CLINICAL STUDY PROTOCOL V130_14

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

A Phase III Efficacy Study with QIVc in Pediatric Subjects

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TABLE OF CONTENTS

TABLE OF CONTENTS....2
PROTOCOL SYNOPSIS V130_14....6
LIST OF ABBREVIATIONS....30
LIST OF DEFINITIONS....32
1. BACKGROUND AND RATIONALE....35
1.1 Background....35
1.2 Potential Risks and Benefits....36
1.3 Rationale....37
2. OBJECTIVES....38
2.1 Primary Objective(s)....38
2.2 Secondary Objective(s)....38
2.3 Exploratory Objective(s)....39
3. STUDY DESIGN....40
3.1 Overview of Study Design....40
3.2 Study Period....43
3.3 Blinding Procedures....43
3.3.1 Subjects 6 through 11 months old at enrollment....43
3.4 Data Collection....44
3.4.1 Data Collected from Subjects....44
3.4.2 Tools Used for Data Collection....44
3.5 Collection of Clinical Specimens....46
3.6 Stopping/Pausing Guidelines....47
3.7 Data Monitoring Committee....47
3.8 Premature Withdrawal from Study....48
3.9 End of Study....51
4. SELECTION OF STUDY POPULATION....52
4.1 Inclusion Criteria....52
4.2 Exclusion Criteria....52

4.3 Criteria for Delay of Vaccination 54
5. STUDY PROCEDURES 55
5.1 Pre-vaccination Procedure(s) 56
5.1.1 Informed Consent 56
5.1.2 Screening 57
5.1.3 Enrolment 58
5.1.4 Randomization 58
5.1.5 Blood draw 59
5.2 Procedure(s) related to Vaccination 59
5.2.1 Vaccination 60
5.2.2 Subject Diary Card Dispense and Training 60
5.2.3 Schedule the next study activity 61
5.2.4 Diary Reminder Calls 61
5.2.5 ILI Symptom Assessment and Documentation Training 62
5.3 Post-vaccination Visit(s) 62
5.3.1 Follow-up Clinic Visit 62
5.3.2 Safety Follow-up Visit 63
5.4 Procedure(s) related to Protocol Defined ILI episodes 64
5.4.1 ILI Reminder Calls 64
5.4.2 Unscheduled Visit(s) 64
5.4.3 ILI Follow-up Call 65
5.5 Study Completion 66
5.5.1 Early Termination Visit 67
5.5.2 Countries without MenC market authorization 68
6. TREATMENT OF SUBJECTS 69
6.1 Study Vaccine(s) 69
6.2 Vaccine Preparation and Administration 70
6.3 Vaccine Administration Error or Overdose of Vaccine 71
6.4 Prior and Concomitant Medications and Vaccines 72

6.5 Vaccine Supply, Labeling, Storage and Tracking 73
7. ASSESSMENTS 76
7.1 Safety Assessment 76
7.1.1 Solicited Adverse Events 76
7.1.2 Unsolicited Adverse Events 79
7.1.3 Evaluation of Adverse Events 79
7.1.4 Serious Adverse Events 81
7.1.5 Methods for Recording Adverse Events and Serious Adverse Events 83
7.1.6 Safety Laboratory Measurements 84
7.2 Efficacy Assessment 84
7.3 Immunogenicity Assessment 85
8. STATISTICAL CONSIDERATIONS 86
8.1 Endpoints 86
8.1.1 Primary Endpoint(s) 86
8.1.2 Secondary Endpoint(s) 86
8.1.3 Exploratory Endpoint(s) 88
8.2 Success Criteria 88
8.2.1 Success Criteria for Primary Objective(s) 88
8.2.2 Success Criteria for Secondary Objective(s) 88
8.3 Analysis Sets 89
8.3.1 All Enrolled Set 89
8.3.2 All Exposed Set 89
8.3.3 Safety Set 89
8.3.4 Full Analysis Set (FAS) Efficacy/Immunogenicity Set 89
8.3.5 Per Protocol (PP) Set Efficacy/Immunogenicity Set 90
8.3.6 Other Analysis Sets 90
8.3.7 Subgroups 90
8.3.8 Protocol Deviations 91
8.4 Statistical Analysis Plan 92

8.4.1 Analysis of Demographic and Baseline Characteristics 92
8.4.2 Analysis of Primary Objective(s) 92
8.4.3 Analysis of Secondary Objective(s) 95
8.4.4 Analysis of Exploratory Objectives 99
8.5 Sample Size and Power Considerations of Multiple Primary and Secondary Objectives 99
8.6 Interim Analysis 101
9. SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING 103
9.1 Source Documentation 103
9.2 Study Monitoring, Auditing and Source Data Verification 104
10. DATA MANAGEMENT 106
10.1 Data Entry and Management 106
10.2 Data Clarification 106
10.3 Data Protection 106
11. RECORD RETENTION 107
12. USE OF INFORMATION AND PUBLICATION 108
13. ETHICAL CONSIDERATIONS 109
13.1 Regulatory and Ethical Compliance 109
13.2 Informed Consent Procedures 109
13.3 Responsibilities of the Investigator and IRB/EC 110
13.4 Protocol Amendments 111
14. REFERENCE LIST 112

PROTOCOL SYNOPSIS V130_14

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus	V130_14	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Non-Influenza Vaccine

Title of Study:

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

Study Period: Until end of influenza season but at least 180 days after last vaccination date (approximately six to ten months)	**Clinical Phase:** Phase III

Background and Rationale:

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

One of the challenges of protecting children against influenza is providing an influenza vaccine with an antigenic match against the circulating strains in a given influenza season. Since 1983, two evolutionarily distinct lineages of influenza B viruses have co-circulated in the human population globally (Biere, 2010) and influenza B viruses account for roughly 20% of total influenza cases in all regions of the world (Ciani, 2015). As only one B lineage is selected for inclusion in current trivalent influenza vaccines (TIV) and in the absence of proven cross protection between the two lineages (Peltola, 2003) (Hu, 2004), there is the risk of a mismatch for the influenza B strain (Couch, 2007) (Belshe, 2010) (Orsi, 2018). Since patients infected with influenza B are

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usually younger than patients infected with influenza A, the effectiveness of vaccination in children seems more dependent on adequate matching (Jayasundara, 2014) (Caini, 2015) (Orsi, 2018). To address this problem, quadrivalent influenza vaccines (QIV) have been developed containing B strains from both lineages. Although results show benefits of QIV vaccination in adults, results from randomized controlled trials in children immunized with QIV, are scarce (Claeys, 2018) (Pepin, 2017).

A second challenge is designing a study that captures the clinically relevant outcomes of influenza rather than mild upper respiratory tract illness. Parents are most likely to seek medical help for children who have symptoms of lower respiratory tract disease, high temperature or earache (Saunders, 2003). Studies that do not differentiate these manifestations of influenza from mild illness cannot assess the effectiveness of the vaccine in attenuating illness and therefore may undervalue its benefit (Jain, 2013) (Ambrose, 2014).

Seqirus' quadrivalent (QIVc) *Flucelvax Quadrivalent/ Flucelvax Tetra*, is a cell based quadrivalent inactivated subunit influenza vaccine prepared from virus propagated in Madin Darby Canine Kidney (MDCK) cells, and approved by the FDA for use in children aged 4 years and older. As a quadrivalent vaccine, QIVc is formulated to contain two influenza A strains and two influenza B strains updated annually as recommended by the World Health Organization (WHO) for a specific influenza season. A shift from eggs to cell culture has several advantages, for example it avoids the risk of egg-adaptive mutations in the HA protein (Lambert, 2010).

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

Study Objectives: Efficacy will be evaluated in all subjects in association with first occurrence of influenza-like illness (ILI) symptoms occurring > 14 days after last

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
Seqirus	V130_14	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Non-Influenza Vaccine

vaccination and until the end of the influenza season in subjects 6 months through 47 months of age at enrollment.

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

Moderate-to-severe ILI episode is defined as an ILI episode complicated by one of the following: physician confirmed lower respiratory tract illness, physician confirmed acute otitis media, or hospitalization in the Intensive Care Unit (ICU), physician-diagnosed serious extra-pulmonary complication of influenza or supplemental oxygen requirement for more than 8 hours.

Primary Efficacy Objectives:
1) To demonstrate the absolute vaccine efficacy of QIVc versus a non-influenza vaccine to prevent at least one of the following:
a) RT-PCR confirmed illness caused by any influenza Type A and/or Type B virus, regardless of antigenic match.
b) Culture confirmed illness caused by influenza virus strains antigenically matched to the influenza strains selected for the seasonal influenza vaccine.

Secondary Efficacy Objectives:
Objectives evaluating QIVc compared to a non-influenza vaccine:
2) Prevention of culture confirmed illness caused by influenza virus strains antigenically dissimilar to the influenza strains selected for the seasonal vaccine.
3) Prevention of culture confirmed illness caused by any Type A and/or Type B virus.
4) Prevention of RT-PCR confirmed moderate-to-severe influenza caused by any influenza Type A and/or Type B virus.

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

Secondary Safety Objective: To evaluate the safety and tolerability of QIVc among subjects 6 months through 47 months of age in the QIVc group and comparator group.

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus	V130_14	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Non-Influenza Vaccine

Study Design:

This multicenter phase III clinical study evaluates the efficacy, immunogenicity and safety of a cell-based quadrivalent subunit influenza virus-vaccine compared to non-influenza vaccine in subjects between 6 months through 47 months of age. The study features an observer blind design, parallel groups and 1:1 randomization between QIVc and a non-influenza vaccine. Based on previous influenza vaccination history, subjects will receive either one or two doses of either QIVc or comparator (non-influenza vaccine/placebo). The non-influenza vaccine is a conjugate vaccine for prevention of invasive disease caused by *Neisseria meningitidis* serogroup C (MenC vaccine). In subjects who require two doses, MenC and placebo (saline for injection) will be administered separated by 28 days. In this study placebo will be used as masking dose. All subjects aged 6 through 11 months at enrollment, regardless of treatment assignment, will receive a dose of the MenC vaccine at the end of the study.

The study has a treatment period and a follow-up period. For subjects with a previous influenza vaccination history, the treatment period begins at the time of vaccination and ends 28 days after vaccination and will consist of 2 clinical visits and one reminder call to complete the subject diary card. The follow up period begins 28 days after vaccination and ends at the time of study completion visit. For subjects without or unknown previous influenza vaccination history, the treatment period begins at the time of first vaccination and ends 28 days after the second vaccination and will consist of 3 clinical visits and two reminder calls to complete the subject diary card, one after each vaccination. The follow up period begins 28 days after second vaccination and ends at the time of study completion visit. All subjects, irrespective of previous influenza vaccination history, will receive 1 safety follow-up call 90 days after last vaccination during the follow up period and the follow-up period will conclude with a study completion visit (clinic visit or call). Safety data collection will include standard solicited adverse event reporting via subject diary card for 7 days after each vaccine administration (including the day of vaccination), all unsolicited adverse events (AEs) for 28 days after each vaccine administration, and special AE categories (serious adverse event (SAE), new onset of chronic disease (NOCD), medically-attended AEs for 30 days after ILI onset) for the full duration of the study. In countries, where the

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus	V130_14	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Non-Influenza Vaccine

MenC vaccine (*Neisvac-C*®, Pfizer) is not licensed, an extra visit will be performed only to assess the safety of MenC vaccine at approximately 28 days after vaccination.

