young children contribute to community spread of influenza with age-appropriate inattention to proper hand hygiene and sneezing/coughing precautions, a longer viral shedding period and higher viral loads (Bodewes et al. 2011).

The burden of influenza B infection falls largely on children. In a study conducted in New York City during influenza seasons 2001/2002 to 2005/2006, influenza B infection was detected mainly in children despite the detection of the co-circulating influenza A (H3N2) strain in both children and adults. Children may experience complications from influenza B infection such as myositis, leukopenia and hospitalizations (Belshe et al. 2007). Results of surveillance studies from 2001 to 2010 in the US show that the B strain in licensed influenza vaccines has not matched circulating strains of influenza B in 5 out of 10 seasons (Belshe et al., 2010). This is largely due to the co-circulation of two B strains, noted since the 1980s, from two separate lineages: B/Victoria and B/Yamagata. Influenza vaccination or infection with a B strain from one lineage provides minimal to no protection against influenza B from the opposite lineage.

Vaccination is currently the most effective measure for reducing the impact of influenza, and the potential benefits of influenza vaccination programs targeted at children have gained increasing attention in recent years. In the US, recommendations for influenza vaccination have expanded over the last decade to include those 6 to 23 mos of age (2004), those 6 to 59 mos of age (2006), and to all children 6 mos to 18 yrs of age (2009) (Fiore et al., 2009). For many years, the traditional seasonal influenza vaccines have included antigens from three influenza strains in their composition, two influenza A strains (largely A/H1N1 and A/H3N2), and a strain from one of the two influenza B lineages (B/Yamagata or B/Victoria). However, interest in expansion of the influenza strains included to address the B mismatch has led to Vaccines and Related Biological

Products Advisory Committee (VRBPAC) endorsement to pursue the development of quadrivalent influenza vaccines.

QIVc is a quadrivalent cell culture derived inactivated influenza vaccine, composed of the WHO recommended influenza strains for quadrivalent influenza vaccine formulated for the 2016/2017 northern hemisphere (NH) influenza season, and based on the manufacturing platform of Flucelvax™ (also licensed under the trade name of Optaflu™), a trivalent inactivated influenza vaccine. The novel production method in mammalian cell lines generates more flexibility, adequate availability of substrate for virus growth, and the possibility of significant higher virus yields compared to the traditional production methods in embryonated eggs (WHO 1995). 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.

U.S. marketing authorization for TIVc (Flucelvax) was received 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 has been submitted to Food and Drug Administration (FDA) in November 2014. This was followed, in April 2015, by a 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 aged four years and older. Final licensure is dependent on demonstration of clinical benefit through the current pediatric absolute efficacy study with QIVc.

The goal of the current randomized, observer-blind, controlled absolute efficacy study is to demonstrate that QIVc prevents influenza in pediatric subjects, and obtained data will be used to support the US licensure of QIVc for the prevention of seasonal influenza in pediatric subjects. Direct comparison with a non-influenza comparator vaccine (licensed for use in pediatric subjects) will enable an estimation of the absolute efficacy of QIVc in preventing influenza in pediatric subjects. A non-influenza vaccine comparator has recently been used to show efficacy of an egg-based quadrivalent influenza vaccine in the pediatric population (Jain et al. 2013). This approach is consistent with Center for Biologics Evaluation and Research (CBER) Guidance for the licensure of seasonal influenza vaccines.

1.2 Rationale

The purpose of this study is to demonstrate the clinical efficacy of Seqirus' cell-based inactivated quadrivalent vaccine (QIVc) in healthy pediatric subjects ≥ 2 years to < 18 years of age. This randomized, observer-blind, non-influenza comparator-controlled study is intended to demonstrate that QIVc prevents laboratory (RT-PCR or culture) confirmed influenza.

In April 2015, a BLA was submitted to obtain marketing authorization of QIVc for the prevention of seasonal influenza in both adult and pediatric subjects (≥ 4 years of age). A sBLA to extend the age indication of TIVc (Flucelvax) to 4 years and above was submitted to FDA in November 2014, resulting in approval in May 2016. This study is a regulatory requirement to support licensure of QIVc for use in children ≥4 years of age in the United States (US). Children ≥2 years of age are enrolled in this study to further evaluate QIVc in a broader age range and to support submissions in various global regions.

2. OBJECTIVES.

2.1 Primary Objective(s)

Primary Efficacy Objective:

To demonstrate absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by first occurrence RT-PCR or culture confirmed influenza, due to any influenza Type A and B strain in subjects ≥2 years to <18 years of age.

In case of successful demonstration (see section 8.2) of the primary efficacy objective:

Co-Primary Efficacy Objective(s):

To demonstrate absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by first occurrence RT-PCR or culture confirmed influenza, due to any influenza Type A and B strain in subjects ≥3 years to <18 years of age.

2.2 Secondary Objective(s):

Secondary Efficacy Objectives:

The following objective will be evaluated in the age cohorts: ≥3 years to <9 years of age, ≥2 years to <9 years of age, and ≥ 9 to < 18 years of age:

1. To demonstrate absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by first occurrence RT-PCR or culture confirmed influenza, due to any influenza Type A and B strain.

The following objectives will be evaluated in the age cohorts: ≥3 years to <18 years of age, ≥2 years to <18 years of age, ≥3 years to <9 years of age, ≥2 years to <9 years of age, and ≥ 9 to < 18 years of age:

2. To demonstrate absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by first occurrence RT-PCR influenza, due to any influenza Type A and B strain.

3. To demonstrate absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by first occurrence culture confirmed influenza, due to any influenza Type A and B strain.

4. To demonstrate absolute vaccine efficacy of QIVc versus a non-influenza comparator determined by first occurrence culture confirmed influenza, caused by influenza strains antigenically matched to the strains selected for the seasonal vaccine

Secondary Immunogenicity Objective:

The following objective will be evaluated, in a subset of subjects in the age cohorts: ≥3 years to <9 years of age, and ≥2 years to <9 years of age:

To characterize the immunogenicity of QIVc by haemagglutination inhibition (HI) assay 3 weeks after last vaccination

Secondary Safety Objective:

To assess the safety and tolerability of QIVc.

2.3 Exploratory Objective(s)

Exploratory Efficacy Objective:

The following objective will be evaluated in the age cohorts: ≥3 years to <18 years of age, and ≥2 years to <18 years of age:

To further characterize the efficacy of QIVc, with specific attention for all-cause mortality, all-cause pneumonia and all-cause otitis media.

Exploratory Immunogenicity Objective:

The following objective will be evaluated in a subset of subjects in the age cohorts: ≥3 years to <9 years of age, and ≥2 years to <9 years of age:

To further characterize the immune response, additional immunogenicity analyses may be conducted using other assays such as MN

3. STUDY DESIGN

3.1 Overview of Study Design

This is a phase III/IV, stratified, randomized, observer blind, multicenter clinical study to evaluate the efficacy, safety and immunogenicity of a cell-based quadrivalent subunit influenza virus vaccine compared to non-influenza comparator vaccine in subjects ≥2 years to <18 years of age.

In this study, a total of 7,692 healthy male and female subjects aged ≥2 years to <18 years of age are planned to be enrolled. Approximate numbers of subjects planned for enrollment in the age groups are presented below.

Table 3.1.1. Approximate Number of Subjects Planned for Enrollment

Age cohort	**≥2 to <9 years of age**		**≥9 to <18 years of age**	**Total**
Vaccine	"not previously vaccinated" Subjects	"Previously Vaccinated" Subjects		
QIVc	1,022 to 1,430	614 to 1,022	1,803	3,846
Men ACWY	1,022 to 1,430	614 to 1,022	1,803	3,846
Total	2,044 to 2,860	1,228 to 2,044	3,606	7,692

A subset of subjects will be required to provide a blood sample and immunogenicity assessments will be conducted. The subset will comprise a total of maximum 444 subjects per season in the ≥2 to <9 years of age cohort for the second season and for the third season, resulting in approximately 400 evaluable subjects per season: approximately 200 evaluable subjects in the QIVc group (100 in "not previously vaccinated" subjects and 100 "previously vaccinated" subjects) and approximately 200 evaluable subjects in the non-influenza comparator vaccine group (100 "not previously vaccinated" subjects and 100 "previously vaccinated" subjects). For the subsequent seasons, the number of subjects enrolled into the immunogenicity subset is maximized at 200 evaluable subjects per season (100 from the active arm and 100 from the non-influenza comparator arm). Assuming a 10% drop out rate approximately 222 subjects will be enrolled per any subsequent season after season three (fourth and fifth season, etc) depending on the duration of the study.

Follow up period of active ILI surveillance is until end of influenza season.

After signing of the informed consent by the subject's parent or legal guardian (and where applicable according to local regulations, informed consent (assent) signed by subjects above the specified age) and undergoing review of medical history, physical examination,

review of prior and concomitant medications/vaccinations, and confirmation of subject eligibility (including pregnancy testing for female subjects of childbearing potential), subjects will be enrolled into the study and randomized via an interactive response technology (IRT) system to receive QIVc or US licensed non-influenza comparator vaccine. Randomized subjects will be stratified in two age cohorts: ≥2 years to <9 years of age and ≥9 years to <18 years of age. Subjects between ≥2 to <9 years of age will be stratified by previous influenza vaccine status as "previously vaccinated" and "not previously vaccinated".

"Previously vaccinated" subjects are defined as any child 9 years of age and older, and any child under the age of 9 years who has received 2 or more doses of seasonal influenza vaccine before or during the last influenza season The two previous doses need not have been given during the same season or consecutive seasons. "not previously vaccinated" subjects are defined as any child under the age of 9 years who did not receive 2 or more doses of seasonal influenza vaccine before or during the last influenza season and any child under the age of 9 years with unknown influenza vaccination history.

Subjects ≥2 to <9 years of age who are "not previously vaccinated" will receive two (2) vaccinations separated by approximately 28 days. Subjects ≥2 to <9 years of age who are "previously vaccinated" and subjects ≥9 to <18 years of age will receive one (1) vaccination. A subset of subjects ≥2 to <9 years of age will be selected to participate in an assessment of immunogenicity, balanced by vaccination status and assigned vaccination allocation. Solicited adverse events will be collected for all subjects.

After randomization, all subjects will receive a dose of 0.5 mL of study vaccine to which they were assigned (QIVc or non-influenza comparator vaccine) on Day 1, administered intramuscularly in the deltoid muscle, preferably of the non-dominant arm. For those subjects who are "not previously vaccinated" a second administration will follow on Day 29, as presented below:

Subjects	**QIVc Group**	**Comparator Group**
"previously vaccinated" ≥2 years to <9 years of age, and ≥9 years to <18 years of age	Day 1: QIVc	Day 1: Men ACWY
"not previously vaccinated" ≥2 years to <9 years of age	Day1: QIVc Day 29: QIVc	Day 1: Men ACWY Day 29: Saline

To maintain the observer-blind design of the study, the roles and responsibilities of "blinded" and "unblinded" team members will be defined. After vaccination, safety assessments and study related procedures and monitoring thereof must be performed by "blinded" team members.

After each vaccination, all subjects will remain under medical supervision at the study site for at least 30 minutes to be monitored and evaluated for adverse events (AEs). The parent/legal guardian or a designated person (e.g., caregiver) will be instructed on the measurement of local and systemic solicited adverse events, including body temperature (preferably oral), and on the completion of the Subject Diary cards. A Subject Diary will be used to describe solicited local and systemic adverse events that may occur post-vaccination from Day 1 through Day 7 (all subjects) and Day 29 through Day 35 ("not previously vaccinated" subjects). Any adverse event and concomitant medication use after vaccination will be collected from Day 1 to Day 22 during the Day 22 clinic visit ("previously vaccinated" subjects) and from Day 1 to Day 50, during the Day 29 and Day 50 clinic visit ("not previously vaccinated" subjects). Information collected at these visits will be documented in the subject's source records and captured in the Electronic Case Report Form (eCRF). All subjects will also receive an ILI booklet on Day 1, and they (or the parent/legal guardian or a designated person) will be instructed to measure their body temperature using the thermometer provided starting from onset day of protocol defined ILI to the day they come in to the clinic for the NP swab collection. The ILI booklet will be returned at the time of their NP visit.

During the remaining follow-up phase of the study (up to Day 181 for "previously vaccinated" subjects or Day 209 for "not previously vaccinated" subjects, or until the end of influenza season, whichever is longer), safety data including adverse events leading to withdrawal, New Onset of Chronic Diseases (NOCDs), Serious Adverse Events (SAEs), ILIs and concomitant medication use related to these events will be captured via safety phone calls as described in the time and events table.

As the nature of safety data reporting differs in younger and older pediatric populations, solicited adverse events reflected on the diary card will be age appropriate in each of two (2) age groups: subjects ≥2 to <6 years of age and subjects ≥6 to <18 years of age.

For each "previously vaccinated" subject, two visits (Day 1, Day 22), one reminder telephone call after vaccination to remind the parents/legal guardians to complete the diary card (Day 3) and two safety follow up telephone calls (Day 91 and Day 181, or the end of influenza season, whichever is longer) are planned. Influenza surveillance will be performed weekly and during planned visits, during influenza season.