Blood samples will be collected from a sub-set of subjects participating in each influenza season (maximum 222 per season), during two clinic visits prior to the first vaccination and 28 days after last vaccination. Immunogenicity analyses will be performed to characterize baseline titers, response to vaccination and to understand the observed efficacy for the study population.

Throughout the study, unscheduled visits are planned for subjects who manifest influenza-like illness (ILI) symptoms during the influenza season. The subject's parent or legally acceptable representative (LAR) or delegate is contacted weekly to capture ILI symptoms throughout the study. When ILI symptoms occur, the parent/LAR/delegate should complete the ILI booklet.

Study Duration:

The study is designed to accrue a minimum number of influenza confirmed cases over several influenza seasons. Each subject will participate until the end of the influenza season as defined in the protocol for the season in which the subject is enrolled but at least 180 days after last vaccination.

Number of Subjects planned:

An approximate number of 3,830 subjects are planned to be enrolled and randomized 1:1 to either QIVc (1,915 subjects) or the comparator group (1,915 subjects) taking into account a 10% drop-out rate. For the immunogenicity assessments, blood samples will be collected throughout the study up to a maximum of 222 subjects per influenza season (with 111 subjects in the QIVc group and 111 subjects in the comparator group).

Study Population and Subject Characteristics:

This study will enroll children aged 6 months through 47 months old from countries across the world, over several influenza seasons. The subjects should be generally

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Seqirus	V130_14	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Non-Influenza Vaccine

healthy and may have a previous history of influenza vaccination. The list of inclusion and exclusion criteria is included in protocol Section 4, Selection of Study Population.

Study Procedures:

Written informed consent must be obtained prior to any study-related procedures according to ICH-GCP (ICH E6 (R2)). After signing of the informed consent by the subject's parent(s) or LAR and undergoing review of medical history, physical examination, review of current and prior medications and vaccinations, and confirmation of subject eligibility, subjects will be enrolled into the study.

The study has a treatment period and a follow-up period. The treatment period has scheduled visits planned depending on the subject's influenza vaccination history and age of the subject. The follow-up period will conclude with a study completion visit (clinic visit or call).

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

Treatment period:
After vaccination, all subjects will remain under medical supervision and will be monitored for any immediate reactions for at least 30 minutes. The 30 minute follow-up data is recorded in the source documentation and the electronic data capture system (EDC) by the site personnel. Local adverse reactions and systemic solicited adverse events that occur from 30 minutes after vaccination will be collected for seven (7) days following each vaccination on a subject diary card. The parent/LAR or a person designated by the parent/LAR of all subjects will receive a reminder to complete the subject diary card two (2) days after vaccination. All unsolicited AEs and concomitant medication will be collected until 28 days after last vaccination. From a sub-set of subjects, a blood specimen will be collected prior to vaccination at Visit 1 and 28 days after last study vaccine administration at scheduled clinic visits.

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus	V130_14	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Non-Influenza Vaccine

Follow-up period:
During the follow-up period, safety data including 'AEs leading to withdrawal', 'SAEs', 'NOCDs', 'medically-attended AEs until 30 days after ILI onset' and all medications used related to these events will be captured. In case of such events, subject's parent(s)/LAR will be instructed to contact the site as soon as possible to report the event(s). Furthermore, a safety follow-up call 90 days after last vaccination will performed.

During treatment and follow-up period:
Unscheduled visits are planned for subjects who manifest signs of influenza-like illness (ILI) during the influenza season and will be evaluated by testing of a nasopharyngeal (NP) specimen for influenza. Thirty (30) days after ILI onset, an ILI follow-up call with associated checklist will be performed to determine if subsequent medically-attended adverse events occurred including concomitant medication associated with these events.

After enrollment, a weekly alert (for example a telephone call) will serve as a reminder to the subject's parent/LAR/designate to report ILI symptoms to the study investigator. Subjects with ILI symptoms and its complications ought to be treated according to recent accepted (national) clinical standards. Subject's parent(s)/LAR will be asked to contact the site immediately if health concerns arise.

At the end of influenza season but at least 180 days after last vaccination date:

A scheduled study visit 5 (clinic / home visit or call) at the end of influenza season but at least 180 days after last vaccination will occur. All subjects aged 6 through 11 months will receive a MenC vaccination, regardless of treatment assignment.

In countries, where the MenC vaccine (*Neisvac-C*, Pfizer) is not licensed, an extra visit (Visit 6) is performed, only to assess the safety of the MenC vaccine at approximately 28 days after vaccination at Visit 5.

Study Vaccines and Schedule:

Investigational vaccine: The investigational vaccine is *Flucelvax Quadrivalent/ Flucelvax Tetra* (QIVc, Seqirus), and contains 0.5 mL including 15 µg purified viral

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
Seqirus	V130_14	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Non-Influenza Vaccine

envelope-glycoprotein hemagglutinin (HA) of each of the four (4) influenza strains recommended by WHO for inclusion in the quadrivalent vaccine formulation for the influenza season corresponding to the season of conduct of study.

Vaccination schedule:

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

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

Vaccination schedule:

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

All subjects aged 6 through 11 months at enrollment, regardless of treatment assignment, will receive a dose of the MenC vaccine at Visit 5.

Primary Efficacy Endpoint(s):

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

1. b. First occurrence of culture confirmed influenza, due to influenza Type A and/or B virus antigenically matched by ferret antigenicity testing to the strains selected for the seasonal influenza vaccine, occurring at > 14 days after the last vaccination and

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
Seqirus	V130_14	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Non-Influenza Vaccine

until the end of the influenza season, in association with protocol-defined ILI symptoms.

Secondary Efficacy Endpoint(s):
Endpoints evaluating QIVc compared to a non-influenza vaccine:

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

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

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

Secondary Immunogenicity Endpoints (immunogenicity sub-set): The measures for immunogenicity are determined by a haemagglutination inhibition [HI] and/or a micro neutralization [MN] assay prior to first vaccination and 28 days after last vaccination for all four influenza strains. For each assay the measures include:

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

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
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c) Geometric mean ratio (GMR): GMR is the geometric mean of the fold increase of post-vaccination HI (or MN) titer over the pre-vaccination HI (or MN) titer.

Secondary Safety Endpoints: The measures for assessing safety and tolerability are as follows:

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

Statistical Analyses:

Statistical Considerations for Sample Size Calculations:

This study is planned using a group sequential design, with one or more interim analyses for efficacy using O'Brien-Fleming accounting for a group sequential design. The study is designed to accrue an approximate number of subjects and a minimum number of cases over several influenza seasons, i.e. both a minimum of 191 RT-PCR confirmed influenza cases and a minimum of 104 culture confirmed influenza cases antigenically matched to the strains selected for the seasonal vaccine. If the overall/pooled influenza attack rate differs from the predicted and/or influenza strain circulation within a study season has drifted or shifted away from the strains selected for the seasonal vaccine, an adjustment of the prospectively specified number of cases, and number of subjects may be required. Extraneous real-life information, from (but not limited to) the influenza surveillance systems of the European Center for Disease Control (ECDC), US Center for Disease Control and Prevention (CDC) or World Health Organization (WHO) may be used to re-assess the influenza event rate.

The statistical test performed will depend on the number of RT-PCR confirmed influenza cases and the number of culture confirmed influenza cases, so the sample size

Name of Sponsor:	Protocol number:	Generic name of study vaccine(s):
Seqirus	V130_14	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Non-Influenza Vaccine

estimate is only for operational reasons (an estimate of number of subjects needed to assess the endpoint).

For the primary efficacy endpoint 1a, assuming an attack rate in the comparator group of 8% and an influenza vaccine efficacy (VE) of 40%, an estimated sample size of 2,974 evaluable subjects (or 1,487 evaluable subjects per study group) with a total of 191 cases are needed to have at least 90% power to reject the null hypothesis that the VE is less or equal to 0% at the significance level alpha (α) = 0.0125 and the risk of infection contained entirely within period covered by follow-up. For the primary efficacy endpoint for vaccine antigenically matched strains (1b.), assuming an attack rate in the comparator groups of 4%, a VE of 50%, α=0.0125, 3,446 evaluable subjects and 104 cases are needed to have at least 90% power to reject the null hypothesis that the VE is less or equal to 0% at the significant level alpha (α) = 0.0125. These results assume that the hazard ratio is constant throughout the study and that Cox proportional hazard regression is used for the analysis. Accounting for 10% early dropout and uncertainty about the assumed parameters, 3,830 subjects are planned to be enrolled (or 1,915 subjects per study group) to demonstrate that the lower limit (LL) of the two-sided 97.5% CI for the VE is greater than 0% for the primary endpoint assessment.

Primary Efficacy Analyses:
The primary efficacy analysis will be based on the Full Analysis Set (FAS). Eligible subjects for FAS analysis are subjects who are randomized and received at least one study vaccine, and will be analyzed according to their randomized study vaccine [intent-to-treat analysis]). Absolute vaccine efficacy will only be assessed for RT-PCR confirmed influenza episodes (primary efficacy objective 1a) and culture confirmed influenza episodes (primary efficacy objective 1b) with first onset of ILI occurring at > 14 days after the last vaccination (since clinical protection is not immediate after vaccination) until the end of the influenza season. Additionally, the primary objective will be evaluated in Per-Protocol Analysis Set (PPAS). Additional detail is provided in Section 8, Statistical Considerations of the protocol and the Statistical Analysis Plan (SAP).

Time-to-event analysis based on a proportional hazard model will be used for all efficacy analyses to estimate the hazard ratio (HR). Absolute vaccine efficacy (aVE)

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus	V130_14	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Non-Influenza Vaccine

against first-occurrence RT-PCR confirmed influenza cases will be defined as the relative reduction in influenza infection rate in the QIVc group to the comparator group, namely aVE = 1 – HR = 1 – [$\lambda_{QIVc(s)}(t)/ \lambda_{Comp(s)}(t)$], where HR is the hazard ratio between QIVc and comparator and $\lambda_{(s)}(t)$ is the stratum-specific hazard rates of each study group. $\lambda_{(s)}(t) = f_{(s)}(t)/S_{(s)}(t)$, where $f_{(s)}(t)$ is the stratum-specific rate of first-occurrence RT-PCR confirmed influenza cases per unit time t and $S_{(s)}(t)$ is the stratum-specific survival function, i.e. function of time without influenza cases. The model will include covariates (for example age and season). The absolute efficacy will be tested according to the following null (H_0) and alternative (H_1) hypotheses: H_0: $1 - HR \leq 0$ versus H_1: $1 - HR > 0$.

Success Criteria for the Multiple Primary Efficacy Objectives:

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

Further details regarding the statistical methods and analyses will be further specified in the statistical Section 8, Statistical Consideration of the protocol and the Statistical Analysis Plan (SAP).

Interim Analysis:

An event-driven interim analysis may be performed if deemed necessary by the Sponsor. In the event an interim is performed, the goal of the interim analysis is to be able to stop the study for early evidence of efficacy. For this analysis a restricted unblinding will be done, i.e. only external DMC members and Contract Research Organization (CRO) employees executing the unblinding receive access to the randomization codes and unblinded data for the purpose of preparing the interim analyses. Interim analyses are only intended to determine if the trial has met criteria for efficacy. Further details regarding the interim analysis are contained in Section 8.6, Interim Analysis.

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus	V130_14	Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Non-Influenza Vaccine

Data Monitoring Committee:

An independent DMC will be utilized for the study for the evaluation of safety during the study and efficacy data for interim analysis. The DMC may recommend to stop the study for efficacy when at least one efficacy objective met the success criteria described in the Statistical Analysis Plan or if a safety concern is identified, otherwise the trial will continue as planned. There are no futility criteria at the interim analysis. Additional details regarding the review of the data by the DMC will be contained in the DMC Charter and Section 3.7, Data Monitoring Committee.

Table 1.1 Time and Events Table – Treatment and Follow-up Period for subjects without or unknown previous influenza vaccination history (two dose regimen)

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

		Treatment Period					Follow-up Period[b,c]		
Visit Type		**Clinic Visit[a]**	**Diary Reminder Call[a]**	**Clinic Visit[a]**	**Diary Reminder Call[a]**	**Clinic Visit[a]**	**Safety Follow-up Call[a]**	**Clinic Visit[a]**	
Study Day			**V1 + 2[d]**	**V1 + 28**	**V2 + 2[c]**	**V2 + 28**	**V2 + 90**	**End of influenza season or 180 days after last vaccination[e],***	**V5 + 28**
Visit Number		**V1**		**V2**		**V3**	**V4**	**V5**	**V6[c]**
Visit Window (Days)		**n/a**	**-1/+1**	**0 to +7**	**-1/+1**	**0 to +7**	**0 to +7**	**0 to +14**	**0 to +7**
Study Event	**References**								
Influenza and MenC Vaccination History[g]	Section 5.1.2	√[g]						√[g]	
Randomization[g]	Section 5.1.4	√[g]							
Subject Diary Card Training	Section 5.2.1	√		√					
Subject Diary Card Reminder	Section 5.2.2		√		√				
Subject Diary Card Review and Collection	Section 5.3.1			√[g]		√			
Assess all AEs[g]	Section 7.1	√[g]		√[g]		√			
Collection of information on SAEs	Section 7.1.4	At any time during the study period							
Assess AEs Leading to Withdrawal, NOCDs	Sections 7.2 and 7.1.3						√	√	√

		Treatment Period					Follow-up Period[b,c]		
	Visit Type	**Clinic Visit[a]**	**Diary Reminder Call[a]**	**Clinic Visit[a]**	**Diary Reminder Call[a]**	**Clinic Visit[a]**	**Safety Follow-up Call[a]**	**Clinic Visit[a]**	
	Study Day		**V1 + 2[d]**	**V1 + 28**	**V2 + 2[c]**	**V2 + 28**	**V2 + 90**	**End of influenza season or 180 days after last vaccination[e],***	**V5 + 28**
	Visit Number	**V1**		**V2**		**V3**	**V4**	**V5**	**V6[c]**
	Visit Window (Days)	**n/a**	**-1/+1**	**0 to +7**	**-1/+1**	**0 to +7**	**0 to +7**	**0 to +14**	**0 to +7**
Study Event	**References**								
Collect Relevant Medications and Vaccinations	Sections 5.1.2 and 6.5	At any time during the study period							
Immunogenicity									
Serology Blood Draw[g,h]	Section 3.5	√[g,h]				√[h]			
Collect Relevant Medications and Vaccinations	Sections 5.1.2 and 6.5	At any time during the study period							
Study Treatment									
Vaccination	Section 5.2	√		√					
30 Minutes Post Injection Assessment	Section 5.2.1	√		√					
Efficacy									

		Treatment Period					Follow-up Period[b,c]		
	Visit Type	**Clinic Visit[a]**	**Diary Reminder Call[a]**	**Clinic Visit[a]**	**Diary Reminder Call[a]**	**Clinic Visit[a]**	**Safety Follow-up Call[a]**	**Clinic Visit[a]**	
	Study Day		**V1 + 2[d]**	**V1 + 28**	**V2 + 2[c]**	**V2 + 28**	**V2 + 90**	**End of influenza season or 180 days after last vaccination[e],***	**V5 + 28**
	Visit Number	**V1**		**V2**		**V3**	**V4**	**V5**	**V6[c]**
	Visit Window (Days)	**n/a**	**-1/+1**	**0 to +7**	**-1/+1**	**0 to +7**	**0 to +7**	**0 to +14**	**0 to +7**
Study Event	**References**								
ILI Symptom Assessment and Documentation Training[i]	Section 5.2.5	√[i]							
ILI Reminder Calls[j]	Section 5.4.1	←	―	―	√[j]	―	―	→	
Study Completion Procedures									
Procedures	Section 5.5							√	
Vaccination[k]	Section 5.5 and 6.2							√[k]	
30 Minutes Post Injection Assessment[k]	Section 5.2.1							√[k]	

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

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

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

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

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

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

g) Procedures that should be completed before vaccination

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

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

j) Performed until End of Influenza Season

k) Subjects aged 6 through 11 months at enrollment will receive a dose of the MenC vaccine at study completion visit.

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

Table 1.2 Time and Events Table – Treatment and Follow-up Period for subjects with a previous influenza vaccination history (one dose regimen)

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

		Treatment Period			Follow-up Period	
	Visit Type	**Clinic Visit[a]**	**Diary Reminder Call[a]**	**Clinic Visit[a]**	**Safety Follow-up Call[a]**	**Clinic Visit[a,b,*]**
	Study Day	**1**	**V1 + 2[c]**	**V1 + 28**	**V1 + 90**	**End of influenza season or 180 days after last vaccination[d]**
	Visit Number	**V1**		**V2**	**V3**	**V4**
	Visit Window (Days)	**n/a**	**-1/+1**	**0 to +7**	**0 to +7**	**0 to +14**
Study Event	**References**					
Subject Diary Card Review and Collection	Section 5.3.1			√[f]		
Assess all AEs[f]	Section 7.1	√[f]		√[f]		
Collection of information on SAEs	Section 7.1.4	At any time during the study period				
Assess AEs Leading to Withdrawal, NOCDs	Sections 7.2 and 7.1.3				√	√
Collect Relevant Medications and Vaccinations	Sections 5.1.2 and 6.5	At any time during the study period				
Immunogenicity						
Serology Blood Draw[f,g]	Section 3.5	√[f,g]		√[g]		
Study Treatment						
Vaccination	Section 5.2	√				
30 Minutes Post Injection Assessment	Section 5.2.1	√				
Efficacy						

		Treatment Period			Follow-up Period	
	Visit Type	**Clinic Visit[a]**	**Diary Reminder Call[a]**	**Clinic Visit[a]**	**Safety Follow-up Call[a]**	**Clinic Visit[a,b,*]**
	Study Day	**1**	**V1 + 2[c]**	**V1 + 28**	**V1 + 90**	**End of influenza season or 180 days after last vaccination[d]**
	Visit Number	**V1**		**V2**	**V3**	**V4**
	Visit Window (Days)	**n/a**	**-1/+1**	**0 to +7**	**0 to +7**	**0 to +14**
Study Event	**References**					
ILI Symptom Assessment and Documentation Training[h]	Section 5.2.5	√[h]				
ILI Reminder Calls[i]	Section 5.4.1	←	———	———	√[i]	——→
Study Completion Procedures						
Study Completion	Section 5.5					√

		Treatment Period			Follow-up Period	
	Visit Type	**Clinic Visit[a]**	**Diary Reminder Call[a]**	**Clinic Visit[a]**	**Safety Follow-up Call[a]**	**Clinic Visit[a,b,*]**
	Study Day	**1**	**V1 + 2[c]**	**V1 + 28**	**V1 + 90**	**End of influenza season or 180 days after last vaccination[d]**
	Visit Number	**V1**		**V2**	**V3**	**V4**
	Visit Window (Days)	**n/a**	**-1/+1**	**0 to +7**	**0 to +7**	**0 to +14**
Study Event	**References**					

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

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

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

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

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

f) Procedures that should be completed before vaccination

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

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

i) Performed until End of Influenza Season

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

Table 1.3 Time and Events Table – Unscheduled visit(s) related to a protocol defined ILI episode[a]

	Visit Type	Unscheduled Clinic Visit[b]	ILI Follow-up Call[c,*]
	ILI Onset Day	1[d]	+ 30
	Visit Number	n/a	n/a
	Visit Window (Days)	0 to +6	0 to +7
Study Event	**References**		
Efficacy			
ILI Booklet Review and Collection	Section 5.4.2	√	
Assess ILI symptoms	Sections 5.4.3 and 7.2	√	√
ILI Nasopharyngeal Swab Collection[d]	Sections 3.5 and 5.4.2	√[d]	
Assess Relevant Medications and Vaccinations	Sections 5.1.2, 5.4.3 and 6.5	√	√
Assess Medically-Attended AEs[e]	Sections 5.4.3 and 7.1.2	√[e]	√[e]
Physical Examination	Sections 5.1.2 and 5.3.1	√	
ILI Symptom Assessment and Documentation Training[f]	Section 5.2.5	√[f]	

	Visit Type	**Unscheduled Clinic Visit[b]**	**ILI Follow-up Call[c,*]**
	ILI Onset Day	**1[d]**	**+ 30**
	Visit Number	**n/a**	**n/a**
	Visit Window (Days)	**0 to +6**	**0 to +7**
Study Event	**References**		

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

b) In the exceptional case that the subject cannot visit the study center, a home visit can be made

c) In countries, in the exceptional case where calls are not feasible, study site personnel may visit the subject's homes to inquire about signs and symptoms of illness in the subject.

d) Subject will be asked to come to the study site within the first 24 hours or as soon as possible following ILI onset to ensure optimal viral yield

e) A "medically-attended adverse event" is an adverse event requiring hospitalization, or emergency room visit, or visit to/by a health care provider. See section Definitions.

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

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

LIST OF ABBREVIATIONS

AE	Adverse Event
BLA	Biologics License Application
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
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
HR	Hazard ratio
IA	Interim Analysis
IB	Investigator's Brochure
ID	Identification
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
ILI	Influenza-Like Illness
IM	Intramuscular
IRB	Institutional Review Board
IRT	Interactive Response Technology
LAR	Legally Acceptable Representative(s)
LL	Lower Limit
MDCK cells	Madin Darby Canine Kidney cells
MedDRA	Medical Dictionary for Regulatory Activities
MenC	Meningococcal (Group C) Conjugate Vaccine

MN	Microneutralization
NA	Neuraminidase
NP	Nasopharyngeal
NH	Northern Hemisphere
NOCD	New Onset of Chronic Disease
PCR	Polymerase Chain Reaction
PDCO	Paediatric Committee
PFS	Pre-filled syringes
PIP	Paediatric Investigation Plan
PP	Per Protocol
PPAS	Per Protocol Analysis Set
PRO	Patient Reported Outcome
PV	Pharmacovigilance
QIVc	Cell-derived Quadrivalent Influenza Vaccine
QIV	Quadrivalent Influenza Vaccine
Qs	Quantity sufficient
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
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
TIV	Trivalent Influenza Vaccine
USPI	United States Patient Information leaflet
VE	Vaccine Efficacy
WHO	World Health Organization

LIST OF DEFINITIONS

Active ILI surveillance: Is from first vaccination through end of the influenza season.

Antigenic match is defined as antigenic similarity to a strain contained in the influenza vaccine. The influenza strain responsible for a confirmed influenza case is considered as antigenically similar to an influenza strain contained in the influenza vaccine if the ferret antigenicity testing (using hemagglutination inhibition or microneutralization method against a panel of known standard ferret reference antisera to different viral strains) shows that the virus detected is similar to any of those contained in the influenza vaccine formulation for the respective season.

Any Type A and/or Type B virus: Defined as any influenza virus strains included in the influenza vaccine, i.e. Type A (A/H1N1, A/H3N2) and/or Type B.

Clinic visit: A clinic visit can be a home visit, clinic visit (at study site) or call.

Culture confirmed influenza case: A case of protocol defined ILI for which a swab specimen yields influenza Type A and/or Type B virus by viral culture analysis.