For each "not previously vaccinated" subject, three visits (Day 1, Day 29, Day 50), two reminder telephone calls after each vaccination to remind the subject and/or the parents/legal guardians to complete the diary card (Days 3, Day 31), and two safety follow up telephone calls (Day 120 and Day 209, or the end of influenza season,

whichever is longer) are planned. Influenza surveillance will be performed weekly and during planned visits, during influenza season.

In addition, all subjects may have additional unscheduled visits if they meet pre-defined study criteria for the unscheduled visit.

A subset of the subjects will have blood drawn, before each vaccination and at 3 weeks after last vaccination (resulting in 2 blood draws per subject in "previously vaccinated" subjects, and 3 blood draws per subject in "not previously vaccinated" subjects). Blood drawn in these subsets will be evaluated for antibody responses as measured by immunogenicity.

Weekly active influenza contacts for ILI will be conducted (when visit not scheduled) from Day 1 until the end of influenza season, or at early discontinuation).

Subjects who show clinical signs of influenza (see ILI case definition) will have an unscheduled visit in order to have a nasopharyngeal (NP) swab (or oropharyngeal swab if collection of NP swab is not feasible) collected for evaluation of the presence of influenza virus, and a safety follow-up call 30 days after ILI onset to determine if subsequent medically-attended adverse events occurred and concomitant medication associated with these events were used. The NP swab should be collected as soon as possible, within 3 days, and up to 6 days following onset of protocol defined ILI symptoms. In case ILI symptoms are present during a scheduled clinic visit, then the NP swab may be collected at this visit. NP swabs will be evaluated by RT-PCR and culture at a central laboratory, followed by characterization of the influenza strains as "vaccine strains" versus other influenza strains. RT-PCR and culture confirmed influenza cases will be evaluated within specific timeframes of first and second study vaccination (i.e., starting 14 days after study vaccination for "previously vaccinated" subjects and starting 14 days after second study vaccination for "not previously vaccinated" subjects). The evaluation for RT-PCR and culture influenza cases will end at the end of influenza season.

Total length of subject participation is until 180 days after last vaccination, or until the end of influenza season, whichever is longer.

This study is planned for multiple influenza seasons. Laboratory confirmed influenza cases will be reviewed on a regular basis (blinded review). Following the end of the second influenza season, and after observing at least 50% of planned events meeting the co-primary endpoint, an interim analysis for efficacy and futility will be performed by a DMC.

If the number of influenza cases is less or equal to 190 (minimum number of cases to

indicate efficacy or futility), no interim analysis for efficacy and futility will be done and the study will be extended.

If the number of influenza cases is greater or equal to 191 but less than 381 an interim analysis for efficacy and futility with an appropriate adjustment of the type I error will be conducted by an DMC, to decide if study objectives have been reached or the study may be extended The need for further interim analyses and further extensions will be assessed by the DMC. If it is determined that the study objectives have been reached, enrolment will be halted.

If the number of influenza cases is greater or equal to 381 (targeted number of cases to be able to evaluate the co-primary objective) the study will be unblinded and the final analysis will be performed.

A final clinical study report will present all efficacy, immunogenicity and safety data collected from the treatment period through to the end of follow-up period (180 days following the last vaccination dose, or until the end of influenza season, whichever is longer).

Study Definition of Influenza-Like-Illness and Influenza Case

An Influenza Like Illness (ILI) Case is defined as follows (The Centers for Disease Control and Prevention (CDC) criteria ILI is modified for young children for the purposes of this study to include additional symptoms): fever of ≥100.0°F / ≥37.8°C along with any of the following: cough, sore throat, nasal congestion, or rhinorrhea.

An influenza case is defined as RT-PCR-confirmed or culture-confirmed influenza in a subject who meets the CDC criteria for ILI modified for young children. RT-PCR or culture confirmed case definition will be used for the primary efficacy objectives. The RT-PCR or culture confirmed case definition will be used for secondary objective 1, the RT-PCR-confirmed case definition will be used for secondary objective 2, and the culture-confirmed case definition will be used for secondary efficacy objectives 3 and 4. The ILI onset day is defined as the first day that the subject meets the primary protocol-defined ILI.

The ILI end date is defined as the date the last symptom resolves.

A new ILI episode will only be taken into account after resolution of the previous one, as judged by the investigator (suggested interval between two ILI episodes is 14 symptom-free days).

3.2 Study Period

Each subject should expect to participate in the study for 180 days after last vaccination, or until the end of the influenza season, whichever is longer (i.e. from the time of enrolment through the last study visit).

3.3 Blinding Procedures

The trial is designed as an observer-blind study. Designated unblinded nurse(s) or physician(s) will be responsible for administrating the study vaccines to the subjects and will be instructed not to reveal the identity of the study vaccines either to the subject or the investigative site staff (i.e., investigator and study nurse) involved in the monitoring of conduct of the trial from vaccination up until completion of the trial and final data review, except in a medical emergency. Vaccines will be selected and administered according to the Pack ID assigned to the subjects by IRT. Neither the subject nor 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 and blinded study personnel. The unblinded personnel should not be involved in data collection after vaccination 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 and Designee. In such instance of medical emergency, every effort should be made to contact the Sponsor and Designee prior to unblinding. If unblinding should occur (by either accidental unblinding or emergency unblinding for an SAE) prior to completion of the study, the investigator must promptly contact the Sponsor and document the circumstances on the appropriate forms.

All personnel involved in performing laboratory assays and others who are directly involved in the conduct of the trial or in the analysis of the final trial results will remain blinded to the treatment codes until at least the database has been locked for final analysis.

3.4 Data Collection

3.4.1 Data Collected from Subjects

The following data will be collected from each subject during their study participation:

- Medical History

- Vaccination History
- Demographic Information.
- Physical examination information, including height and weight.
- Post-vaccination solicited Adverse Events (from Day 1-7 in "previously vaccinated" subjects, from Day 1-7 and Day 29-35 in "not previously vaccinated" subjects.
- Post-vaccination unsolicited Adverse Events (from Day 1-22 in "previously vaccinated" subjects; from Day 1-50 in "not previously vaccinated" subjects).
- Adverse Events
  - AEs leading to withdrawal
  - NOCDs
  - SAEs
  - ILIs
  - Medically-attended adverse events within 30 days after the ILI onset
- Relevant concomitant Medications/ vaccinations (as defined in Section 6.5)
- Reason for study termination
- Body temperature measurements from the onset of ILI until day of clinic visit for NP sample collection.

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

3.4.2 Tools Used for Data Collection

ILI Booklet

Subject's experiencing an ILI will be asked to document their daily body temperature in an ILI booklet. An ILI booklet will be given to all subjects at their Day 1 visit. The booklet will be used to collect information on body temperature measurements which are to be completed daily (preferably orally, using the supplied thermometers) until the subject comes in for their NP sample collection. At the ILI clinic visit the subject will be asked to turn in their ILI booklet, and a new booklet will be provided.

Subject Diary

All subjects will be given a paper diary at their Day 1 clinic visit to complete. The paper diaries to be completed by subjects/subjects's parent(s)/legal guardian(s)/care-giver participating in the solicited safety subset, hereafter referred to as Subject Diaries, will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial 30 minute post-vaccination period at the clinic through Day 7.

At the Day 22 clinic visit ("previously vaccinated" subjects) or at the Day 29 and Day 50 clinical visit ("not previously vaccinated" subjects), subjects participating in the solicited safety subset are to return their completed diary and the site staff should review the completed diary with them. The following additional rules apply to documentation of safety information collected in the Subject Diary.

1. No corrections or additions to the information recorded by the subject/subject's parent(s)/legal guardian(s)/designated caregiver within the Subject Diary and/ or related CRF diary pages will be allowed after it is delivered to the site.

2. Any blank or illegible fields on the Subject Diary must be described as missing in the CRF.

Case Report Forms

This study utilizes electronic Case Report Forms (eCRFs) to collect study-related data from each subject. A qualified site staff member(s) 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 eCRF 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.

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

1. The site must enter all readable entries in the Subject Diary into the CRF, including those values that may be biologically implausible (e.g. body temperature: 400°C).
2. Any illegible or implausible data should be reviewed with the subject/subject's parent(s)/legal guardian(s). If an underlying solicited or unsolicited adverse event is described on review with the subject, this should be described in the source document

and reported as an unsolicited adverse event in the Adverse Event CRF (e.g., if the subject above confirms body temperature of 40°C on the day in which body temperature: 400°C was written into his/her Subject Diary, this fever of 40°C should be recorded in the Adverse Event CRF).

3. Any newly described safety information (including a solicited adverse event) must not be written into the Subject Diary 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 CRF.

3.5 Collection of Clinical Specimens

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

- Nasopharyngeal swabs (as needed from subjects experiencing symptoms that meet primary protocol-defined ILI criteria).

The following clinical specimens are required to be collected from subjects participating in the immunogenicity subset:

- Blood at the Day 1 and 22 clinic visit ("previously vaccinated" subjects) or at the Day 1, Day 29, and Day 50 visit ("not previously vaccinated" subjects)

Collection and processing of each specimen should be completed by a qualified site member and in accordance with the study-specific Laboratory Manual. Testing of clinical specimens will be performed by a Seqirus or designated laboratory. Refer to the study-specific Laboratory Manual for additional details.

Blood Specimens

Approximately 7 mL sample of blood will be drawn from all subjects participating in the immunogenicity subset at Days 1 and 22 ("previously vaccinated" subjects), or at Days 1, 29 and 50 ("not previously vaccinated" subjects). (see Section 7.3, Immunogenicity Assessments for additional details). Stored samples may be used for additional immunogenicity analyses using other assays such as microneutralization (MN), to further characterize the immune response.

The total amount of blood collected over the study period per subject will be approximately 14 mL ("previously vaccinated") or 21 mL ("not previously vaccinated").

Nasopharyngeal Swabs

Subjects, who from Visit 1 (Day 1) onwards, experience symptoms meeting the primary protocol-defined ILI criteria (i.e. fever of ≥100.0°F / ≥37.8°C along with any of the following: cough, sore throat, nasal congestion, or rhinorrhea), will have a NP swab collected for evaluation of the presence of influenza virus by RT-PCR. The NP swab will be collected as soon as possible, preferably within 3 days, but up to 6 days following the onset of protocol-defined ILI symptoms.

All samples will also be cultured for the growth of the strain of influenza obtained from the subjects. The data will be used for antigenic characterization (to determine whether the clinical isolate is antigenically matched or antigenically unmatched to the vaccine strain).

Urine Specimens

Urine will be collected for pregnancy testing in females of child bearing potential. Urine will be collected at visit 1 before vaccination (for "previously vaccinated" subjects), or at visit 1 before vaccination, and visit 2 before vaccination (for "not previously vaccinated" subjects). The results will be recorded in the source document and eCRF.

3.6 Stopping/Pausing Guidelines

NP swabs will be analyzed in batches on a rolling basis throughout the study. At least one interim analysis will be performed based on the number of RT-PCR or culture confirmed influenza cases accrued at the time of the first interim analysis. After periodic review of safety and efficacy data, the DMC will make a recommendation as to whether enrolment in the study should continue, be stopped or paused.

Independent of the DMC, the Sponsor can halt the study at any time. If the study is halted, the Sponsor or delegate will promptly notify the health authorities and investigators, who will promptly inform the study subjects and local Ethics Committee/ Institutional Review Board (EC/IRB) as per local regulations. Study vaccinations and further enrolment will only occur after written authorization is provided by the Sponsor in conjunction with a recommendation to proceed by the DMC and in consultation with the health authorities and EC/IRB, as appropriate.

There are no predetermined stopping rules other than circumstances for which subjects may not be eligible for additional study vaccinations as described in section 4, Selection of Study Population or may be withdrawn from the study according to the best interests of the subject as described in Section 3.8, Premature Withdrawal from Study.

3.7 Data Monitoring Committee

A DMC will be constituted for this trial. The members of the DMC shall have no involvement in the design or conduct of the trial and no financial interest in the outcome of the trial. The DMC will comprise solely of non-Seqirus employees, and include medical experts and a biostatistician. DMC will provide recommendation on stopping the study for either efficacy or futility after unblinded review of efficacy data in a pre-planned interim analysis. In addition, the DMC will monitor study progress and ensure the safety of subjects on an ongoing basis during the trial.

Primary efficacy endpoint.

Unblinded interim analyses for efficacy and futility will be executed by the DMC, after the majority of cases for the second season have been collected, and after observing at least 50% of planned events meeting the co-primary endpoint. In addition, the DMC will also review blinded, and if requested, semi-or fully-unblinded safety data at pre-specified intervals during the study. Another interim analysis might be recommended before target 381 cases are observed. Any unblinded data will be reviewed in closed sessions of the DMC, without participation of the Sponsor. All descriptions of these closed sessions will be unavailable to the Sponsor until study unblinding has occurred. All reports, following open sessions of blinded data review will be available to the Sponsor as appropriate. DMC recommendations will be expressed clearly to the Sponsor, at minimum in written communication.