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

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

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

Influenza-like illness (ILI) onset is defined as the first day that a subject meets the criteria for protocol defined ILI.

Influenza-like illness (ILI) resolution is defined as the first day when the following conditions are met simultaneously: temperature < 37.5°C (< 99.5°F) with no fever reducers used, other symptoms (cough, sore throat, nasal congestion, rhinorrhea, earache

or ear discharge) either absent or mild, and a return of the child to normal activities (Jacobs, 2000) (Shepperd, 2004).

Influenza confirmed case: RT-PCR confirmed influenza in a subject who meets the criteria for protocol defined ILI.

Legally Acceptable Representative(s): An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial (see ICH-GCP, ICH E6 (R2)).

Lower respiratory tract illness: Defined as either shortness of breath, pulmonary congestion, pneumonia, bronchiolitis, bronchitis, wheezing, or croup.

Medically attended visit: Defined as a hospitalization, emergency room/ department visit or a visit to/ by a healthcare provider for symptoms or illnesses. Scheduled clinic study visits and unscheduled study visits related to protocol defined ILI are not part of this definition.

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

Moderate-to-severe ILI episode: ILI episode complicated by one of the following: physician confirmed lower respiratory tract illness, physician confirmed acute otitis media, or hospitalization in the Intensive Care Unit (ICU), physician-diagnosed serious extra-pulmonary complication of influenza or supplemental oxygen requirement for more than 8 hours.

New onset of ILI episode: As a guidance, another episode and swab sample should only be collected when the interval between the onset of protocol defined ILI to the next onset of protocol defined ILI is 14 days or more.

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

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

RT-PCR confirmed influenza case: A case of protocol defined ILI for which a swab specimen yields influenza Type A and/or Type B virus by reverse transcription-polymerase chain reaction (RT-PCR).

Serious extra-pulmonary complications of influenza are defined as complications including myositis, encephalitis or other neurologic condition including seizure, myocarditis / pericarditis or other serious medical condition.

Solicited adverse events are either solicited local adverse reactions or solicited systemic adverse events.

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

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

1. BACKGROUND AND RATIONALE

1.1 Background

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

One of the challenges of protecting children against influenza is providing an influenza vaccine with an antigenic match against the circulating strains in a given influenza season. Since 1983, two evolutionarily distinct lineages of influenza B viruses have co-circulated in the human population globally and influenza B viruses account for roughly 20% of total influenza cases in all regions of the world (Caini, 2015). As only one B lineage is selected for inclusion in current trivalent influenza vaccines and in the absence of proven cross protection between the two lineages (Peltola, 2003) (Hu, 2004), there is the risk of a mismatch for the influenza B strain (Couch, 2007) (Belshe, 2010) (Orsi, 2018). Since patients infected with influenza B are usually younger than patients infected with influenza A, the effectiveness of vaccination in children seems more dependent on adequate matching (Jayasundara, 2014) (Caini, 2015) (Orsi, 2018). Furthermore, at such young age children have not been exposed greatly to circulating influenza viruses and immune priming by (repeated exposure to) vaccination cannot protect them against disease (Quiñones-Parra, 2016).

To address this challenge, quadrivalent influenza vaccines (QIV) have been developed containing B strains from both lineages. Although results show benefits of QIV vaccination in adults, results from randomized controlled trials in children immunized with QIV, are scarce (Jefferson, 2012) (Jain, 2013) (Claeys, 2018) (Pepin, 2017). Furthermore, limited data from randomized trials on the efficacy of inactivated trivalent influenza vaccines in children < 6 years are available and results are inconsistent (Jefferson, 2012) possibly explained by mild influenza virus activity, short study duration and suboptimal vaccine-match during the studies (Hoberman, 2003) (Jansen, 2008)

(Dewe, 2013) (Rolfes, 2017) including insufficient power to show effects in young children (Li-Kim-Moy, 2017).

A second challenge is designing a study that captures the clinically relevant outcomes of influenza rather than mild upper respiratory tract illness. Parents are most likely to seek medical help for children who have symptoms of lower respiratory tract disease, high temperature or earache (Saunders, 2003). Studies that do not differentiate these manifestations of influenza from mild illness cannot assess the effectiveness of the influenza vaccine in attenuating illness and therefore may undervalue its benefit (Jain, 2013) (Ambrose, 2014).

Seqirus' quadrivalent (QIVc) *Flucelvax Quadrivalent / Flucelvax Tetra*, is a cell based quadrivalent inactivated subunit influenza vaccine prepared from virus propagated in Madin Darby Canine Kidney (MDCK) cells, and approved by the FDA for use in children aged 4 years and older. A shift from eggs to cell culture has several advantages, for example it avoids the risk of egg-adaptive mutations in the HA protein and providing better manufacturing control through a closed-system fermentation process (Lambert, 2010). As a quadrivalent vaccine, QIVc is formulated to contain two influenza A strains and two influenza B strains updated annually as recommended by the World Health Organization (WHO) for a specific influenza season, thereby increasing the adequate match to circulating influenza strains.

1.2 Potential Risks and Benefits

There are risks associated with study participation and vaccination. These risks include those associated with the investigational (QIVc) or the comparator vaccine (meningococcal group C vaccine), the vaccination procedure, blood collection (if applicable), and NP swab(s) collection (if applicable). The Investigator´s Brochures 'Trivalent Influenza Vaccine (TIVc) and Quadrivalent Influenza Vaccine(QIVc)', section 'Effects in Humans' provides an overview of all the clinical data on QIVc.

Meningococcal conjugate group C vaccines are routinely used in infant and toddlers' immunization schedules in many European countries and globally since 1999. The MenC vaccine will be given according to the indications and dosing regimen described in the Summary of Product Characteristics (SPC). The potential risks are described and available in the SPC.

Seqirus' quadrivalent influenza vaccine is approved by the FDA for use in children aged 4 years and older and this study is to confirm the clinical benefit of QIVc in children 6 through 47 months of age. Therefore, the Investigator's Brochure should be reviewed prior to study start.

1.3 Rationale

The aim of this Phase III randomized clinical study is to evaluate the absolute vaccine efficacy of QIVc in the prevention of RT-PCR confirmed influenza Type A and/or Type B disease in children 6 through 47 months of age, compared to a non-influenza vaccine, using conventional endpoints and an additional endpoint that captures clinically relevant outcomes of influenza, associated with influenza-like illness. To overcome risks associated seasonal variations in influenza virus circulation, the study will continue for several seasons. By successfully demonstrating that QIVc decreases influenza disease in this age group, it will have the potential to play an important role in the prevention of influenza worldwide.

The study is part of a paediatric investigation plan (PIP) agreed by the European Medicines Agency's (EMA) Paediatric Committee (PDCO) to support the authorization of QIVc in children ≥ 6 months of age.

2. OBJECTIVES

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

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

2.1 Primary Objective(s)

Primary Efficacy Objective(s)

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

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

2.2 Secondary Objective(s)

Secondary Efficacy Objective(s)

Objectives evaluating QIVc compared to a non-influenza vaccine:

2) Prevention of culture confirmed illness caused by influenza virus strains antigenically dissimilar to the influenza strains selected for the seasonal vaccine.

3) Prevention of culture confirmed illness caused by any Type A and/or Type B virus.

4) Prevention of RT-PCR confirmed moderate-to-severe illness caused by any influenza Type A and/or Type B virus.

Secondary Immunogenicity Objective(s)

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

Secondary Safety Objective(s)

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

2.3 Exploratory Objective(s)

Exploratory objectives:

1) To characterize the immune response by other assays.

2) To use genotypic methods to characterize circulating strains of influenza collected during the study.

For exploratory endpoints refer to Section 8.1.3, Exploratory Endpoint(s).

3. STUDY DESIGN

3.1 Overview of Study Design

This multicenter phase III clinical study evaluates the efficacy, safety and immunogenicity of a cell-based quadrivalent subunit influenza virus-vaccine (QIVc) compared to non-influenza vaccine in subjects between 6 months through 47 months of age. The study features an observer blind design, parallel groups and 1:1 randomization between QIVc and the non-influenza vaccine. Based on previous influenza vaccination history, subjects will receive either one or two doses of either QIVc or comparator (non-influenza vaccine/placebo). The non-influenza vaccine is a conjugate vaccine for prevention of invasive disease caused by *Neisseria meningitidis* serogroup C (MenC vaccine). In subjects who require two doses, MenC and placebo (saline for injection) will be administered separated by 28 days. In this study placebo will be used as masking dose. All subjects aged 6 through 11 months at enrollment, regardless of treatment assignment, will receive a dose of the MenC vaccine at the end of the study. For the subjects allocated to the immunogenicity sub-set, blood samples will be collected during clinical visits to allow immunogenicity analyses to further characterize the study population for baseline titers, response to vaccination and to understand the observed efficacy. An Interactive Response Technology (IRT) system will be used for subject randomization into the treatment group and into the immunogenicity sub-set.

The study is designed to accrue an approximate number of subjects and a minimum number of cases over several influenza seasons, i.e. both a minimum of 191 RT-PCR confirmed influenza cases and a minimum of 104 culture confirmed influenza cases antigenically matched to the strains selected for the seasonal vaccine. If the overall/pooled influenza attack rate differs from the predicted and/or influenza strain circulation within a study season has drifted or shifted away from the strains selected for the seasonal vaccine, an adjustment of the prospectively specified number of cases, and number of subjects may be required. Extraneous real-life information, from (but not limited to) the influenza surveillance systems of the European Center for Disease Control (ECDC), US Center for Disease Control and Prevention (CDC) or World Health Organization (WHO) may be used to re-assess the influenza event rate.

Throughout the study, unscheduled visits are planned for subjects who manifest signs of influenza-like illness (ILI) during the influenza season and will be evaluated by testing of a, preferably, nasopharyngeal (NP) specimen for influenza (see Section 5.2.5, ILI Symptom Assessment and Documentation Training). A parent or LAR of the subject or a delegate is contacted weekly to capture these cases throughout the study, resulting in 30 to 45 ILI reminder calls.

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

All subjects aged 6 through 11 months at enrollment, irrespective of randomization to investigational or comparator group, will receive a dose of the MenC vaccine at the end of the study.

Safety data collection will include standard solicited adverse event reporting via subject diary card for 7 days after each study vaccine administration, all unsolicited AEs for 28 days after each vaccine administration, and special AE categories (SAEs, NOCDs, AEs leading to withdrawal, medically-attended AEs for 30 days after ILI onset) for the full duration of the study. In countries without a marketing authorization to use of *Neisvac-C* vaccine, safety (SAEs and NOCDs, and AEs leading to withdrawal) will be assessed 28 days after the MenC dose (given at Visit 5).

Two blood samples will be collected from a sub-set of subjects participating in each influenza season (maximum 222 per season), one prior to vaccination and one 28 days after last vaccination. The timing of blood sampling depends on the subject's previous influenza vaccination history and is specified in Section 3.5, Collection of Clinical Specimen.

Table 3.1 Not-previously influenza vaccinated subjects: Subjects not-previously vaccinated or with unknown influenza vaccination history

Age	Vaccine	Visit 1	Visit 2	Visit 5
6-11 months	Investigational	QIVc	QIVc	MenC vaccine
	Comparator	MenC vaccine	Saline	MenC vaccine

≥ 12 months	Investigational	QIVc	QIVc	-
	Comparator	MenC vaccine	Saline	-

Table 3.2 Previously influenza vaccinated subject: Subjects previously vaccinated with at least two (2) influenza vaccine doses

Age	**Vaccine**	**Visit 1**	**Visit 2**	**Visit 4**
6-11 months	N/A^	-	-	-
≥ 12 months	Investigational	QIVc	-	-
	Comparator	MenC vaccine	-	-

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

The subject's previous influenza vaccination history is determined by assessment of the influenza vaccination history of the subject (see Section 5.1.2, Screening). Not-previously influenza vaccinated subjects are subjects that have not received two or more doses of influenza vaccine prior to the current influenza season, or who do not know their influenza vaccine history. These not-previously influenza vaccinated subjects are randomized to receive two study vaccinations separated by 28 days. Previously influenza vaccinated subjects are subjects with a history of at least two doses of an influenza vaccine prior to the current influenza season, and are randomized to receive 1 study vaccination.

Each subject will participate until the end of the influenza season as defined in the protocol for the season in which the subject is enrolled but at least 180 days after last vaccination.

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

3.2 Study Period

Each subject should expect to participate in study until the end of the influenza season, but at least 180 days after last vaccination (approximately six to nine months).

3.3 Blinding Procedures

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

3.3.1 Subjects 6 through 11 months old at enrollment

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

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

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

3.4 Data Collection

3.4.1 Data Collected from Subjects

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

- Informed Consent related information
- Demographic Information (see Section 5.1.2, Screening).
- Physical Examination Information (see Section 5.1.2, Screening).
- Adverse Events (see Section 7.1, Safety Assessment).
- Medical History (see Section 5.1.2, Screening).
- Relevant Concomitant Medications (see Sections 5.1.2, Screening and 6.4, Prior and Concomitant Medications and Vaccines).
- All Vaccination History (see Section 5.1.2, Screening).

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

Data will be recorded in the Subject diary card and collected on electronic Case Report Forms (eCRFs).

Subject Diary Card

Paper Diaries (pDiaries), hereafter referred to as subject diary cards 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. The following additional rules apply to documentation of safety information collected in the subject diary card.

The Investigator or delegated staff should monitor the subject's diary card status during the treatment period of the study for compliance and review any solicited local and systemic adverse events (see Section 7.1.1, Solicited Adverse Events for instructions for review of the subject's diary card). The subject's parent(s)/LAR/delegate will receive training on diary completion before entering data (see Section 5.2.2, Subject Diary Card Dispense and Training)

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

Case Report Forms

This study utilizes EDC system to collect study-related data from each subject. A trained healthcare professional is required to enter subject data in the eCRFs in English based on the (medical) information available in each subject's source record.

Data should be entered into the eCRF in a timely fashion following each subject's clinic visit, study procedure, or phone call. Each subject's eCRF may be compared with the subject's source records by an 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 card information collected in the CRFs:

1. The site must enter all readable entries in the subject diary card into the eCRF, 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's parent(s)/LAR/delegate. 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 eCRF (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 card, this fever of 40°C should be recorded in the Adverse Event eCRF).
3. Any newly described safety information (including a solicited adverse event) must not be written into the subject diary card and must be described in the study file as a verbally reported adverse event. Any adverse event reported in this fashion must be

described as an unsolicited adverse event and therefore entered on the Adverse Event eCRF.

Influenza-like illness Booklet

If a subject experiences signs and symptoms that meet the protocol defined criteria for ILI, the subject's parent(s)/LAR/delegate will be asked to document the subjects body temperature (a body temperature of ≥ 37.8°C (≥ 100.0°F), using the supplied thermometer) and the ILI symptom(s) in an ILI Booklet. The highest recorded body temperature of the subject for the day should be recorded. Instructions and explanations on ILIs and the Booklet are provided by a trained healthcare professional during the ILI Symptom Assessment and Documentation Training (see Section 5.2.5, ILI Symptom Assessment and Documentation Training). Subjects with ILI symptoms and its complications ought to be treated according to recent accepted (national) clinical standards. In countries, in the exceptional case where calls are not feasible, study site personnel may visit the subject's homes to inquire about signs and symptoms of illness in the subject.

3.5 Collection of Clinical Specimens

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

- Blood.
- Nasopharyngeal swabs.

Blood specimens are only drawn from subjects participating in the immunogenicity sub-set. Nasopharyngeal swabs are only taken from those subjects that report a protocol defined ILI episode.

Processing of each specimen should be completed by a trained healthcare professional and in accordance with the study-specific Clinical Specimen Laboratory Manual. Testing of clinical specimens will be performed by a Seqirus or a Seqirus designated (contracted) laboratory. Further additional detail is available in the study-specific Clinical Specimen Laboratory Manual.

Blood Specimens

A maximum of 5 mL sample of blood will be drawn from all subjects participating in the immunogenicity sub-set at visit 1 before vaccination, and 28 days after last vaccination. The blood volume will not exceed 5 mL at each time point in order to provide the

necessary serum volume (approximately half of the blood draw volume) for the serology assays.

The blood will be used for immunological assays as measured by the HI and MN assay. Stored samples may be used for additional immunogenicity analyses using other assays, to further characterize the immune response. See Section 7, Assessments for additional details.

The total amount of blood collected over the study period per subject will be 10 mL.

Nasopharyngeal Specimens

Subjects who experience symptoms meeting the per protocol defined ILI criteria will have a nasopharyngeal (NP) swab collected for evaluation of the presence of influenza virus by RT-PCR (see Clinical Specimen Lab manual). NP swab is the preferred swab method; other methods/routes are: nasal swab or oropharyngeal swab.

All samples will also be cultured for the growth of the clinical strain of influenza obtained from subjects in order to conduct antigenic characterization (to determine whether the clinical isolate is antigenically matched, or not, to the influenza vaccine strain). See Section 7, Assessments for additional details.

3.6 Stopping/Pausing Guidelines

An event-driven interim analysis may be performed by the Sponsor with the possibility to stop the trial early for efficacy. In addition, an independent Data Monitoring Committee (DMC) can make a recommendation as to whether the study should be stopped /paused if there is a safety concern. The predetermined stopping guidelines are described in Section 3.7, Data Monitoring Committee and the DMC charter.

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 Regulatory 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.

3.7 Data Monitoring Committee

An independent DMC will be utilized for the study for periodic evaluation of safety and efficacy data during the study. 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. The DMC will advise on a stop for efficacy only when the pre-specified criteria of the interim analysis are met, otherwise the DMC will recommend that the trial will continue as planned.

A DMC charter will be written documenting 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. 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.

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. 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, other, and protocol deviation. These reasons are described in greater detail below.

Adverse Event

For any subject withdrawn from study participation prior to the planned study completion 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 eCRF 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 but the subject will be asked to be followed for safety for the duration of the study.

If a medically-attended adverse event occurred within 30 days following a protocol definition of ILI, the event should also be reported on the AE eCRF page (see Section 7.1, Safety Assessment)."

Death

For any subject withdrawn from study participation due to death, this should be noted on the study completion eCRF and the associated SAE that led to the death must be reported on the (S)AE page.

Withdrawal of Consent

The subject's parent(s)/LAR 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's parent(s)/LAR intends to withdraw consent from the study, the investigator should clarify if the subject will withdraw completely from the study or if the subject will continue study participation for safety. If the subject requests complete withdrawal from the study, no further study interventions or data collection will be performed with the subject.

In countries where the Health Insurance Portability and Accountability Act (HIPAA) is applicable, if a subject's parent(s)/LAR 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's parent(s)/LAR revokes only the HIPAA authorization, the Sponsor will have full access to all of the subject's medical records prior to the date and time of written revocation.

Lost to Follow-Up

For subjects who fail to show up for planned visits (clinic or telephone contacts), or for three consecutive visits (clinic or (safety or diary) telephone contacts), or fail to reply to ILI reminder calls for 4 weeks, study staff are encouraged to make at least three documented attempts to contact the subject's parent(s)/LAR by telephone and at least one documented written attempt to contact the subject's parent(s)/LAR to encourage the completion of study completion procedures. These efforts to contact the subject should be recorded in the source document. The termination date for the subject to be captured on the study completion eCRF page is the date of the last successful contact (clinic visit or telephone) with the subject.

Other

Examples for subjects withdrawn from the study due to other reasons can include: Sponsor decision to terminate the study, subject meeting a pre-specified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the Study Completion CRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilization.

Study Terminated by Sponsor

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

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. Five main categories can be identified:

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

Protocol deviations might impact the analysis. Protocol deviations and its consequences are defined in the study Statistical Analysis Plan. 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.

3.9 End of Study

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

Evaluation of the primary and/or secondary immunogenicity/efficacy objectives requires the testing of biological samples from the study subjects, which can only be completed after all samples are collected. The last samples for the analysis of the primary and/or secondary objectives will be taken up to the end of the 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 the date of last unscheduled visit by a subject who manifested signs of influenza-like-illness (ILI) during the protocol defined influenza season and from whom a NP sample was taken.

4. SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

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

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

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

4.2 Exclusion Criteria

Each subject must not have:

1. Acute (severe) febrile illness (see Section 4.3 Criteria for Delay of Vaccination). Enrollment could be considered if the fever is absent for 72 hours.
2. History of any anaphylaxis, serious vaccine reactions or hypersensitivity, including allergic reactions, to any component of vaccine or medical equipment whose use is foreseen in this study.
3. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws. These may include known bleeding disorders, or treatment with anticoagulants in the 3 weeks preceding vaccination.
4. A known history of Guillain-Barré Syndrome or other demyelinating diseases such as encephalomyelitis and transverse myelitis.

[1] A subject and parent(s)/LAR are considered to be able to comply if the Investigator judges that the subject can complete all study procedures such as subject diary card, return for all the follow-up visits, be available for telephone calls (if applicable), ILI booklet as scheduled in the study.

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

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

4.3 Criteria for Delay of Vaccination

There may be instances when individuals meet all eligibility criteria for vaccination yet have a transient infection which may warrant delay of vaccination: clinical signs of fever and/or 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 vaccination after the appropriate visit window has passed and inclusion/exclusion criteria have been rechecked and if the subject is confirmed to be eligible. In these instances, missing the visit window is not considered a protocol deviation.

5. STUDY PROCEDURES

The sections that follow provide an overview of the procedures that are to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either clinic visits or safety follow-up telephone calls, as specified in the Table below and in the Time and Events Table 1.1 and 1.2. Not all study procedures are to be performed at all clinical visits or calls. The Time and Events Table 1.1 and 1.2 specifies which procedure should be performed at which visit.

In the exceptional case where calls or clinic visits are not feasible in some countries, study site personnel may visit the subject's homes to inquire about signs and symptoms of illness in the subject, collect a NP swab specimen or perform other study assessments (Table 5-1), when agreed upon by the Sponsor and in line with country specific requirements and/or regulations.

Table 5-1 Study Procedures

Visit Category	Procedures
Pre-vaccination Procedure(s)	Section 5.1 describes procedures to be followed prior to study vaccination: informed consent, screening, enrolment, and randomization
Procedure(s) related to Vaccination	Section 5.2 describes procedures to be followed during a clinic visit involving vaccination: blood draw, vaccination, 30 minutes observation, Subject diary card training, ILI Symptom Assessment and Documentation Training, next visit schedule, and diary reminder call
Post-vaccination Visit(s)	Section 5.3 describes activities after last vaccination: Follow up clinic visit and safety follow-up call
Procedure(s) related to Protocol Defined ILI episodes	Section 5.4 describes possible procedures to be followed: ILI Symptom Assessment and Documentation, ILI reminder calls, unscheduled visit, ILI follow-up call
Study Completion Visit	Section 5.5 describes procedures to be followed at study completion (may include early termination visit and MenC vaccine administration)

5.1 Pre-vaccination Procedure(s)

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

5.1.1 Informed Consent

"Informed consent" is the voluntary agreement of an individual or his/her LAR 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.