After reviewing safety and efficacy data, the DMC will recommend that enrolment be continued, halted temporarily (pending additional information from the Sponsor or modification to the study design) or halted permanently as specified in the DMC charter.

The DMC charter will be written to clearly describe the operational processes and the roles and responsibilities, including the timing of meetings, methods of providing information to and from the DMC, format and content of data to be reviewed, frequency and format of meetings, and membership requirements.

3.8 Premature Withdrawal from Study

Subjects 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 related procedures or for administrative reasons. 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 want to withdraw from the study before all doses are administered or prior to the last planned study visit, the subject will be asked to be followed for safety for the duration of the study. When a subject withdraws, or is withdrawn, from the study, the procedures described in section 5.5.1, Early Termination Visit should be completed if possible.

The reasons for premature withdrawal from the study include:

- Adverse event,
- Death
- Withdrawal of consent
- Lost to follow-up
- Administrative reason
- Protocol deviation
- Other

These reasons are described in greater detail below.

Adverse Event

For any subject withdrawn from study participation prior to the planned Study Termination Visit, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the AE CRF 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 a serious adverse event (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 within 30 days following a primary protocol definition of ILI, the event should also be reported on the AE eCRF page.

Death

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

Withdrawal of consent

The subject and/or parent(s)/legal guardian(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 (i.e., reason other than AE). If the subject and/or parent(s)/legal guardian(s) 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, or a subset of other study procedures. If the subject requests complete withdrawal from the study, no further study interventions will be performed with the subject.

In countries where the Health Insurance Portability and Accountability Act (HIPAA) is applicable, if a subject and/or parent(s)/legal guardian(s) withdraws consent but does not revoke the HIPAA authorization, the Sponsor will have full access to the subject's medical records, including termination visit information. If a subject and/or parent(s)/legal guardian(s) 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 final visits (clinic or telephone contacts), or for three consecutive visits (clinic or (safety or diary) telephone contacts), study staff are encouraged to make at least three documented attempts to contact the subject by telephone and at least one documented written attempt to contact the subject and/or parent(s)/legal guardian(s) to encourage the completion of study termination 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 Termination CRF page is the date of the last successful contact (visit or telephone) with the subject.

Administrative Reason

Examples for subjects withdrawn from the study due to administrative reason 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 Termination CRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilization.

If the clinical study is prematurely terminated by the Sponsor, the investigator is to promptly inform the study subjects and local EC/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.

For subjects who are withdrawn from the study due to receipt of an excluded medication/vaccination or due to significant protocol non-compliance , this reason should be noted in the Study Termination CRF page. A subject (or legal guardian) is considered to be compliant if the Investigator judges that the subject will complete the Subject Diary when applicable, return for all the follow-up visits, and be available for telephone calls as scheduled.

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/EC and health authorities it cannot be implemented.

Any subject who becomes pregnant during the study, despite the protocol requirement for adequate contraception, will not receive further vaccination(s) but should be encouraged to continue participating in the study for safety follow-up. The site must complete a paper Pregnancy Report form (initial report) as soon as possible after learning of pregnancy occurrence (see section 7.1.6, Pregnancies for further details). If the pregnant subject withdraws from the study for any of the above categories except death, the site will obtain permission from the subject to continue to remain in contact with her until the outcome of the pregnancy is known, even if the outcome is not known until after the subject reaches the end of follow-up period.

3.9 End of Study

Evaluation of the primary and secondary efficacy objectives requires the testing of biological samples from the study subjects, which can only be completed after all samples are collected. Nasopharyngeal swabs may be collected up to end of influenza season. For the purpose of this protocol, end of study is defined as the completion of the testing of such biological samples, to be achieved no later than 8 months after LSLV.

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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. Males or females ≥2 years to <18 years of age on the day of first study vaccination;
2. Individual has and/or has (a) parent(s) or legal guardian(s) who has/have given informed consent/assent after the nature of the study has been explained in accordance with the practices described in protocol Section 5.1.1. and according to local regulatory requirements;
3. If the individual is of an age where, according to local regulations, informed assent is required, that individual has provided assent to participate in the study.
4. Individual and individual's parent or legal guardian can comply with study procedures and are available for follow-up;
5. Individual is in generally good health as per the Investigator's medical judgement;

4.2 Exclusion Criteria

Each subject must not have:

1. Individual with clinical signs of fever and/or an oral temperature of ≥ 100.4°F (38.0°C) within three days prior to vaccination;
2. Individuals with a known history of any anaphylaxis, serious vaccine reactions or hypersensitivity to any of the vaccine components described in investigator brochure, or having any of the contraindications listed in the package insert of the comparator vaccine;
3. Individuals with history of Guillain-Barré syndrome or other demyelinating diseases such as encephalomyelitis and transverse myelitis;

4. Female subject "of childbearing potential[1]", sexually active, and not used any of the "acceptable contraceptive method[2]" for at least 2 months prior to study entry and intend to use until the end of subject participation;
5. Individual is pregnant or breast feeding female;
6. Individual and/or individual' parent/guardians who are not able to comprehend or follow all required study procedures for the whole period of the study;
7. Individual has received prior Meningococcal ACWY vaccination that conflicts with national recommendations or local practices for timing of primary or booster vaccination
8. Individual has received influenza vaccination or has had documented influenza disease in the last 6 months;
9. Known or suspected congenital or acquired immunodeficiency; or receipt immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or systemic corticosteroid therapy (prednisone or equivalent) at any dose for more than 2 consecutive weeks (14 days) within the past 3months. Topical, inhaled and intranasal corticosteroids are permitted. Intermittent use (one dose in 30 days) of intra-articular corticosteroids is also permitted;
10. Administration of immunoglobulin and/or any blood products within the 3 months preceding vaccination, or planned administration during the study;
11. Individual has participated in any clinical trial with another investigational product 30 days prior to first study visit or intent to participate in another clinical study at any time during the conduct of this study. Concomitant participation in an observational study (not involving drugs, vaccines, or medical devices) is acceptable;
12. Medical conditions or treatments contraindicating intramuscular vaccination due to increased risk of bleeding. These may include known bleeding disorders (such as thrombocytopenia), or treatment with anticoagulants (such as warfarin) in the 3

[1] A female is considered to be of childbearing potential if post onset of menarche and before natural or induced menopause. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea for which there is no other obvious pathological or physiological cause. Induced menopause is recognized to have occurred after hysterectomy, after bilateral oophorectomy, or iatrogenic ablation of ovarian function.

[2] The following birth control methods are considered effective:

- Abstinence
- Hormonal contraceptive (such as oral, injection, transdermal patch, implant)
- Diaphragm with spermicide, tubal occlusion device
- Intrauterine device (IUD)
- Tubal ligation
- Male partner using condom
- Male partner having been vasectomized

weeks preceding vaccination. However, antiplatelet agents such as low-dose aspirin, ticlopidine (Ticlid) and clopidogrel (Plavix) are permitted;

13. Evidence, or history (within the previous 12 months) of drug or alcohol abuse;
14. Study personnel or immediate family members (brother, sister, child, parent), the spouse of study personnel or individuals who are financially or emotionally dependent on study staff
15. Participation in this trial in a prior season, if applicable.
16. Any 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

Prior to receipt of study vaccination, subjects must be evaluated to confirm that they are eligible for subsequent vaccination. If subjects do not meet any of the original inclusion criteria listed above, they should not receive additional vaccinations.

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 may warrant delay of vaccination: 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 enrolment after the appropriate window for delay of vaccination has passed and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

4.4 Criteria for Repeat Vaccination in the Study

Prior to receipt of second study vaccination (“not previously vaccinated” subjects), 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 4.3) or the criteria listed below, they should not receive additional vaccinations.

- Subjects who experience any SAE judged to be related to study vaccine including hypersensitivity reactions.
- Subjects who develop any new condition which, in the opinion of the investigator, may pose additional risk to the subject if he/she continues to participate in the study.

Subjects who meet any of these criteria must not receive further study vaccinations. However, these subjects should be encouraged to continue study participation, as discussed in Section 3.6.

There are also circumstances under which repeat vaccination is a contraindication in this study. These circumstances include anaphylaxis or severe hypersensitivity reactions following vaccination. If these reactions are to occur, the subject must not receive additional vaccinations but is encouraged to continue in study participation.

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 follow-up telephone calls, as specified in the Table below and in the

Table 5-1 Study Procedures

Visit Category	Procedures
Pre-vaccination Clinic Visit(s)	Section 5.1 describes procedures to be followed prior to study vaccination: informed consent/assent, screening, enrolment, and randomization
Vaccination Clinic Visit(s)	Section 5.2 describes procedures to be followed during each clinic visit involving vaccination: vaccination, post-vaccination procedures, and post-vaccination reminders
Post-vaccination Visit(s)	Section 5.3 describes follow-up clinic visits and safety follow-up calls
Unscheduled Visit(s)	Section 5.4 describes possible procedures to be followed at unscheduled clinic visit
Study Termination Visit	Section 5.5 describes procedures to be followed at the last study visit for a subject (may include early termination visit)

5.1 Vaccination Clinic Visits / Day 1 Pre-vaccination

This section describes the procedures that must be performed for each potential subject prior to vaccination, including obtaining informed consent/assent, screening, enrolment and randomization. Please refer to Time and Events Table 3, 4 and 5.

5.1.1 Informed Consent/Assent

"Informed consent" is the voluntary agreement of an individual or his/her legal guardian(s) to participate in research. Consent must be given with free will of choice, and without undue inducement. The individual 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.

"Assent" is a term used to express willingness to participate in research by persons who are by definition too young to give informed consent but who are old enough to understand the proposed research in general, its expected risks and possible benefits, and the activities expected of them as subjects. Assent by itself is not sufficient, however. If assent is given, informed consent must still be obtained from the subject's parent(s) or legal guardian(s). Local laws define who constitutes a "child," and such definitions dictate whether or not a person can legally consent to participate in a protocol (Levine 1988).

Informed consent of the parent(s)/legal guardian(s) and assent of subject following local IRB/EC guidance **must** be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent and assent 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 and assent processes are located in section 13.2, Informed Consent Procedures.

If the parent(s)/legal guardian(s) are required to sign the informed consent form but are unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature. Similarly, when the subject is required to sign the informed consent form, and is 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 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 and/or parent(s)/legal guardian(s) and after the subject and/or parent(s)/legal

guardian(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 and/or parent(s)/legal guardian(s) and that informed consent was freely given by the subject and/or parent(s)/legal guardian(s).

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

5.1.2 Screening

After an individual/parent(s)/legal guardian(s) has consented to participate in the study and informed consent/assent is signed, the individual will receive a unique Screening Number. The subject's unique Screening Number will be documented in the Screening and Enrolment 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: age, sex, race, ethnicity, height and weight.

2. The subject's prior 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 and/or subject's parent(s)/legal guardian(s). 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 and/or subject's parent(s)/legal guardian(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 and/or subject's parent(s)/legal guardian(s) are unable to recall previous vaccination status then they should be considered "not previously vaccinated".
3. Medical history will be collected, including but not limited to any medical history that may be relevant to subject eligibility for study participation such as prior vaccinations, concomitant medications, 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 systems by interview that queries the subject or subject's parent(s)/legal guardian(s) as to any complaints the subject has experienced across each organ system.
5. Perform physical examination. The physical examination must be performed by the investigator or designee of the investigator, who is qualified to perform a physical examination in accordance with their institutional policy. Corresponding information is documented in the source documents and eCRFs.
6. For females of childbearing potential, privately review the ability to become pregnant (defined as subjects with confirmed onset of menses). Verify that they have used a reliable birth control method for at least two months prior to study entry, if sexually active. Confirm their commitment to continue to use a reliable birth control method until end of study participation. Determine the date of the subject's last menstrual period. A urine pregnancy test will be performed on all female subjects of childbearing potential (see Section 3.5). If the pregnancy test is positive or indeterminate, the subject must not be enrolled and must not be vaccinated (see Sections 3.8 and 7.1.6).
7. If applicable, prior and concomitant medications or vaccinations taken prior to start of study should be collected (refer to Section 6.5, Prior and Concomitant Medications and Vaccines for further details).
8. Collection of vital signs is to be performed: heart rate, blood pressure, respiratory rate and pre-vaccination body temperature (preferably oral). If body temperature is ≥38.0°C (or ≥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).
9. The use of any analgesics (oral, topical, etc.) and/or antipyretics within 24 hours prior to vaccination is an exclusion criteria (see section 6.5). 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.

10. Prior to vaccination, blood will be drawn (approximately 7 mL) from all subjects participating in the immunogenicity subset for serology testing. Details regarding the volume of blood and testing to be performed are in Section 3.5.

Measurement and recording of vital signs, height, weight and body temperature, may be conducted by a trained health care professional.

A general physical examination is to be performed by a qualified health care practitioner (see definitions).

The data described above will be written in the source document (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 Enrolment log. If the individual is determined to be eligible for the study, he/she will be enrolled into the study.