Informed consent following local IRB/EC guidance **must** be obtained before conducting any study-specific procedure (i.e., all of the procedures described in the protocol). The informed consent process may be conducted up to 10 days prior to any study procedure on Visit 1 (see Section 13.2, Informed Consent Procedures) The process of obtaining informed consent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent.

If a subject's parent(s)/LAR is unable to read, an impartial witness should be present during the entire informed consent discussion. 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 LAR 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's parent(s)/LAR and after the subject's parent(s)/LAR has verbally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject's parent(s)/LAR and that informed consent was freely given by the subject's parent(s)/LAR.

All subjects will sign a generic or a separate ICF which includes the possibility of being included into the immunogenicity sub-set study.

5.1.2 Screening

After an individual has consented to participate in the study and informed consent is signed, that individual will be given 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 procedure(s) includes:

- Demographic data. Prior to study enrolment, demographic data will be collected from the subject, including: sex, date of birth, race, ethnicity. These data will be written in the source document (see Section 9.1, Source Documentation) and must be documented in the eCRF.

- Medical history. Relevant medical history will be collected, including but not limited to any medical history that may be relevant to subject eligibility for study participation and previous and ongoing illnesses or injuries. 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. Preferably medical history should be obtained from medical record review. In the exceptional case that medical record information is not available, medical history can be obtained by parent(s)/LAR verbal reporting. These data will be written in the source document (see Section 9.1, Source Documentation), including a confirmation that written medical records are not available, and must be documented in the eCRF. In general, worsening of a pre-existing event reported in the Medical History should be reported as an AE as described in Sections 5.1.2, Screening and 7.1.2, Unsolicited Adverse Events.

- Prior and concomitant medications or vaccinations. If applicable, prior and concomitant medications or vaccinations taken prior to start of study should be collected by review of the subject's medical record and vaccination card (see Section 6.5, Prior and Concomitant Medications and Vaccines for further details). In the exceptional case that documentation of medication or vaccination history is not available, subject's parent(s)/LAR verbal recall of prior medication or vaccination will be recognized as sufficient medical history; this attempt and information must be captured in the source documentation. If the parent(s)/LAR is unable to recall previous vaccination status, then they should be considered not-previously influenza vaccinated. These data will be written in the source document (see Section 9.1, Source Documentation) and must be documented in the eCRF.

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

- Symptom-directed physical examination. An interview with the subject's parent(s)/LAR will be performed before enrolment if the subjects has reported any complaints (review of systems). This interview is used to guide physical examination. A symptom-directed physical examination is to be performed by a qualified health care professional. As part of the physical examination, the following clinical signs: weight, height and body temperature should be measured and documented in both the source and eCRF by a trained healthcare professional allowed by institutional policy including a check of general appearance. If body temperature is ≥ 38.0°C (≥ 100.4° F) at the time of screening, vaccination must be postponed (see Section 4.3, Criteria for Delay of Vaccination). These data 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 in the eCRF.

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 form, if an individual is determined to be eligible for study participation, the investigator will enroll the subject and enter the Subject ID into the EDC system. The Subject ID will be the subject's unique identification number for all eCRFs and associated study documentation that will be used for duration of the study. After enrollment, the Screening ID ceases to be used and remains in the Screening and Enrolment Log only.

5.1.4 Randomization

All enrolled subjects will be randomly assigned to one of the two study groups (QIVc or comparator) in a pre-specified ratio of 1:1, with stratification factors such as age cohort (6 through 23 months / 24 through 47 months, with a at least 30% of the subjects between 6 through 23 months of age and at least 30% of the subjects between 24 through 47 months

of age), previous influenza vaccination history. For immunogenicity assessments, a sub-set of subjects (a maximum of 222 subjects per influenza season) will be assigned to the immunogenicity sub-set at a 1:1 ratio to QIVc or comparator respectively with stratification factors such as age cohort, and previous influenza vaccination history.

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

If for any reason, after signing the informed consent form (ICF), the subject who is eligible and enrolled fails to be randomized, this is called a randomization failure. Further guidance is provided in the CRF Instructions and the early termination study procedures must be applied. 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 early termination study procedures must be applied, including reason should be recorded in source document as specified in the SDA. The information on these Early Termination subjects should be kept distinct in the source documentation from randomization failures.

5.1.5 Blood draw

After randomization, but prior to vaccination, a maximum of 5 mL of blood will be drawn from subjects randomized into the sub-set for the immunogenicity testing (see Section 3.5, Collection of Clinical Specimens. These data will be written in the source document (see Section 9.1, Source Documentation) and must be documented in the eCRF.

5.2 Procedure(s) related to Vaccination

A study vaccine will be given on Visit 1 for previously influenza vaccinated subjects and on Visit 1 and 28 days (window: 0/+7 days) after first study dose for not-previously influenza vaccinated subjects using the study vaccine identified by the via IRT assigned Pack ID. The pack ID is the medication number printed on each individual kit and is specific to a treatment type (QIVc or MenC vaccine or saline for injection (placebo). Subjects aged 6 through 11 months at enrollment will receive a (second) dose of the

MenC vaccine during at Visit 5 (see Section 5.5, Study Completion Visit, and Section 6.2, Vaccine Preparation and Administration).

All serology samples for the immunogenicity sub-set should only be taken if the subjects are randomized in the immunogenicity sub-set. Samples are taken **prior** to vaccination on Visit 1 and 28 days after last study vaccine has been given.

Prior to administration of each vaccination, confirm that the subject is eligible for additional study vaccinations and does not meet any criteria for delaying additional study vaccinations as described in Section 4, Selection of Study Population.

5.2.1 Vaccination

After completing the pre-vaccination procedures, administer the study vaccine to the subject according to the procedures described in Section 6.3, Vaccine Preparation and Administration. Observe the blinding procedures described in Section 3.3, Blinding Procedures.

After each vaccination the subject will be observed for at least 30 minutes including observation for unsolicited adverse events, solicited adverse events, and body temperature measurement. Record all safety data collected during this time in the subject's source document.

5.2.2 Subject Diary Card Dispense and Training

A subject diary card will be used in this study to document solicited adverse events after a study vaccine has been given. The subject diary card is the only source for collection of these data; therefore, it is critical that the subject's parent(s)/LAR completes the subject diary card correctly. The subject's parent(s)/LAR should be trained on how and when to complete each field of the subject diary card.

The subject's parent(s)/LAR should be (re-)trained on how to measure local solicited adverse reactions and body temperature. The measurement of solicited local adverse reactions is to be performed using the ruler provided by the site.

The subject's parent(s)/LAR should be instructed how to perform body temperature measurement using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject's parent(s)/LAR should check body temperature. If the subject has fever, the highest recorded body temperature observed for that day should be recorded in the subject diary card.

Subject diary card training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the subject diary card. This individual may not be the subject's parent(s)/LAR, but if a person other than subject's parent(s)/LAR enters information into the subject diary card, this person's identity must be documented in the subject's source record. Any individual that makes entries into the Subject diary card must receive training on completion of the subject diary card at the time of the visit. This training must be documented in the subject's source record.

It is preferred that the same individual should complete the subject diary card throughout the course of the study.

5.2.3 Schedule the next study activity

The site should schedule the next study activity: clinic visits, or safety follow-up call with the subject's parent(s)/LAR.

The subject's parent(s)/LAR should be reminded of the next planned study activity. The subject's parent(s)/LAR will be reminded to complete the subject diary card and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit or to a visit to/by a doctor or is of concern. Contact must be documented in the subject's source record.

5.2.4 Diary Reminder Calls

Reminder telephone calls are not intended to be an interview for collection of safety data. If the subject's parent(s)/LAR wishes to describe safety information, this information should only be collected by a trained healthcare professional at the site, and the safety data described must be written down in the subject's source document and on an Adverse Events eCRF, as specified in Section 7.1, Safety Assessment.

A subject diary card reminder call will be performed approximately 2 days after vaccination. The purpose of this call is to remind the subject's parent(s)/LAR about completion of the subject diary card. The call follows the subject diary card Reminder Telephone Call Script provided to the site. The subject's parent(s)/LAR should be reminded to contact the site via the telephone number provided in the informed consent to discuss medical questions.

In countries, in the exceptional case where calls are not feasible, study site personnel may visit the subject's homes to inquire about signs and symptoms of illness in the subject.

5.2.5 ILI Symptom Assessment and Documentation Training

The ILI Symptom Assessment and Documentation Training contains, at least, explanations and instructions for subject's parent(s)/LAR how to recognize influenza-like illness, how to use the supplied thermometer to measure body temperature, how to report the ILI symptoms using the ILI Booklet, who to contact for an unscheduled clinic visit to have a nasopharyngeal (NP) swab collected, and not to use antiviral therapy prior to swab sampling.

5.3 Post-vaccination Visit(s)

Post-vaccination visits will be performed 28 days, and 90 days after last vaccination (Section Time and Event Table). For some subjects aged 6 through 11 months at enrollment, also a Visit 6 is scheduled (approximately 28 days after MenC-dose at Visit 5) (Section 5.5.2, Countries without a MenC market authorization).

5.3.1 Follow-up Clinic Visit

A follow-up clinic visit (e.g. Visit 2 or Visit 3, depending on influenza vaccination history) will be performed 28 days after last vaccination for all subjects.

During the follow-up clinic visit, the subject diary card will be reviewed. No changes to the information recorded within the subject diary card are permissible. For details on the subject diary card as specified in Sections 3.4.2, Tools Used for Data Collection, 5.2.2, Procedure(s) related to Vaccination and 7.1.1, Solicited Adverse Events. The subject's parent(s)/LAR will be interviewed to determine if any unsolicited adverse events occurred and if any concomitant medications or vaccines were taken/received in the time since the last clinic visit. The qualified health care professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or adverse events are present. Adverse events reported by the subject's parent(s)/LAR at this follow-up clinic visit must be recorded in the subject's source document and on an Adverse Events eCRF, as specified in Section 7.1, Safety Assessment.

Perform a 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, and concomitant medication use. This assessment may include: measurement of clinical signs, body temperature 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. Corresponding information is documented in the subject's source document.

In subjects participating in the immunogenicity sub-set, a maximum of 5 mL of blood will be drawn for the immunogenicity testing (Section 3.5, Collection of Clinical Specimens).

The site should schedule the next study activity, being safety follow-up call with the subject's parent(s)/LAR.

The subject's parent(s)/LAR will receive a reminder of the next planned study activity. The subject's parent(s)/LAR will be reminded to complete the subject diary card and to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit or to a visit to/by a doctor. Contact including the medical condition/event must be documented in the subject's source record.

5.3.2 Safety Follow-up Visit

The Safety Follow-up visit is a telephone call performed 90 days after last vaccination (e.g. Visit 3 or Visit 4, depending on influenza vaccination history). In countries, in the exceptional case where calls are not feasible, appropriate study site personnel may visit the subject's homes to inquire about signs and symptoms of illness in the subject.

Safety follow-up calls are calls made to the subject's parents(s)/LAR by qualified health care professional designated on the site's roles and responsibilities log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject's parent(s)/LAR will be interviewed according to the script, and information relating to unsolicited adverse events including: serious adverse events (SAEs), new onset of chronic disease (NOCD), all medically-attended AEs within 30 days after the onset of ILI episode, and/or AEs leading to withdrawal, 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 script will also include a question on ILI occurrence.

The site should schedule the next safety follow-up call (if applicable) with the subject's parent(s)/LAR.

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

or to a visit to/by a doctor. Contact including the medical condition/event must be documented in the subject's source record.

5.4 Procedure(s) related to Protocol Defined ILI episodes

5.4.1 ILI Reminder Calls

Active surveillance for per protocol defined ILI will be conducted weekly via a reminder call or during planned clinic visits, from Visit 1 until the end of the influenza season. The subject's parent(s)/LAR will be asked via a checklist to determine if symptoms of ILI are present. The purpose of the reminder call is to trigger an unscheduled visit and nasopharyngeal (NP) swab collection. During every reminder call, the subject's parent(s)/LAR will be instructed to report and visit the study site in case of an ILI episode as soon as possible (see Section 5.4.2, Unscheduled Visit(s)). The reminder calls are not intended to collect any clinical data. If during the ILI reminder call an ILI is identified, a visit to the study site should be planned as soon as possible, as described in Section 5.4.2, Unscheduled Visit(s). In countries, in the exceptional case where calls are not feasible, study site personnel may visit the subject's homes to inquire about signs and symptoms of illness in the subject.

5.4.2 Unscheduled Visit(s)

An unscheduled visit describes a non-routine study visit triggered by a specific event: (onset of) ILI symptoms during active ILI surveillance

Subject will be asked to come to the study site for an unscheduled visit within the first 24 hours or as soon as possible following ILI onset to ensure optimal viral yield. Preferably, samples will be accepted if collected up to 6 days following the day of ILI onset. In the exceptional case that a clinic visit is not feasible, a home visit may be considered.

The following procedures should be carried out during this unscheduled visit:

a) The ILI symptoms and ILI Booklet will be reviewed and collected. The information should be mentioned in the subject's source documentation and recorded on the ILI event eCRF.

b) Subjects meeting the protocol defined criteria for ILI will have a nasopharyngeal (NP) swab collected for evaluation for the presence of influenza virus. A NP swab is strongly preferred sampling method to ensure consistency across the study population (see Clinical Specimen Lab Manual for detailed procedures for collecting, processing and shipping ILI swab samples). NP swabs should be taken prior to antiviral therapy.

If an antiviral therapy has been given prior to swab sampling, this should be mentioned in the subject's source documentation and recorded on the Concomitant Medication page in eCRF. Subjects with ILI symptoms and its complications ought to be treated according to recent accepted (national) clinical standards.

c) The Investigator will record the subjects body temperature as part of the Physical Examination (see Section 5.1.2, Screening).

d) Physical examination findings will be recorded in the medical source documents and Adverse Events eCRF.

e) The use of relevant medications and the occurrence of medically-attended AEs within 30 days after the onset of ILI episode will be assessed.

f) ILI Symptom Assessment and Documentation Training including an ILI Booklet will be provided (see Section 5.2.5, ILI Symptom Assessment and Documentation)

The site should schedule the ILI follow-up call with the subject's parent(s)/LAR.

The subject's parent(s)/LAR will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit or to a visit to/by a doctor. Contact including the medical condition/event must be documented in the subject's source record.

5.4.3 ILI Follow-up Call

An ILI follow-up call will be performed at 30 (+7) days after protocol defined ILI onset, amongst subjects who have had their NP swab obtained. The subject's parent(s)/LAR will be asked a set of questions to:

a) Assess ILI symptoms and associated medications, if any.

b) Assess medically-attended adverse events within 30 days after protocol defined ILI.

c) Remind subject of next study activity.

The subject's parent(s)/LAR will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. Both contact and the medical condition/event must be documented in the subject's source record.

In countries, in the exceptional case where calls are not feasible, study site personnel may visit the subject's homes to inquire about signs and symptoms of illness in the subject.

5.5 Study Completion

Study completion will occur at the per protocol defined end of the influenza season but at least 180 days after last vaccination, except for some subjects aged 6 through 11 months at enrollment (see Time and Events Table and Section 5.5.2, Countries without MenC market authorization). For all subjects, the study completion visit is a telephone call by a qualified health care professional, or in an exceptional case a clinic or home visit performed by a qualified health care professional.

Subjects aged 6 through 11 months at enrollment, irrespective of treatment allocation, will receive a dose of the MenC vaccine at Visit 5.

The date of study completion is the date of the last contact (clinic or home visit or telephone call) in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded in the source documents and on the study completion eCRF 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.

During the telephone call or clinic/home visit, the following procedures will be performed: Interview of subject's parent(s)/LAR to collect potential: medically-attended AEs within 30 days after the onset of ILI episode, NOCDs, AEs leading to withdrawal, SAEs, ILIs and interview to collect concomitant medications/ vaccinations.

If during the study completion visit, ILI symptoms are reported by the parent/LAR and if the onset of the ILI is within (≤) 6 days before the study completion visit, an NP swab should be collected from the subject for influenza testing and study staff will document the ILI in the subject's source records and on the ILI eCRF (see procedures described in Section 5.4.2 Unscheduled Visit(s). Should an ILI be identified and a NP swab taken, it is recommended to postpone the study completion visit, to allow for the ILI follow-up visit to occur. In these instances, missing the study completion visit window is not considered a protocol deviation. Should the subject have experienced a protocol defined ILI for which an NP swab was obtained, please collect the information of any medically-attended adverse events which have occurred within 30 days after the onset of the of ILI. If study completion is after the end of influenza season (i.e. after active ILI surveillance), documentation of an ILI and collection of a swab is not applicable.

For subjects who will receive a dose of the MenC vaccine (see Section 6.2, Vaccine Preparation and Administration) during Visit 5, the vaccine is administrated according to the procedures described in Section 6.2, Vaccine Preparation and Administration, and the subject will be observed for at least 30 minutes.

The site will review with the subject's parent(s)/LAR 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's parent(s)/LAR chooses to share this information.

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

5.5.1 Early Termination Visit

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor or Delegate 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 or home visit or during the telephone call, the same procedures will be performed as during the study completion visit, see Section 5.5, Study Completion, if possible. In addition, if applicable, review of subject diary card, collection of subject diary card, interview of subject's parent(s)/LAR to collect: unsolicited adverse events, medically-attended adverse events, NOCDs, AEs leading to withdrawal, SAEs, ILIs, interview of subject's parent(s)/LAR to collect concomitant medications/ vaccinations, blood sampling for immunogenicity. Subject' parent(s)/ LAR of subjects enrolled at the age of 6 through 11 months will be asked to return to the study site at least 6 months after last vaccination to receive a dose of the MenC vaccine. If the subject's parent(s)/LAR is not willing to return, the consequences of not receiving this dose of the MenC- vaccine should be explained and discussions should be documented in the source documentation.

The site will review with the subject's parent(s)/LAR 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's parent(s)/LAR chooses to share this information.

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

5.5.2 Countries without MenC market authorization

In countries where the MenC vaccine is not licensed for use, a Visit 6 for subjects aged 6 through 11 months will be performed, at approximately 28 days after MenC vaccination at Visit 5 (see Time and Events Table). For these subjects, Visit 6 is the study completion visit. During Visit 6 safety data will be collected (SAE, NOCD, AE leading to withdrawal). Visit 6 may be performed as a telephone call. For all other subjects a Visit 6 is not required.

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 and if it has experienced a temperature deviation prior to use. Expired vaccines or those that have experienced a temperature deviation must not be administered to subjects, as specified in Section 6.5, Vaccine Supply, Labeling, Storage and Tracking.

6.1 Study Vaccine(s)

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

Investigational Vaccine:

Cell-derived seasonal quadrivalent influenza vaccine: The investigational vaccine is the cell-derived seasonal quadrivalent influenza vaccine (*Flucelvax Quadrivalent/ Flucelvax Tetra*, QIVc, Seqirus).

The *Flucelvax Quadrivalent/ Flucelvax Tetra* vaccine is a is a sterile, slightly opalescent suspension in phosphate buffered saline. The dose to be administrated (0.5 mL) is formulated to contain a total of 60 µg hemagglutinin (HA) per 0.5 mL dose in the recommended ratio of 15 µg HA of each of the four (4) influenza strains recommended by WHO for inclusion in the quadrivalent vaccine formulation for the influenza season corresponding to the season of conduct of study. Each dose of *Flucelvax Quadrivalent/ Flucelvax Tetra* may contain residual amounts of MDCK cell protein (≤ 25.2 µg), protein other than HA (≤ 240 µg), MDCK cell DNA (≤ 10 ng), polysorbate 80 (≤ 1500 µg), cetyltrimethlyammonium bromide (≤ 18 µg), and β-propiolactone (< 0.5 µg), which are used in the manufacturing process. The 0.5 mL pre-filled syringes contain no preservative or antibiotics.

A comprehensive review of the *Flucelvax Quadrivalent/ Flucelvax Tetra* vaccine is available in the Investigators Brochure supplied by Seqirus (or delegate). This document should be reviewed by the Investigator prior to initiating the study.

Comparator vaccine(s):

The comparator is *NeisVac-C* (MenC vaccine, Pfizer Limited), a *Neisseria meningitidis* serogroup C polysaccharide conjugate vaccine. A masking dose of placebo (saline for

injection) will be administered to subjects who required a 2-dose vaccination to maintain the blind in the study.

Meningococcal (Group C) Conjugate Vaccine: A dose of 0.5 mL of the *Neisseria meningitidis* serogroup C polysaccharide conjugate vaccine (*NeisVac-C*, Pfizer Limited) will be administered as comparator vaccine.

The *NeisVac-C* vaccine is a sterile, homogenous semi-opaque white to off-white suspension in a single dose syringe. Each dose of 0.5 mL *NeisVac-C* vaccine contains the following active ingredients: 10 µg of meningococcal group C polysaccharide conjugated with 10 to 20 µg of tetanus toxoid protein, absorbed to aluminium hydroxide (1.4 µg, equivalent to 0.5 µg aluminium), plus the following ingredients: sodium chloride and water (4.1 µg) for injection, Qs to 0.5 mL. *NeisVac-C* vaccine does not contain preservatives or antibacterial agent.

A comprehensive review of the *Neisvac-C* vaccine is available in the Summary of Product Characteristics / Package Insert supplied by Seqirus (or delegate). This document should be reviewed by the Investigator prior to initiating the study.

Placebo (Saline for injection): A dose of 0.5 mL of saline for injection (placebo) will be administrated as second dose in not-previously influenza vaccinated subjects randomized to the MenC comparator group (see Table 3.1, Not-previously influenza vaccinated subjects).

Saline for injection is a clear, colorless liquid. Each dose of 0.5 mL saline for injection (placebo) contains the following ingredients: Sodium chloride, 4.5 mg; Water for Injection, Qs to 0.5 mL.

6.2 Vaccine Preparation and Administration

The investigator or designee will be responsible for oversight of the administration vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. All study 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.

Detailed vaccine preparation and administration instructions will be provided to investigators 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 vaccination prior to first study vaccine administration is determined by evaluating the entry criteria outlined in protocol Sections 4.1, Inclusion Criteria and 4.2, Exclusion Criteria.

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

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

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

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

6.3 Vaccine Administration Error or Overdose of Vaccine

A 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 is administered in one dose of vaccine as per dosing regimen described in Section 6.1, Study Vaccines.

An overdose would also occur if two doses of the study vaccine are administered within half the time of the recommended interval between doses, as defined in the protocol.

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 Serious Adverse Event (SAE), it must be reported as such within 24 hours to the Sponsor.