5.1.3 Enrolment

After signing the informed consent/assent form, 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 1:1 ratio to receive either QIVc or the non-influenza comparator vaccine (Men ACWY), and will be automatically assigned a unique Subject ID. The Subject ID will be the subject's unique identification number for all CRFs and associated study documentation that will be used for duration of the study. The Subject ID consists of a 11-digit number resulting from the combination of the site number, and the subject's order of randomization at the site. After randomization, the Screening Number ceases to be used and remains in the Screening and Enrolment Log only. The list of randomization assignments is produced by the IRT service provider and approved by Seqirus or delegate.

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 Enrolment Log and in the source document as specified in the Source Data 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.

Subjects will have blood samples collected for inclusion in an immunogenicity subset. A subset of evaluable subjects from multiple countries participating in the trial will be randomly selected for participation in the immunogenicity subset (in a 1:1 ratio). Subjects participating in the immunogenicity subset will have blood samples collected at Days 1 and 22 ("previously vaccinated"), or at Days 1, 29, and 50 ("not previously vaccinated"). Detailed information regarding the randomization procedures associated with the selection of the subjects participating in this subset can be found in the Statistical Analysis Plan (SAP).

5.2 Vaccination Clinic Visits

Please refer to Time and Events Table 3 and 5. 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.

The Day 1 (all subjects) and Day 29 ("not previously vaccinated" subjects) serology sample collected from subjects participating in the immunogenicity subset must be taken **prior** to vaccination.

After completing the pre-vaccination procedures as described in Section 5.1, Vaccination Clinic Visit – Day 1 Pre-vaccination 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 Post-vaccination Procedures (all subjects)

The following post-vaccination procedures will be performed:

1. Careful training of the subject or subject's parent(s)/legal guardian(s)/designated caregiver on how to measure local reactions and body temperature (preferably oral), how to complete and how often to complete the diary card is crucial. Training should be directed at the individual(s) who will perform the measurements of reactions and those who will enter the information into the diary card. This individual may not be the subject or subject's parent(s)/legal guardian(s), but if a person other than the subject or subject's parent(s)/legal guardian(s) enters information into the 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 or subject's parent(s)/legal guardian(s) on how to measure an injection site reaction should be performed while the subject is under observation after vaccination.

   Diary card instruction must include the following:

   a. The subject or subject's parent(s)/legal guardian(s) must understand that timely completion of the diary card on a daily basis is a critical component to study participation. The subject or subject's parent(s)/legal guardian(s) should also be instructed to write clearly and to complete the diary card in pen. Any corrections to the diary card that are performed by the person completing the diary card should include a single strikethrough line with a brief explanation for any change. **No changes can be made to the diary card when it is returned to the clinic.**

   b. Starting on the day of vaccination, the subject or subject's parent(s)/legal guardian(s) will check in the evening for specific types of reactions at the injection site (solicited local adverse events), any specific generalized symptoms (solicited systemic adverse events), body temperature (taken preferably orally) 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 hour" location on the diary card.

   c. Body temperature measurement is to be performed using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject or subject's parent(s)/legal guardian(s) should check body temperature. If the subject has fever, the highest body temperature observed that day should be recorded on the diary card. The measurement of solicited local adverse events is to be performed using the ruler provided by the site. The collection of body temperature, solicited local adverse events, solicited systemic adverse events on the diary card will continue for a total of 7 days after vaccination. The collection

of unsolicited AEs and medications/vaccinations on the diary card will continue for 21 days after vaccination, or up to the evening prior to the next clinic visit.

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 or subject's parent(s)/legal guardian(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 diary card.**
3. Schedule the next study activities, reminder telephone calls, and clinic visit, with the subject and if applicable subject's parent(s)/legal guardian(s)/ caregiver.
4. Remind the subject or subject's parent(s)/legal guardian(s) to complete the 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 medically attended AE, hospitalization or a visit to the emergency room.

Note: There are two (2) versions of the diary cards for this study:

- One version for subjects ≥ 2 years to < 6 years of age at the time of enrollment.
- One version for subjects ≥ 6 years to <18 of age at the time of enrollment.

The subject or subject's parent(s)/legal guardian(s) should be given the diary card that is based on the age of the subject at the time of enrollment.

Note: For a "not previously vaccinated" Subject who meets all of the following:

(1) Is to receive two (2) vaccinations, and

(2) Is enrolled in the study at the age of 5, and

(3) Is enrolled in the "not previously vaccinated" cohort, and

(4) Then has a birthday during the trial and becomes 6 years of age

The same version of the diary card given on the day of the 1st vaccination is also the version to be given on the day of the 2nd vaccination. Therefore, the version of the diary card to be used is the version for subject's ≥ 2 years to < 6 years of age at the time of enrollment for both vaccinations periods.

5.2.2 Day 29 Pre-vaccination 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 diary card will be reviewed. Please see section 3.4.2 for additional guidance on diary card review. The healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject or subject's parent(s)/legal guardian(s) and will determine if any additional diagnoses, including NOCDs, and/or AEs are present. Any concomitant medications taken and vaccinations received since the last clinic visit will also be reviewed.

   If the Visit 1 diary card is not brought back, interview the subject or subject's parent(s)/legal guardian(s) to obtain information relating to unsolicited AEs including SAEs, medically attended AEs, AEs leading to study or vaccine withdrawal, NOCDs, associated concomitant medications and all vaccinations (see section 6.5). All safety information described by the subject or subject's parent(s)/legal guardian(s) must be written down in the source documents.

2. Perform a review of systems by interview that queries the subject or subject's parent(s)/legal guardian(s) as to any complaints the subject has experienced across each organ system.
3. Perform brief symptom-directed physical examination. The physical examination must be performed by the investigator or designee of the investigator, who is qualified to perform a physical examination in accordance with their institutional policy. Corresponding information is documented in the source documents and eCRFs.
4. For females of childbearing potential privately verify that they have been and will continue to use a reliable birth control method during the entire study participation. Determine the date of the subject's last menstrual period. A urine pregnancy test will be performed on all female subjects of childbearing potential (see section 3.5). If the pregnancy test is positive or indeterminate, the subject must not be vaccinated (see sections 3.8 and 7.1.6).
5. Assess for influenza-like symptoms (see sections 5.3.3).
6. Prior to vaccination, blood will be drawn (approximately 7 mL) from all subjects participating in the immunogenicity subset for serology testing. Details regarding the volume of blood and testing to be performed are in section 3.5.
7. Take body temperature (preferably oral). If the body temperature is ≥38.0°C (≥100.4°F), vaccination must be postponed until three 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).

8. The use of any analgesics (oral, topical, etc.) and/or antipyretics within 24 hours prior to vaccination is an exclusion criteria (see section 6.5). 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 4.3) or meet any of the criteria listed under section 4.4 they should not receive additional vaccinations.

5.2.3 Day 29 Post-vaccination Procedures ("not previously vaccinated" subjects)

After confirming subjects continues to meet study eligibility criteria by completing procedures outlined in section 5.2.2 above, perform vaccination of the subject according to the assigned study vaccine and according to the procedures described in section 6.

The following post vaccination procedures should be carried out on Day 29:

1. Careful re-training, if necessary, of the subject or subject's parent(s)/legal guardian(s) on how to measure local reactions and body temperature, how to complete and how often to complete the diary card is crucial. Reference section 5.2.1 for 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 or subject's parent(s)/legal guardian(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 diary card.**
3. Schedule/review the next study activities, reminder telephone calls, and clinic visit, with the subject and if applicable subject's parent(s)/legal guardian(s).

Remind the subject or subject's parent(s)/legal guardian(s) to complete the 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 medically attended AE, hospitalization or a visit to the emergency room.

5.2.4 Post-vaccination Reminders

Reminder calls or alerts are not intended to be an interview for collection of safety data. If the subject and/or parent(s)/legal guardian(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 Reminder Calls

Subject Diary 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 and/or parent(s)/legal guardian(s)/ caregiver about completion of the Subject Diary. The call follows the Subject Diary Reminder Telephone Call Script provided to the site. The subject and/or parent(s)/legal guardian(s) should be reminded to contact the site via the telephone number provided in the informed consent to discuss medical questions.

5.3 Post-vaccination Visit(s)

Please refer to Time and Events Table 3, 4, 5 and 6. Post-vaccination visits (clinic visit or safety phone call) will be performed on Days 22, 91, 181, or end of influenza season. whichever is longer ("previously vaccinated" subjects) or on Days 50, 120 and 209, or end of influenza season. whichever is longer ("not previously vaccinated" subjects). In the event that a scheduled or unscheduled visit or call/message coincides, procedures may be combined.

5.3.1 Post-vaccination Clinic Visit(s)

The following procedures will be performed on Day 22 for "previously vaccinated" subjects and on Day 50 for "not previously vaccinated" subjects:

1. At the clinic visit, the diary card will be reviewed. Please see section 3.4.2 for additional guidance on diary card review. Any AEs/Unsolicited AEs and concomitant medications reported on the diary cards should be reviewed by a trained health care professional.

   If the diary card is not brought back, interview the subject or subject's parent(s)/legal guardian(s) to obtain information relating to unsolicited AEs including SAEs, medically attended AEs, AEs leading to study or vaccine withdrawal, NOCDs and

associated concomitant medications and all vaccinations (see Section 6.5). All safety information described by the subject or subject's parent(s)/legal guardian(s) must be written down in the source documents.

2. Perform a review of systems by interview that queries the subject or subject's parent(s)/legal guardian(s) as to any complaints the subject has experienced across each organ system.
3. Perform brief symptom-directed physical examination. The physical examination must be performed by the investigator or designee of the investigator, who is qualified to perform a physical examination in accordance with their institutional policy. Corresponding information is documented in the source documents and any relevant AE and/or NOCD findings noted during the physical examination are documented in both the source documents and electronic Case Report Forms (eCRFs).
4. Assess for influenza-like symptoms (see Sections 5.3.3).
5. Blood will be drawn (approximately 7 mL) from all subjects participating in the immunogenicity subset for serology testing. Details regarding the volume of blood and testing to be performed are in Section 3.5.
6. Schedule safety telephone calls on Days 91 and 181, or end of influenza season whichever is longer, for "previously vaccinated" subjects and on Days 120 and 209, or end of influenza season whichever is longer, for "not previously vaccinated" subjects.

Remind the subject or subject's parent(s)/legal guardian(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 a medically attended AE, or an emergency room visit.

5.3.2 Safety Follow-up Calls

Safety follow-up calls will be performed on Days 91 and 181, or end of influenza season whichever is longer ("previously vaccinated" subjects) or Days 120 and 209, or end of influenza season whichever is longer ("not previously vaccinated" subjects).

Safety follow-up calls are calls made to the subject by a blinded healthcare professional designated on the site log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject/subject's parent(s)/legal guardian(s) will be interviewed according to the script. Safety follow-up calls performed on Days 91 and 181, or end of influenza season whichever is longer ("previously vaccinated" subjects) or Days 120 and 209, or end of influenza season whichever is longer ("not previously vaccinated" subjects) will collect information relating to a subset of unsolicited adverse events including SAEs, AEs leading to withdrawal, new onset of

chronic disease (NOCD), ILI and concomitant medications or vaccinations associated with those events. All safety information described by the subject 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 will be asked as to whether he or she 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, 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.

ILI assessments will be performed to determine if symptoms of ILI are present. If the subject reports during phone contact that a medical event has occurred with symptoms consistent with an ILI, the subject will be asked to visit the site for further evaluation and potential NP swab taking. An NP swab for evaluation of the presence of influenza virus should be collected as soon as possible, preferably within 3 days, but up to 6 days following onset of protocol defined ILI symptoms (see Section 5.4.1).

The subject/subject's parent(s)/legal guardian(s) will receive a reminder of the next planned study activity, if applicable. The subject/subject's parent(s)/legal guardian(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.

The subject/subject's parent(s)/legal guardian(s) will be reminded to contact the site immediately if the subject experiences symptoms meeting primary protocol-defined ILI criteria to have a NP swab collected for evaluation of the presence of influenza virus (see Section 5.4.1).

5.3.3 Active Influenza Surveillance Phone Calls

Active surveillance for ILI for each subject will be conducted weekly via telephone from Day 1 and until the end of the influenza season. The subject and/or subject's parent/legal guardian/ caregiver will be asked via phone a scripted set of questions to determine if symptoms of ILI are present. The purpose of the phone call is to trigger a clinic (or home) visit and a NP swab sample collection if ILI symptoms are present. Should ILI symptoms be present, the subject and/or subject's parent/legal guardian will also be reminded to complete the ILI booklet. Phone calls are not intended to collect any clinical data. Site personnel's follow up on all cases meeting primary protocol-defined ILI criteria is to be documented in the subject's source records and monitored in order to ensure that all subjects with ILI symptoms are scheduled for the NP swab sample collection visit as soon

as possible within 3 days, and up to 6 days following onset of protocol defined ILI symptoms.

The subject and/or subject's parent/legal guardian will also be reminded to contact the site immediately if he or she experiences symptoms meeting primary protocol-defined ILI criteria to have a NP swab collected for evaluation of the presence of influenza virus.

5.4 Unscheduled Visits

5.4.1 Subjects Meeting the Influenza-Like-Illness Criteria

Clinic Visit or Home Visit – Obtaining NP Swab

Subjects will be asked to come to the site for an unscheduled clinic visit when experiencing symptoms meeting the primary protocol-defined ILI criteria. Subjects will be reminded to bring their ILI booklet. In the exceptional case that a clinic visit is not feasible, a home visit may be considered. The visit should occur as soon as possible, preferably within 3 days, and up to 6 days following onset of protocol defined ILI symptoms. During the visit the following procedures should be carried out:

- Assess ILI symptoms and assess associated medication. Document any anti-viral medication use from the first day of onset of ILI symptoms.
- Collect a NP swab for evaluation of the presence of influenza virus following the procedures for collecting, processing and shipping as described in the Lab Manual.
- Evaluate the subject's body temperature (preferably oral), heart rate, respiratory rate and blood pressure and perform a symptom-directed physical examination.
- Record the ILI, related information, medically-attended adverse events from ILI onset and associated concomitant medication in the source documents and in the eCRF (ILI-report and adverse events section).
- Schedule in next study activity and hand out new ILI booklet.

ILI Follow-up Safety Call

An ILI follow-up safety call will be performed at 30 (+7) days after primary protocol-defined ILI onset, amongst subjects who have had their NP swab obtained

During the visit the following procedures should be carried out:

- Assess ILI symptoms and associated medication, if any.
- Assess for medically-attended adverse event.
- Remind subject of next study activity.

5.5 Study Termination Visit

The study termination phone call will occur on Day 181 ("previously vaccinated" subjects) or Day 209 ("not previously vaccinated" subjects,or until the end of influenza season, whichever is longer). The termination visit consists of a telephone call. The date of termination is the date of the last contact (telephone call) in which the subject's health status was assessed or, in cases where the subject and/or parent/legal guardian does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the termination 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 termination phone call, the following procedures will be performed:

- Interview the subject to obtain information regarding potential SAEs, ILIs, NOCDs, AEs leading to withdrawal and the medication to treat these.
- Ask the subject or parent/legal guardian 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, this SAE must be reported by the site within 24 hours to Seqirus or delegate. Record any additional relevant medical history as needed.

  Potential ILI symptoms will be documented in the subject's source records. If the onset of the ILI is 3, or at most 6, days before the visit, an NP swab should be collected from the subject for influenza testing and study staff will document the ILI on an Adverse Event and ILI CRF. See procedures described in Section 5.4.1. Should an ILI be identified, it is recommended to postpone the study termination visit, to allow for the ILI follow-up visit to occur.
- Should the subject have experienced a protocol defined ILI for which an NP swab was obtained, please ensure collection and review of the ILI booklet and collect the information of any medically-attended adverse events which have occurred within 30 days after the onset of the of ILI.
- A qualified healthcare professional will perform a brief symptom-directed physical examination if necessary according to symptoms the subject has reported. This is a physical examination that will include an examination of organ systems that are relevant to the investigator based on review of the subject's reported adverse events, concomitant medication use. This assessment may include: measurement of vital signs (respiratory rate, blood pressure and heart rate), body temperature (preferably oral) and a check of general appearance. The physical assessment must be performed by the investigator or designee of the investigator, who is qualified to perform a physical

assessment in accordance with their institutional policy. Measurement and recording of vital signs and body temperature may be conducted by a trained health care professional. Corresponding information is documented in the subject's source document and eCRF(s). Measurement and recording of vital signs and body temperature may be conducted by a trained health care professional.

The site will review with the subject/subject's parent(s)/legal guardian(s) the plan of when information relating to the subject's participation in the study may be available (e.g., 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)/legal guardian(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.

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 termination visit, see Section 5.5, Study Termination Visit, if possible.

In addition, the following procedures will be performed:

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

The site will review with the subject/subject's parent(s)/legal guardian(s) the plan of when information relating to the subject's participation in the study may be available (e.g., 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)/legal guardian(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.

Investigational Vaccine: 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 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/dose)	Function
Active Ingredients Haemagglutinin (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	**4.0mg**	**Isotonic aid**
potassium chloride	**0.1mg**	**Isotonic acid**
magnesium chloride hexahydrate	**0.05mg**	**Stabilizer**
disodium hydrogen phosphate dihydrate	**0.646mg**	**Buffer**

Names of Ingredients	Quantity per dose* (0.5 mL/dose)	Function
potassium dihydrogen phosphate	**0.1865mg**	**Buffer**
Water for injection	**Up to 0.5 mL**	**diluent**

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

** residues of special relevance: beta-propiolactone, cetyltrimethylammonium bromide and polysorbate 80.

Non-influenza comparator vaccine:

Meningococcal (Group ACWY) Conjugate Vaccine

Menveo® will be used as non-influenza comparator vaccine.

Menveo® is a meningococcal (Groups A, C, Y and W-135) oligosaccharide diphtheria CRM197 conjugate vaccine for intramuscular injection. Menveo is supplied in two vials that must be combined prior to administration, to reconstitute the MenA lyophilized conjugate vaccine component with the MenCYW-135 liquid conjugate vaccine component immediately before administration.

For a comprehensive review of Menveo® please refer to the Summary of Products Characteristics/ Package Insert supplied by Seqirus or delegate; this document should be reviewed by the Investigators prior to initiating the study.

Saline Placebo

The saline placebo is a clear, colorless liquid. The dose to be administered is 0.5 mL and has the following composition per dose (0.5 mL):

Table 6.1-2 Composition of Saline Placebo

Component	Unit and/or Percentage Formula (Dose 0.5 mL)
Sodium chloride	4.5 mg
Water for injection	Qs to 0.5 mL

6.2 Non-Study Vaccines

The term ‘non-study vaccine’ refers to those vaccines which will be intentionally given to study subjects but not formally included in the analysis of study objectives. Non-study vaccines will not be provided by Seqirus.

6.3 Vaccine Preparation and Administration

The vaccine must be prepared according to the instruction sheet (QIVc) or package insert Menveo® before use. Expired vaccines must not be administered.

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.

QIVc will be provided in prefilled syringes (PFS), with an injectable volume of approximately 0.5 mL. The full volume contained in the PFS is to be administered. Menveo is supplied in two vials that must be combined prior to administration, to reconstitute the MenA lyophilized conjugate vaccine component with the MenCYW-135 liquid conjugate vaccine component immediately before administration.

Vaccination will be performed intramuscularly, preferably in the deltoid muscle of the non-dominant arm.

Detailed vaccine preparation and administration instructions will be provided to investigators in the Protocol Ancillary Document prior to study start.

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 study vaccine administration is determined by evaluating the entry criteria outlined in protocol Sections 4.1, Inclusion Criteria and 4.2, Exclusion Criteria.

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

Study vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines.

Shake the vaccine well before use to form a homogeneous suspension. The vaccine should be visually inspected for particulate matter and discoloration prior to administration. In the event of any foreign particulate matter and/or variation of physical aspect being observed, do not administer the vaccine and contact the Sponsor and report the issue as a Pharmaceutical Technical Complaint. Do not discard the vaccine until authorized by Seqirus.

Standard vaccination practices are to be observed and care should be taken to administer the injection intramuscularly. Before administering vaccine, the vaccination site is to be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. **DO NOT inject intravascularly**.

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 should 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 Table 6.1-1 or as per the package insert of Menveo®) 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

Data on medications including any vaccinations that were taken by the subject up to 2 months prior to enrollment will be recorded in the source documents and collected on the relevant Prior and Concomitant Medications eCRF. Data on influenza vaccinations that were administered to the subject up to 6 months prior to enrollment will recorded in the source documents and collected on the Prior and Concomitant Medications eCRF.

When recording prior and concomitant medications/vaccinations, these should be checked against the study entry and continuation criteria in Sections 4.1 through 4.3 to ensure that the subject should be enrolled/continued in the study.

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 documents and/or diary card and Concomitant Medications eCRF.

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.

From study entry through termination, concomitant medications will be recorded in the Concomitant Medications eCRF as outlined below:

- All medications, with the exception of vitamins and minerals, will be recorded beginning from the time of vaccination and continuing for 21 days following each vaccination received.
- Medications associated with SAEs, AEs leading to study withdrawal, NOCDs, and all vaccinations will be recorded from Day 1 to Day 181, or until the end of influenza season whichever is longer, for "previously vaccinated" subjects and from Day 1 to Day 209, or until the end of influenza season whichever is longer, for "not previously vaccinated" subjects.
- All medications associated with any medically-attended adverse events within 30 days after the ILI onset

The following treatments, if used within the Treatment Period (Day 1 through 3 weeks following subject's last study vaccination only), e.g., in case of a medical need, represent a protocol deviation and may result in the subject being excluded from the Per Protocol Set (PPS):

- Cancer chemotherapy.
- Immunosuppressive agents or systemic corticosteroids at any dose (topical, inhaled, and intranasal corticosteroids are permitted). A single dose of intra-articular corticosteroids is also permitted).
- Blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation.
-
- Any non-study investigative agents.

A non-study influenza vaccination(s) is considered a protocol deviation if received from Day 1 until the end of season or Day 181/ 209 whichever comes first and may result in the subject being excluded from the Per Protocol Set (PPS).

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor or delegate will ensure the following:

- Supply the study vaccine(s)/saline.

- Appropriate labeling of all study vaccines provided that complies with the legal requirements of each country where the study is to be performed.

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
  - Confirmation to the Sponsor or delegate of the temperature range during shipment from the Sponsor to the investigator's designated storage location
  - 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.
  - Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.
- Appropriate use of the study vaccines, including:
  - Not use of vaccines 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 blinded 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 or delegate. 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 or delegate, as applicable.
- Proper adherence to the local institutional policy with respect to destruction of study vaccines.

- Complete record keeping of 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 (or delegate) provides written authorization for use. In the event that the use cannot be authorized, the Sponsor or delegate 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/delegate) or returned to the Sponsor or delegate.

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 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), or until the end of influenza season, whichever is longer. 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 subject diaries or interview.

7.1.1 Solicited Adverse Events

The term "reactogenicity" refers to selected signs and symptoms ("reactions") occurring in the hours and days following a vaccination, to be collected by the subject for seven (7) consecutive days, using a pre-defined checklist in a diary card (i.e., solicited adverse events).

The following adverse events are included in the diary card check list. Each adverse event will be assessed using the grading system reported in the SAP.

Subjects < 6 years of age

Solicited local adverse events:

- Injection site induration
- Injection site erythema
- Injection site ecchymosis
- Injection site tenderness

Solicited systemic adverse events:

- Change of eating habits
- Sleepiness
- Vomiting
- Diarrhea
- Irritability
- Shivering
- Fever is also solicited but this is based on actual recorded body temperatures rather than subjective interpretation of fever by the subject.

Subjects ≥ 6 years of age

Solicited local adverse events:

- Injection site induration
- Injection site erythema
- Injection site ecchymosis
- Injection site pain

Solicited systemic adverse events:

- Shivering
- Nausea

- Generalized myalgia
- Generalized arthralgia
- Headache
- Fatigue
- Vomiting
- Diarrhea
- Loss of appetite
- Fever is also solicited but this is based on actual recorded body temperatures rather than subjective interpretation of fever by the subject.

Other solicited adverse events:

- Use of analgesics / antipyretics for prophylaxis.
- Use of analgesics / antipyretics for treatment
- Body temperature described in degrees Celsius or degrees Fahrenheit and summarized by route of body measurement.

The study staff must review the diary card with the subject and/or parent(s)/legal guardian(s) at the following visit (see sections 3.4.2, 5.2 and 5.3.1) and must directly record the solicited local and systemic adverse events on the appropriate Local and Systemic Adverse events eCRF. As described in Section 3.4.2, all solicited local and systemic adverse events that are legible must be recorded verbatim in the eCRFs, even if the values do not appear to be plausible.

If a solicited local or systemic adverse event continues beyond day 7 after vaccination, it will also be recorded as an AE on the AEs eCRF.

7.1.2 Unsolicited Adverse Events

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

Potential unsolicited AEs 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 and/or parent(s)/legal guardian(s). In case of such events, the subject and/or parent(s)/legal guardian(s) will be instructed to contact the site as soon as possible to report the event(s). The detailed information about the reported

unsolicited AEs will be collected by the qualified site personnel during the interview and will be documented in the subject's records.

Unsolicited AEs that are not medically attended nor perceived as a concern by subjects (and/or parent(s)/legal guardian(s)) will be collected during interview with the subject and/or parent(s)/legal guardian(s) and by review of available medical records at the next visit (see section 5.3, Post-vaccination Visit(s)).

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 CRF 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. 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.

3. 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. Each adverse event will be assessed using the grading system reported 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 that leads to a visit to a healthcare provider.
- "New onset of chronic disease" (NOCD): 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 enrolment.
- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal.

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

When the subject and/or parent(s)/legal guardian(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 medical chart.

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 (i.e., 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 (i.e., 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 SAE need not, by definition, be severe.

Serious adverse events will be captured both on the Vaccines Serious Adverse Event (VSAE) form as well as on the AE CRF. All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are judged 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 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 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 (e.g., 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 Events CRF, as specified in section 7.1.1, Solicited Adverse Events, and on the VSAE form, if applicable, which is part of the Investigator Site File. 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 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 EC/IRB or applicable regulatory authorities 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/EC. 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 investigator will be responsible for submitting this information to the EC/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 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 6 months afterwards. Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the investigator.

7.1.6 Pregnancies

To ensure subjects' safety, each pregnancy in a subject after study vaccination must be reported to Seqirus or delegate within 72 hours of the site learning of its occurrence. If the subject agrees to submit this information, the pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of safety follow-up for the study has ended.

Pregnancy data must be recorded on a Pregnancy Report paper form (initial report) and Pregnancy Follow-Up paper form (outcome report) and reported to Seqirus or delegate. The pregnancy forms can be requested from the CRA. Instructions and contact details for submitting the Pregnancy form will be provided to the investigator.

Any pregnancy outcome meeting the definition of a SAE (see section 7.1.4, Serious Adverse Events) must also be reported on the SAE Report Form in the CRF.

7.1.7 Safety Laboratory Measurements

No scheduled safety laboratory measurements are planned for this study.

7.2 Efficacy Assessment

Confirmation of influenza infection by RT-PCR or culture from a nasopharyngeal swab sample is necessary for the efficacy assessment in the study. Nasopharyngeal swab retrieval will be initiated after primary protocol-defined ILI has been identified. Primary

protocol-defined ILI can occur at any time during the study and will be evaluated in each subject from Visit 1 (Day 1) through Study Termination. ILI symptoms will be captured during study visits. The ILI onset day is defined as the first day that the subject meets the primary protocol-defined ILI. The end date is defined as the date the last symptom resolves. A new ILI episode will only be taken into account after resolution of the previous one, as judged by the investigator (suggested interval between two ILI episodes is 14 symptom-free days).

Subjects with protocol defined ILI will have a NP swab collected for evaluation of the presence of influenza virus. NP swabs should be targeted for collection within 3 days from the ILI onset to ensure optimal viral yield, however samples will be accepted if collected up to 6 days following the day of ILI onset. NP swabs will not be taken beyond a total of 7 days (6 days following onset of ILI) as the level of virus detectable beyond this period can be negligible, particularly for influenza A.

All NP swabs collected from subjects with ILI will be shipped under pre-specified conditions in viral transport media to a qualified lab and stored for analysis for influenza.

NP swabs will be analyzed by RT-PCR and placed into culture. The result of the RT-PCR assay will be the presence or absence of influenza virus. The viral culture will be used for the purpose of viral expansion to enable phenotypic characterization of the influenza virus (e.g. antigenic match). Testing will be conducted by a designated laboratory in a blinded manner towards the treatment arm. Please see the Protocol Ancillary Document for name(s) and details.

The efficacy of QIVc will be further characterized with specific attention for all-cause mortality, all-cause pneumonia and all-cause otitis media.

7.3 Immunogenicity Assessment

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

The secondary immunogenicity analysis will evaluate immunogenicity of QIVc measured by the HI assay by titrating antibodies against the influenza strains homologous to the seasonal vaccine (see Section 2.2, Secondary Objectives). To further characterize the immune response, additional immunogenicity analyses may be conducted on the immunogenicity subset using other assays such as microneutralization (MN). In case of additional immunogenicity analyses, the immune response will be characterized in a similar manner as described in the Secondary Immunogenicity Endpoint section.

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 non-influenza comparator vaccine at Day 1 (baseline) and 22 ("previously vaccinated" subjects) or at Day 1 (baseline), Day 29 and Day 50 ("not previously vaccinated" subjects) for HI Peak antibody responses to the strains selected for the seasonal vaccine are typically observed after 3 weeks of vaccination.

- Testing will be conducted by Seqirus or designated laboratory in a blinded manner towards the treatment arm and the visit. Please see the Protocol Ancillary Document for name(s) and details.

8. STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Primary Endpoint(s)

8.1.1.1 Primary Safety Endpoint(s)

Not applicable.

8.1.1.2 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the time from the last study vaccination to the onset of the first occurrence confirmed influenza by either RT-PCR-confirmed or culture-confirmed, due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, occurring >14 days after the last vaccination and until the end of the influenza season.

8.1.1.3 Primary Immunogenicity Endpoint(s)

Not applicable.

8.1.2 Secondary Endpoint(s)

8.1.2.1 Secondary Safety Endpoint(s)

Safety will be assessed by calculating:

- The percentage of subjects with solicited local and systemic adverse events for 7 days following vaccination at Day 1 (“previously vaccinated” subjects) or Day1 and Day 29, (“not previously vaccinated” subjects) in the QIVc group and the non-influenza comparator vaccine group.

- The percentage of subjects with all unsolicited AEs will be assessed from Day 1 to Day 22 for “previously vaccinated” subjects or Day 1 to Day 50 for “not previously vaccinated” subjects in the QIVc group and in non-influenza comparator vaccine group.

- Percentage of subjects with SAEs, AEs leading to withdrawal from the study and NOCDs reported during the subject’s entire participation in the study, i.e. from Day 1 to Day 181 (for “previously vaccinated” subjects) or to Day 209 (for “not previously

vaccinated" subjects), or until the end of influenza season, whichever is longer, and all medications associated with these events.

- Percentage of subjects with medically-attended adverse events within 30 days after of first occurrence RT-PCR confirmed ILI.

8.1.2.2 Secondary Efficacy Endpoint(s)

The efficacy endpoint for secondary objective 1 is the time from the last study vaccination to the onset of the first occurrence confirmed influenza by either RT-PCR-confirmed or culture-confirmed, due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, occurring at >14 days after the last vaccination and until the end of the influenza season.

The efficacy endpoint for secondary objective 2 is the time from the last study vaccination to the onset of the first-occurrence confirmed influenza by RT-PCR-confirmed, due to any influenza Type A or B strain regardless of antigen match to the strains selected for the seasonal vaccine, (occurring at >14 days after the last vaccination and until the end of the influenza season).

The efficacy endpoint for secondary objective 3 is time from the last study vaccination to the onset of the first-occurrence confirmed influenza by culture-confirmed, due to any influenza Type A or B strain regardless of antigenic match to the strains selected for the seasonal vaccine, (occurring at >14 days after the last vaccination and until the end of the influenza season)

The efficacy endpoint for secondary objective 4 is the time from the last study vaccination to the onset of the first-occurrence confirmed influenza by culture-confirmed, due to influenza Type A or B strain antigenic matched to the strains selected for the seasonal vaccine, (occurring at >14 days after the last vaccination and until the end of the influenza season).

8.1.2.3 Secondary Immunogenicity Endpoints

The measures for assessing immunogenicity as determined by HI are as follows:

- HI Geometric mean titers (GMTs) on Day 1 (all subjects), Day 22 (all "previously vaccinated" subjects receiving a single vaccine dose) or Days 29 and 50 (all "not

previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains.

- Percentage of subjects achieving seroconversion (defined as: either a pre-vaccination HI titer < 1:10 and a post-vaccination HI titer ≥ 1:40 or a pre-vaccination HI titer ≥ 1:10 and a ≥ 4-fold increase in post-vaccination HI titer) on Day 22 (all "previously vaccinated" subjects receiving a single vaccine dose) or Days 29 and 50 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains.

- HI Geometric mean Ratio (GMR) of Day 22/Day 1 (all "previously vaccinated" subjects receiving a single vaccine dose) or Day 29/Day 1 and Day 50/Day 1 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains.

- Percentage of subjects with HI titer ≥ 1:40 on Day 22 (all "previously vaccinated" subjects receiving a single vaccine dose) or Days 29 and 50 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains.

8.1.3 Exploratory Endpoint(s)

8.1.3.1 Exploratory Safety Endpoint(s)

There are no exploratory safety endpoints in this study.

8.1.3.2 Exploratory Efficacy Endpoint(s)

The measures for exploring efficacy are as follows:

- Number of deaths as derived from SAE forms
- Number of subjects with pneumonia as derived from AE forms
- Number of subjects with physician-confirmed otitis media as derived from AE forms

8.1.3.3 Exploratory Immunogenicity Endpoint(s)

In case of additional immunogenicity analyses, such as MN, the immune response will be characterized in a similar manner as described in Secondary Immunogenicity Endpoints:

- MN Geometric mean titers (GMTs) on Day 1 (all subjects), Day 22 (all "previously vaccinated" subjects receiving a single vaccine dose) or Days 29 and 50 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza

strains.

- MN Geometric mean Ratio (GMR) of Day 22/Day 1 (all "previously vaccinated" subjects receiving a single vaccine dose) or Day 29/Day 1 and Day 50/Day 1 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains.

- Percentage of subjects with at least a 4-fold rise in MN titer on Day 22 (all "previously vaccinated" subjects receiving a single vaccine dose) or Day 29 and Day 50 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains

- Percentage of subjects with at least a 4-fold rise in MN titer on Day 22 (all "previously vaccinated" subjects receiving a single vaccine dose) or Day 29 and Day 50 (all "not previously vaccinated" subjects receiving 2 doses) for all 4 influenza strains

8.2 Success Criteria

The study is considered successful if the primary efficacy objective is 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 Evaluation of Primary Efficacy Objective

Vaccine Efficacy (VE) and its CI will be calculated for the RT-PCR-confirmed or culture confirmed influenza A and B disease presenting as influenza like illness (ILI).

The primary efficacy objective is achieved if the lower limit (LL) of the two-sided 95% confidence interval (CI) of the estimator of absolute vaccine efficacy of QIVc versus non-influenza comparator vaccine calculated from cases of all strains in subjects ≥2 years to <18 years of age is greater than 20%.

In case an interim analysis will be performed the 95% CI will be adjusted accordingly; further details will be specified in the SAP.

8.2.1.3 Success Criteria for Evaluation of Co-Primary Efficacy Objective

In case the primary efficacy objective (see above) is achieved, then the efficacy of QIVc in preventing laboratory confirmed influenza A and or B disease in subjects ≥3 years to <18 years of age will be demonstrated.

Vaccine Efficacy (VE) and its CI will be calculated for the RT-PCR-confirmed or culture confirmed influenza A and B disease presenting as influenza like illness (ILI).

The co-primary efficacy objective is achieved if the lower limit (LL) of the two-sided 95% confidence interval (CI) of the estimator of absolute vaccine efficacy of QIVc versus non-influenza comparator vaccine calculated from cases of all strains in subjects ≥3 years to <18 years of age is greater than 30%.

8.2.1.4 Success Criteria for Primary Immunogenicity Objective(s)

Not applicable.

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

8.3.1 All Enrolled Set

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

8.3.2 All Exposed Set

All subjects in the enrolled set who receive a study vaccination.

8.3.3 Safety Set

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

All subjects in the Exposed Set with any solicited adverse event data, indicating the occurrence or lack of occurrence of solicited adverse events (e.g., use of analgesics/antipyretics medication) i.e., a subject does not have to have any solicited adverse events to be included in this population.

Unsolicited Safety Set (unsolicited adverse events)

All subjects in the Exposed Set with unsolicited adverse event data, indicating the occurrence or lack of occurrence of an adverse event i.e., a subject does not have to have any adverse events to be included in this population.

Overall Safety Set

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

Subjects in the Safety sets will be analyzed as "treated" (i.e., according to the vaccine a subject received, rather than the vaccine to which the subject may have been randomized).

Subjects with reportable stratification errors will be analyzed "as corrected", (i.e. analyze subject in corrected stratum) in safety. Subjects with non-reportable stratification errors will be shifted and analyzed in their correct stratum in safety.

8.3.4 Full Analysis Set (FAS) Efficacy/Immunogenicity Set

Full Analysis Set Efficacy

All subjects in the All Enrolled Set who are randomized, receive a study vaccination and provide efficacy data.

Full Analysis Set Immunogenicity

All subjects in the All Enrolled Set who are randomized, receive at least one study vaccination and provide immunogenicity data both at baseline and after last vaccination at Day 50 for subjects "not previously vaccinated" and Day 22 for subjects "previously vaccinated".

Subjects in the FAS will be analyzed "as randomized" (i.e., according to the vaccine a subject was designated to receive, which may be different from the vaccine the subject actually received).

8.3.5 Per Protocol (PP) Set Efficacy/Immunogenicity Set

All subjects in the FAS Efficacy / Immunogenicity who:

- Correctly receive the vaccine (i.e., receive the vaccine to which the subjects is randomized and at the scheduled time points).
- Have no protocol deviations leading to exclusion (see Section 8.3.8, Protocol Deviations) as defined prior to unblinding / analysis.
- Are not excluded due to other reasons defined prior to unblinding or analysis (see Section 8.3.8, Protocol Deviations)

PPS are subsets of FAS and should be always defined even if the objectives do not require it.

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

In case of misrandomization with regard to treatment arm, the subject is excluded from the PPS. If a subject receives a vaccine, labelled for another subject but the same as the one the subject was randomized to, the subject will not be removed from the PPS.

If a subject received the correct study vaccine (dose, batch) but from another ongoing study at the site then the subject should be excluded from the PPS.

Subjects with reportable stratification error will be excluded from the PPS. A stratification error is considered "reportable" when it has a major impact to the vaccination dose and/or to the vaccination schedule of a subject.

Subjects with non-reportable stratification errors will be analyzed in the correct stratum in 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 efficacy analyses will be performed by stratifying for the following subgroups:

- Subjects ≥3 to <9 years of age, ≥2 to <9 years of age and ≥9 to <18 years of age

- Subjects "previously vaccinated" and “not previously vaccinated”
- Subjects by race
- Subjects by sex
- Subjects by country or region
- Subjects by season/year treated

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

- Subjects with pre-vaccination HI titer <1:10 and pre-vaccination HI titer ≥ 1:10
- Subjects "previously vaccinated" and “not previously vaccinated”
- Subjects by race
- Subjects by sex
- Subjects by country or region
- Subjects by season/year treated

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

- Subjects ≥3 to <9 years of age, ≥2 to <9 years of age and ≥9 to <18 years of age.
- Subjects "previously vaccinated" and “not previously vaccinated”
- Subjects by race
- Subjects by sex
- Subjects by country or region
- Subjects by season/year treated

Safety and immunogenicity analyses will also be performed by time periods as detailed in SAP. Any other additional analyses may be performed, as described in 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. CSR-reportable protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoints, which will be specified in the statistical analysis plan. 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

8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (number of observations, mean, standard deviation, median, minimum and maximum) for quantitative variables i.e., age, height, weight and BMI will be calculated for the overall and by vaccine group.

Frequencies and percentages for qualitative variables i.e., sex, race and ethnicity, will be summarized for the overall, by vaccine group, and by age group and vaccine group.

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 Hypotheses for Primary and Co-Primary Efficacy Objectives

The primary measure of efficacy is the estimate of absolute vaccine efficacy (aVE) of QIVc relative to the non-influenza comparator vaccine for preventing first-occurrence influenza-confirmed disease by either RT-PCR-confirmed or culture-confirmed influenza strains contained in QIVc and the non-influenza comparator, regardless of antigenic match.
Absolute vaccine efficacy (aVE) will only be assessed for laboratory confirmed influenza cases (by either RT-PCR-confirmed or culture-confirmed) with illness occurring at >14 days after the last vaccination and until end of the influenza season, since clinical protection is not immediate with vaccination.

Time-to-event methodology based on a proportional hazard model will be used for all efficacy analyses. Absolute vaccine efficacy (aVE) against first or only confirmed influenza cases will be determined using a standard formula: aVE = 1 - HR where HR is the hazard ratio for influenza confirmed (by either RT-PCR-confirmed or culture-confirmed) ILI in the QIVc group versus the non-influenza comparator group. The HR will be estimated by a proportional hazards regression model, described in Section 8.4.2.2.3. For which the following null (H_0) and alternative (H_1) hypotheses will be tested:

$$H0: 1 - HR \leq 0.2 \text{ versus } H1: 1 - HR > 0.2$$

where HR is a hazard ratio of QIVc versus non-influenza comparator and VE is vaccine efficacy. The primary objective will be achieved if the lower limit of the two-sided confidence interval of VE estimate, with at least 95% coverage in a multiple sequential hypothesis testing, exceeds 0.2 in subjects ≥2 years to <18 years of age.

The co-primary objective will be achieved if the lower limit of the two-sided confidence interval of VE estimate, with at least 95% coverage in a multiple sequential hypothesis testing, exceeds 0.3 in subjects ≥3 years to <18 years of age.

The co-primary objective will only be demonstrated in case of successful demonstration of the primary efficacy objective (i.e. in hierarchical testing procedure, only after demonstration of absolute vaccine efficacy of QIVc in subjects ≥2 years to <18 years of age).

In case an interim analysis will be performed the 95% CI will be adjusted accordingly. If an interim analysis is performed and the trial doesn't stop, then all the subsequent analysis will be tested at a reduced alpha level, i.e. what's left from the interim analysis. The confidence interval will be higher than 95% instead of 95% for the final analysis.

Further details of statistical methods and analyses will be fully specified in the Statistical Analysis Plan (SAP).

8.4.2.2.3 Analysis Populations for Primary and Co-Primary Efficacy Objectives

The analysis population for primary vaccine efficacy analyses will be based on the Efficacy FAS and repeated on the Efficacy PPS.

8.4.2.2.4 Statistical Methods for Primary and Co-Primary Efficacy Objectives

For each of the age groups (≥2 to < 18 and ≥3 to < 18 years) , the HR[3]and the related 95% CI of HR, for onset of first RT-PCR or culture confirmed influenza will be estimated by a proportional hazards regression model with treatment effect as a fixed effect and stratifying covariates as random effect:

$h_i(t|X) = h_0(t) \exp(\beta^T X + b^T Z)$, with t denoting time to the influenza, β is the effect of treatment group indicated by X, b is random effect (assumed as a multivariable random gaussian variable with zero mean and diagonal covariance matrix), Z is random effect covariate (reflecting randomization strata, see SAP for further discussion of the covariates utilized).

Subjects that did not experience ILI during observation period and subjects that dropped out from the study during observational period will be censored (right-censoring). The estimate of the hazard ratio, the respective estimate for absolute VE and the pertaining two-sided CIs will be calculated based on this model. If the study continues over several seasons, estimates will be also adjusted for the factor season (s). In case of one or two (interim) analyses, confidence levels at each stage will be adjusted to provide 95% overall coverage.

For each of the age groups (≥2 to < 18 and ≥3 to < 18 years), estimates for hazard ratio in Cox Proportional hazard (PH) model will be calculated using Maximum Likelihood (ML) method. In case of problems with convergence (algorithm does not converge or converges to infinite estimates) penalized ML approach will be used (Heinze and Schemper).

Vaccine efficacy VE = 1 – HR, that is, $1- \exp(\widehat{\beta})$

with $\hat{\beta}$ with 100(1- α) percent confidence interval as:

[3] Formula: VE=1-HR

[1- exp (+ Z(s.e.($\widehat{\beta}$)*); 1- exp (*$\hat{\beta}$ - Z(s.e.($\widehat{\beta}$))]. Z is the 100(1- α) percent point of the standard normal distribution, and s.e. denotes the standard error of β.

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

The estimate of the hazard ratio, the respective estimate for absolute VE and pertaining two-sided 95% CIs will be calculated based on this model. If the study continues over several seasons, estimates will be also adjusted for the factor season (s). Factor site/center or country might be added to the model if appropriate. In case of more than one interim analysis confidence level for the estimates at the final stage will be adjusted.

In case interim analyses will be performed a k-stages group - sequential test procedure for time-to-event data will be implemented. As the K-stage interim analysis for aVE introduces a multiple test problem, alpha will be adjusted as described in section 8.6 via an error-spending function. For this group sequential test procedure parameters like information level and/or standard error at each stage will be calculated by the above described model and then used to calculate the actual group sequential test that compared the test statistic at each stage with the respective boundaries. Repeated CIs for each stage and also the final estimator and the respective CI can be retrieved by the group sequential test method to maintain simultaneous coverage probability.

Further details of the statistical methods will be provided in the statistical analysis plan (SAP).

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

Not applicable.

8.4.2.3.1 Statistical Hypotheses for Primary Immunogenicity Objectives

Not applicable.

8.4.2.3.2 Analysis Populations for Primary Immunogenicity Objectives

Not applicable.

8.4.2.3.3 Statistical Methods for Primary Immunogenicity Objectives

Not applicable.

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

The solicited local and systemic adverse events for each age group is described in Section 7.1.1.

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.

Post-vaccination solicited adverse events reported from day 1 to Day 7 will be summarized for the intervals Day 1-3, Day 4-7, Day 1-7 by maximal severity and by vaccine group, excluding the 30 minute measurement, which will be summarized separately (and similarly for Day 29 to Day 35 solicited adverse events, for “not previously vaccinated” subjects). Injection-site erythema, ecchymosis and induration will be summarized according to categories based on linear measurements, please refer to the SAP for definition of categories.

Injection site pain 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 please refer to the Section 7.1.3 of the protocol.

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 and percentage of subjects reporting use. Summaries by type of use (prophylactic versus treatment) and by treatment arm will be provided.

Body temperature will be summarized by 0.5°C and 1.0°C increments from 36.0°C up to ≥40°C and will be broken down by route of measurement and by age cohort (≥2 to <9 years of age and ≥9 to <18 years of age). In addition, fever will be summarized according to "mild", "moderate" or "severe" categorization. For the definition of severity grades please refer to the SAP.

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. 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 22, Day 23 to Day 181 in "previously vaccinated" subjects and Day 1 to Day 50, Day 51 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;
- Adverse events that are possibly or probably related to vaccine;
- NOCD;
- Adverse event leading to withdrawal;
- Adverse event resulting in death.

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

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 Hypotheses for Secondary Efficacy Objectives

Secondary efficacy objectives are not associated with any hypothesis testing.

8.4.3.2.2 Analysis Populations for Secondary Efficacy Objectives

All secondary efficacy objectives will be evaluated based on the FAS Efficacy and will be also repeated based on PPS Efficacy.

8.4.3.2.3 Statistical Methods for Secondary Efficacy Objectives

The model used to estimate absolute vaccine efficacy for the secondary objectives is similar to the model used for the primary efficacy objectives.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

8.4.3.3.1 Statistical Hypotheses for Secondary Immunogenicity Objectives

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

8.4.3.3.2 Analysis Populations for Secondary Immunogenicity Objectives

Secondary immunogenicity objectives will be evaluated based on the PPS Immunogenicity and FAS Immunogenicity for non-matching strains.

8.4.3.3.3 Statistical Methods for Secondary Immunogenicity Objectives

All statistical analyses for HI titers will be performed on the logarithmically (base 10) transformed values. Individual HI titers below detection limit (<10) will be set to half of that limit (5).

Crude estimates for GMTs, GMRs and pertaining 2-sided 95% CIs will be calculated assuming log-normal distribution of the titers and will be completed by providing minimum, maximum and median titers for each 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 95% CIs calculated according to Clopper's and Pearson's (1934) method. No multiplicity adjustment to the CI levels will be implemented.

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

8.4.4 Analysis of Exploratory Objectives

8.4.4.1 Analysis of Exploratory Safety Objective(s)

There are no exploratory safety objectives in this study.

8.4.4.2 Analysis of Exploratory Efficacy Objective(s)

The efficacy of QIVc will be further characterized with specific attention for all-cause mortality, all-cause pneumonia and all-cause otitis media by descriptive statistics of the following.

- Number of deaths as derived from SAE forms
- Number of subjects with pneumonia as derived from AE forms
- Number of subjects with physician-confirmed otitis media as derived from AE forms

8.4.4.3 Analysis of Exploratory Immunogenicity Objective(s)

If other assays such as MN are available, the immune response can be further characterized in the similar manner as described in the analysis of secondary immunogenicity endpoints.

8.5 Sample Size and Power Considerations of Primary, Co-Primary and Secondary Objectives

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

Primary Efficacy Objective *≥2 years to <18 years of age*

Estimated sample size to arrive at 298 events, is 4,814 evaluable subjects (or 2,407 evaluable subjects per treatment group), assuming attack rate in non-influenza comparator vaccine subjects of 8%, vaccine efficacy of 45%, and the risk of infection contained entirely within period covered by follow-up. Accounting for early dropout and uncertainty about the assumed parameters, 5,349 subjects are planned to be enrolled to demonstrate that the lower limit of the two-sided 95% CI for the VE is greater than 20% for the primary endpoint assessment, with approximately 90% power.

Co-primary Efficacy Objective *≥3 years to <18 years of age*

Assuming a true vaccine efficacy of 50% it was calculated that approximately 381 observed confirmed ILI cases would be needed to demonstrate that the lower limit of the two-sided 95% CI for the VE is greater than 30% with approximately 90% power.

The statistical test performed will depend only on number of confirmed ILI cases (events), so sample size estimate is only for operational reasons. Estimated sample size to arrive at 381 events, is 6,350 evaluable subjects (or 3,175 evaluable subjects per treatment group), assuming attack rate in non-influenza comparator vaccine subjects of 8%, assumed vaccine efficacy of 50%, VE is greater than 30%, and the risk of infection contained entirely within period covered by follow-up. Accounting for early dropout and uncertainty about the assumed parameters, 7,056 subjects are planned to be enrolled to demonstrate that the lower limit of the two-sided 95% CI for the VE is greater than 30%.

Table 8.5.1 summarizes the power calculations assumptions and the number of events required to meet primary and co-primary endpoint.

Table 8.5.1 Power calculation for Primary and Co-Primary Endpoints

Age group	VE Success Criteria	Assumed Vaccine Efficacy	Influenza attack rate in comparator group	Power	Minimal total evaluable subjects per Treatment Group	Minimal enrolled subjects needed per Treatment group*()	Minimal total Number Enrolled*	otal Number of ILIs to demonstrate LL 95% CI for VE is > 30% or 20%
≥2 years to <18 years of age	20%	45%	8%	>90%	2,407	2,674	5,349	298
≥3 years to <18 years of age	30%	50%	8%	>90%	3,175	3,528	7,056	381

*accounted for early dropout and uncertainty

A provision for triggering a new cohort of subjects is also included, and is based on either attainment of an inadequate total number laboratory confirmed influenza case in both seasons, or paired with the outcome of an interim analysis (noted below).

Nasopharyngeal swab samples will be analyzed in batches and the number of laboratory confirmed influenza cases will be reviewed on a regular basis (blinded review). Following the end of the second influenza season, and after observing at least 50% of planned events meeting the co-primary endpoint, an interim analysis for efficacy and futility will be performed by a Data Monitoring Committee (DMC). Stopping rules for futility and efficacy and any additional details regarding the interim analysis will be specified in the DMC Charter and in the SAP.

For this analysis a restricted unblinding will be done, i.e. only external DMC members and Contract Research Organization (CRO) employees executing it will receive access to the randomization codes and unblinded data for the purpose of preparing the interim analyses.

Strata such as age group and history of previous vaccination will be accounted for in the final analysis as a covariate “strata” in proportional hazard’s model. The use of strata in such context does not affect sample size calculation.

To account for the sample size requirements to demonstrate that the lower limit of the two-sided 95% CI for the VE is greater than 30% in ≥3 to <18 years old (co-primary objective) and the contributable 2 year plus enrolment for the co-primary objective , the total sample size is estimated to be minimally 7,692 subjects. While minimum enrolment for the 2+ age cohort will not be pre-defined a maximum of 635 subjects (=7,692 – 7,056)) in this age group can be enrolled to maintain a power >90% for the co-primary endpoint. Thus, in total minimally 7,692 subjects are planned be enrolled over the entire age distribution of ≥2 to <18 years of age.

Sample Size for Secondary Immunogenicity Objectives (Immunogenicity Subset):

The immunogenicity study will be performed in the second season and subsequent seasons. The immunogenicity endpoint is descriptive and the number of subjects aged ≤ 2 to > 9 years of age is maximized at 444 subjects with approximately 400 evaluable subjects, per season for the second season and for the third season. With a 1:1 allocation, approximately 200 evaluable subjects will be enrolled from the active arm and 200 evaluable subject would be from the non-influenza active comparator arm. Assuming a 10% drop out rate approximately 444 subjects will be enrolled per season. For the subsequent seasons, the number of subjects enrolled into the immunogenicity subset is maximized at 200 evaluable subjects per season (100 from the active arm and 100 from the non-influenza comparator arm). Assuming a 10% drop out rate approximately 222 subjects will be enrolled per every subsequent season after season three (fourth season, fifth season, etc) depending on the duration of the study.

In the case of early study termination, in the event that the number of ILI cases has been reached, the total number of subjects evaluated may be lower than the number of evaluable subjects described per season.

Sample Size for Safety:

With a Safety Population of 2,674 evaluable subjects in the safety set of QIVc, AEs with population rates of 1 in 1,000 have a 93.1% probability of being detected.

Events with population rates of 1 in 893 have a 95% chance of being observed with n=2,674) Events with population rates of 1 in 2,000 have a 73.7% chance of being observed with n=2,674

Sample size calculations were performed using PASS v12.0.2.

8.6 Interim Analysis

As the circulation of influenza viruses is seasonal and the event rates of influenza are difficult to predict, this study is group sequentially, with a case count-driven interim analysis. The goal of the Interim Analyses is, first, to minimize the risk of not being able to take a significant test decision after the end of the study, and second, to be able to stop the study for early evidence of efficacy or for futility.

Primary Efficacy Analysis:
The number of laboratory confirmed influenza cases will be reviewed on a regular basis. After the majority of cases for the second season have been collected, and after observing at least 50% of planned events meeting the co-primary endpoint, an interim analysis for efficacy and futility will be performed by a DMC. The two influenza seasons are defined as the first 2 influenza seasons after study start but no later than through April 2018, guided by influenza seasonality and peak season in Northern Hemisphere.

- If the number of influenza cases is less or equal to 190 overall, no interim analysis for efficacy and futility will be done and the study will be extended because the probability to make a conclusion for futility or efficacy is too low.

- If the number of influenza cases is greater or equal to 191 but less than 381 an unblinded interim analysis for efficacy and futility will be performed by a DMC. To maintain the overall alpha, $\alpha = 2.5\%$ (1-sided), for the hypotheses testing for the primary objectives, an error-spending-function will be used. The benefit of using an error-spending-function is that no maximum number of analysis stages and the timing of the analyses need to be pre-specified, what in practice means that the duration of the study in terms of number of seasons can be left open. In this case α-boundaries, forming the adjusted probabilities for the type I error, are calculated using error-spending function and if the p-values for both primary objectives are lower than the respective α-boundary the trial stops early (i.e., without reaching the targeted number of cases of 381) for efficacy. Similarly β-boundaries are calculated, i.e. the adjusted probabilities for the type II error β, and if the p-values are higher than the β-boundaries, the trial stops early for futility at that stage. In other words the trials stops early for futility, when the data provides sufficient evidence that the alternative hypotheses is not true, i.e. that the test vaccine is not as good as expected. Otherwise, the trial continues enrollment. Decisions to stop or continue the trial will be made on the basis of discussions between the DMC and Senior Management.

- If the number of influenza cases is greater or equal to 381 (targeted number of cases to be able to evaluate the co-primary objective) the study will be unblinded

and the final analysis will be performed by the Sponsor. If the trial proceeds to the final analysis (upon reaching 381 cases) the boundaries for acceptance or rejection are identical to the assumed type I and type II errors for the overall design, and the trial stops to either reject or accept the null hypothesis of either one or / and the other of the primary objectives.

In case the DMC states that the observed data provides already the full information level needed for the final test decision, then the final analysis can be done on full alpha level (2.5 % 1-sided) and no further enrollment is needed. However if the decision of the group-sequential test is to continue the study then it is on the DMC to determine the number of subjects needed to be enrolled. The monitoring committee should not be influenced by the individual results of the vaccine groups observed at an interim analysis stage when planning further subjects' accrual or the times of future analysis. Only the overall number of cases is allowed to be used for further planning. The following formula for determination of sample sizes for further enrollment may be used:

$$N_{total} = (C_{planned} - C_{observed}) / [(ER_{QIVc} + ER_{comp})/2],$$

where N_{total} denotes the total number of subjects needed for further enrollment, $C_{planned}$ is the overall number of cases needed for the test, i.e. 381 cases, $C_{observed}$ are the at that stage observed number of cases overall, and ER are the respective event rates assumed for each group, i.e., 8,0% for non-influenza comparator group and 4,0% for QIVc. A consideration of early dropout and uncertainty about assumed parameters will be accounted for number of enrolled subjects. The method of stopping rules given above is statistical and should be completed by clinical and strategic stopping rules that allow the DMC to make a decision on a broader picture of the data which includes safety endpoints and the other endpoints of the study.

Stopping rules for futility and efficacy and any additional details regarding the interim analysis will be specified in the DMC Charter and in the SAP.

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

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 and applicable regulatory requirements (e.g., FDA, EMA, and ICH guidelines).

Prior to enrolment 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 or delegate 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 enrolment.

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 and/or parent(s)/legal guardian(s) and date of completion and reason.

The subject and/or parent(s)/legal guardian(s) must also allow access to the subject's medical records. Each subject and/or the parent(s)/legal guardian(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 subjects must be written down in source documents prior to entry of the data into the eCRFs. If there are multiple sources of information (e.g., Subject Diary, 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, 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 (AE eCRF).

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to enrolment 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 eCRFs will be verified by checking the eCRF 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 (e.g., FDA, EMA and others) and/or ECs/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 entered onto eCRFs are stored on a secure website. The data collected on this secure website are assimilated into an electronic data capture (EDC) system, 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 prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the eCRFs 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 exclusively "read only" access.

10.2 Data Clarification

As part of the conduct of the trial, the Sponsor or delegate may have questions about the data entered by the site, referred to as queries. The monitors and the Sponsor 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 European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data (95/46/EC) confirms herewith compliance to Directive 95/46/EC 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 or delegate before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files. Essential documents must be retained for 15 years. “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.

These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

12. USE OF INFORMATION AND PUBLICATION

Seqirus assures 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 assures 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, 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 Council 2001, US Code of Federal Regulations, ICH 1997).

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written informed consent or assent, as described in Section 5.1.1, Informed Consent/Assent. Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject/subject's parent(s)/legal guardian(s) of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject or the designee. The subject/designee 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 (and/or subject's parent(s)/legal guardian(s)) **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.

Prior to the start of the study, Seqirus or its delegate 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 or its delegate before submission to the IRB/EC and a copy of the approved version must be provided to the Seqirus monitor after IRB/EC approval.

Women of childbearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements indicated in the protocol for the duration of the study. If case of doubts on

the ability of a subject to adhere to these requirements, that subject should not be allowed in the study

In addition, the investigator or designee should explain pertinent aspects of the study in an age appropriate manner to pediatric subjects who are eligible for informed assent in accordance with local policies. The subject and parent*(s)*/legal guardian*(s)* 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 and parent*(s)*/legal guardian*(s)* must sign the consent/assent forms indicating their agreement to participate in the study before any study-related procedures are conducted. If the parent(s)/legal guardian(s) are required to sign the informed consent form but are unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature. Similarly, when the subject is required to sign the informed consent form, and is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

13.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in ICH Guideline for Good Clinical Practice E6 (R1), Section 3 (ICH 1997). 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/ECs, 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 appropriately trained health care 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 and/or parent(s)/legal guardian(s), 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/IEC 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 (e.g., 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/IEC 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/IEC 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 (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by Seqirus, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/EC 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/EC at the study site, and, if required by local regulations, the relevant health authority) should be informed within 10 working days.

14. REFERENCE LIST

Belshe RB, Edwards KM, Vesikari T et al. Live attenuated versus inactivated influenza vaccine in infants and young children. N Engl J Med 2007; 356: 685-696.

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

Bodewes R, de Mutsert G, van der Klis FRM et al. Prevalence of antibodies against seasonal influenza A and B viruses in children in Netherlands. Clin Vaccin Immunol 2011; 18: 469-476.

Clopper CJ; Pearson ES. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika. 1934; 26(4): 404-413.

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.

Couch RB. 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 (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

Fairbrother G, Cassedy A, Ortega-Sanchez IR et al. High costs of influenza: Direct medical costs of influenza disease in young children. Vaccine 2010; 28: 4913-4919.

Fiore AE, Shay DK, Broder K, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009.MMWRRecommRep 2009; 58 (RR-8): 1-52.

Fiore AE. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Recomm Rep 2010; 59:1-62; PMID: 20689501.

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, Chen CM, Lee CY, Lu CY, et al. Clinical features of influenza A and B in children and association with myositis. J Microbiol Immunol Infect 2004; 37: 95–8.

ICH (1997) ICH Harmonised Tripartite ICH Guideline for Good Clinical Practices E6 (R1). Federal Register, 62(90): 25691-25709.

ICH (1998) ICH Harmonised Tripartite ICH Guideline for Statistical Principles for Clinical Trials E9. Federal Register, 63(179): 49583.

Jain VK, Rivera L, et al. (2013). Vaccine for prevention of mild and moderate-to-severe influenza in children. N Engl J Med. 369(26): 2481-91.

Levine RJ. (1988) Ethics and Regulations of Clinical Research. New Haven: Yale University Press.

Nair H, Abdullah Brooks W, Katz M, Roca A, Berkley JA, et al. Global burden of respiratory infections due to seasonal influenza in young children: a systematic review and meta-analysis. Lancet. 2011 Dec 3; 378(9807): 1917-30. Epub 2011 Nov 10.

Neuzil KM, Mellen BG, Wright PF, Mitchel EF, Griffin MR. The Effect of Influenza on Hospitalizations, Outpatient Visits, and Courses of Antibiotics in Children. N Engl J Med 2000 Jan 27; 342: 225-231.

O'Brien, PC, Fleming, TR. A Multiple Testing Procedure for Clinical Trials. Biometrics. 1979; 35: 549–556.

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

Rota PA. Co-circulation of two distinct evolutionary lineages of influenza type B virus since 1983. Virology 1990; 175: 59-68; PMID:2309452

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

World Health Organization. Cell culture as a substrate for the production of influenza vaccines: memorandum from a WHO meeting. Bull. World Health Organ.73(4): 431–435 (1995).

World Health Organization. Weekly Epidemiologic Record. 2012; 87(47): 461-476.

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

PROTOCOL SIGNATURE PAGE

Protocol number:	V130_12
Protocol title:	A Phase III/IV, Stratified, Randomized, Observer Blind, Multicenter Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of a Cell-Based Quadrivalent Subunit Influenza Virus Vaccine Compared to Non-Influenza Comparator Vaccine in Subjects ≥2 years to <18 Years of Age
Document:	Final Protocol
Version:	3.0
Date:	30 NOV 2017

As an approver, I agree with the content and format of this document:

Name: PPD

Signature:

Date: 11-DEC-2017
(DD-MMM-YYYY)