6.4 Prior and Concomitant Medications and Vaccines

All medications, vaccines and blood products taken or received by the subject within 1 month prior to the start of the study are to be recorded on the Prior and Concomitant Medications eCRF. In addition, the following are considered prior medications for this protocol: all medication/vaccines described in the inclusion and exclusion criteria of this protocol including:

a) Influenza vaccination in the last 6 months.
b) Systemic administration of corticosteroids (PO/IV/IM) within 90 days prior to informed consent. Topical, inhaled and intranasal corticosteroids are permitted. Intermittent use (one dose in 30 days) of intra-articular corticosteroids is also permitted.
c) Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent.
d) Received immunoglobulins or any blood products within 180 days prior to informed consent.

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

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

Concomitant medications include all medications (including vaccines; with the exception of vitamins, minerals and alternative medicines) taken by/administered to the subject at and after enrolment continuing up to the end of the treatment period and must be documented on the Concomitant Medications eCRF. During the follow-up period, all vaccinations should be documented and only those concomitant medications are documented on the Concomitant Medications eCRF if associated with an SAE, medically-attended AEs within 30 days after the onset of ILI episode, NOCD, or AE leading to study withdrawal.

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

The following additional treatments, if used within the treatment period, e.g. in case of medical need, represent a protocol deviation and may result in the subject being excluded from the Per Protocol Set (PPS):

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

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

6.5 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following:

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

The investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including:
  - Confirmation that the vaccines were received in good condition and in the right amount.
  - Confirmation to the Sponsor that temperature range during shipment from the Sponsor to the investigator's designated storage location in the correct range (2°C to 8°C / 35.6°F to 46.4°F).
  - Report any temperature deviation and do not use vaccines until further confirmation by the Sponsor or delegate that the vaccines are authorized for use.
- Proper storage of the study vaccines, including:
  - Storage in a secure, locked, temperature-controlled location.

  - Proper storage according to the instructions specified on the labels and in the Pharmacy Manual.
  - Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.

- Appropriate management of the study vaccines, including:
  - Non-use of vaccines in case of temperature deviation, prior to receipt of authorization for use from the Sponsor or delegate.
  - Use only in accordance with the approved protocol.
  - Proper handling, including confirmation that the vaccine has not expired prior to administration.
  - Appropriate documentation of administration of vaccines to study subjects including:
    - Date, dosage, batch/lot numbers, expiration dates, unique identifying numbers assigned to subjects and study vaccines, and time of vaccine administration. This information will be maintained in an accountability log that will be reviewed by the site monitor.
    - Reconciliation of all vaccines received from the Sponsor. Reconciliation is defined as maintaining records of which and how many vaccines were received, which vaccines were administered to subjects, which vaccines were destroyed at the site, and which vaccines were returned to the Sponsor, as applicable.
- Proper adherence to the local institutional policy with respect to destruction of study vaccines.
- Complete record keeping of study vaccine use, wastage, return or destruction, including documentation of:
  - Copy of the site's procedure for destruction of hazardous material.
  - Number of doses destroyed, date of destruction, destruction code (if available), method of destruction, and name of individual performing destruction.

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

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

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

7. ASSESSMENTS

7.1 Safety Assessment

The measures of safety used in this study are routinely used in clinical studies. 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 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 or terminates the study early. AEs occurring after the informed consent form is signed but prior to receiving study vaccine/product will be documented as an adverse event and recorded within source document and eCRF. 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 diary cards or interviews.

7.1.1 Solicited Adverse Events

The term "reactogenicity" refers to solicited signs and symptoms ("solicited adverse events") occurring in the hours and days following a vaccination, to be collected by the subject's parent(s)/LAR for seven (7) consecutive days after each vaccination (including the day of vaccination), using a pre-defined subject diary card.

Each solicited adverse reaction and/or event is to be assessed and entered into the subject diary card, as described in Section 3.4.2, Tools Used for Data Collection. Each solicited adverse event is to be assessed according to a defined severity grading scale (see Statistical Analysis Plan (SAP) for further details). The following solicited adverse reactions and/or events are included in the subject diary card.

Solicited Local Adverse Reactions

Injection site:
- induration (hardness), in mm
- erythema (redness), in mm
- ecchymosis (bruising), in mm
- tenderness, grading:
    - 0=none
    - 1=no interference with daily activity
    - 2=interferes with daily activity
    - 3=prevents daily activity

Solicited Systemic Adverse Events

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

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

Other Solicited Adverse Events

The following are captured as "other solicited AEs":

- Use of analgesics/antipyretics are captured as "absent" or "present" and is also summarized by "for treatment" and "for prophylaxis".

- Fever derived from measured body temperature (defined as ≥ 38.0°C (≥ 100.4°F)). Measurement of temperature with a digital thermometer is preferred, the acceptable routes for temperature measurement in the study are: oral, axilla, ear or rectal.

The study staff must review the data entered into the subject diary card as described in Section 3.4.2, Tools Used for Data Collection and Section 5.3.1, Follow-up Clinic Visit(s). All solicited local reactions and solicited systemic adverse events are considered causally related to vaccination.

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

- Solicited local adverse reaction or systemic adverse event that leads to a visit to a healthcare provider (medically-attended adverse event, see Section 7.1.3, Evaluation of Adverse Events).
- Solicited local adverse reaction or systemic adverse event leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (adverse event leading to withdrawal, see Section 7.1.3, Evaluation of Adverse Events).
- Solicited local adverse reaction or systemic adverse event that otherwise meets the definition of a serious adverse event (see Section 7.1.4, Serious Adverse Events).

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

7.1.2 Unsolicited Adverse Events

All unsolicited adverse events need to be collected during the treatment period, which from informed consent to visit 2 for subjects with a history of previous influenza vaccination, or visit 3 for subjects with an unknown or without an influenza vaccination history (see Time and Event Table). During the follow-up period, from visit 2 or visit 3 respectively depending on previous influenza vaccination history up to the study completion visit, only those unsolicited adverse events that either are medically-attended AEs occurred within 30 days after the onset of ILI episode, or lead to withdrawal or are Serious Adverse Events, need to be reported on the Adverse Events eCRF (see Time and Events Table).

An unsolicited adverse event is an adverse event that was not solicited using a subject diary card and that was spontaneously communicated by a subject's parent(s)/LAR 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's parent(s)/LAR. In case of such events, subject's parent(s)/LAR will be instructed to contact the site as soon as possible to report the event(s). Unsolicited AE may also be reported during post-vaccination clinic visits or safety assessment phone calls. The detailed information about the reported unsolicited AEs will be collected by a qualified health care professional during the interview and will be documented in the subject's source records. Depending on the timing and nature of the event, the AE should be reported in the AE CRF (see Section 7.1.3, Evaluation of Adverse Events, Section 7.1.4, Serious Adverse Events, and Section 7.1.5, Methods for Recording Adverse Events and Serious Adverse Events).

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

7.1.3 Evaluation of Adverse Events

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

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

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

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

1. Not Related

The AE is not related to an investigational vaccine if there is evidence that clearly indicates an alternative explanation. If the subject has not received the vaccine, the timing of the exposure to the vaccine and the onset of the AE are not reasonably related in time, or other facts, evidence or arguments exist that reasonably suggest an alternative explanation, then the AE is not related.

2. Related

a. Possibly Related

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

b. Probably Related

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

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

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

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

- "Medically-attended adverse event": an adverse event requiring hospitalization, or emergency room visit, or visit to/by a health care provider.

- "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 study vaccine withdrawal.

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

When the subject's parent(s)/LAR 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 serious adverse event need not, by definition, be severe.

Serious adverse events will be captured on the AE/SAE eCRF. 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 by the investigator based on the following definitions:

1. Related/suspected

The SAE is judged by the investigator to be possibly or probably related to the study vaccine on the AE eCRF 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 eCRF. The hospitalization itself should be reported in the AE/SAE eCRF. In general, worsening of a pre-existing event should be reported as an AE as described in Sections 5.1.2, Screening and 7.1.2, Unsolicited Adverse Events. 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.

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

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

All SAEs which occur during the course of the study, whether considered to be associated with the study vaccination or not, must be reported **within 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 AE/SAE eCRF. Any medication or other therapeutic measures used to treat the AE will be recorded on the appropriate eCRF(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 or 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 will communicate the information to the investigator and the investigator will be responsible for submitting this information to the EC or IRB and other relevant authorities.

An RT-PCR confirmed influenza event in a subject randomized to and vaccinated with QIVc, can be considered as a case of vaccine failure. These cases will be entered in the database but not sent as an expedited report to applicable health authorities as these are related to the primary efficacy endpoint of the study and is an anticipated risk from participating in the study.

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, until 180 days after study completion. Instructions and contact details for collecting and reporting these suspected SAEs will be provided to the investigator.

7.1.6 Safety Laboratory Measurements

This study has no safety laboratory measurements.

7.2 Efficacy Assessment

The case definition of influenza-like illness for this study is the presence of a temperature ≥ 37.8°C (≥ 100.0°F) and at least one of the following symptoms on the same day: cough, sore throat, nasal congestion, rhinorrhea, earache or ear discharge and can occur at any time throughout the study and are to be reported immediately see Section 3, Study Design.

Subjects who meet the protocol defined ILI criteria, will have a NP swab collected at an unscheduled visit. NP swab should be targeted for collection within the first 24 hours or as soon as possible after ILI onset (see Section 5.4, Unscheduled Visits). ILI onset is defined as the first day that the subject meets the protocol defined ILI criteria. The end date is defined as the date the subject does not meet the criteria anymore. A new ILI episode will only be taken into account after resolution of the previous one, as judged by the Investigator. As a guidance, another episode and swab sample should only be collected when the interval between the onset of protocol defined ILI to the next onset of protocol defined ILI is 14 days or more.

Confirmation of influenza by RT-PCR from NP swab sample is necessary for the efficacy assessment in the study. In addition, all samples will also be cultured for the growth of the clinical strain of influenza obtained from the subject. Culture will allow to conduct antigenic characterization (to determine whether the clinical isolate is antigenically matched or unmatched to the influenza vaccine strain). Details on testing can be found in the Clinical Specimen Lab Manual.

The case definition for moderate-to-severe influenza-like illness for this study is the presence of an ILI episode complicated by one of the following medically-attended AEs reported in the eCRF being either physician confirmed lower respiratory tract illness, or physician confirmed acute otitis media, or hospitalization in the Intensive Care Unit

(ICU), or physician-diagnosed serious extra-pulmonary complication of influenza, or supplemental oxygen requirement for more than 8 hours. Subjects with ILI symptoms and its complications ought to be treated according to recent accepted (national) clinical standards.

Information on occurrences of any hospitalization, and administered or prescribed antibiotics or antivirals will be collected from the subject for the purposes of healthcare resource utilization assessment (regardless of whether or not the medical event, healthcare contact or the use of medications is considered to be directly linked to the ILI). Analyses on these endpoints will cover the period from ILI onset until 30 days after.

For exploratory objectives, identification of influenza by genotypic methods may be conducted by a Seqirus or Seqirus designated (contracted) laboratory.

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 measures are determined by the hemagglutination inhibition (HI) assay or microneutralization (MN) by titrating antibodies against the influenza strains homologous to the seasonal influenza vaccine (see Section 2, Objectives). The HI and MN tests will be conducted on serum samples collected immediately before first vaccination and 28 days after last vaccination, see Section 3, Study Design.

To further characterize the immune response, additional exploratory immunogenicity analyses may be conducted on the immunogenicity sub-set using other tests such as an anti-neuraminidase assay. In case of exploratory immunogenicity analyses, the immune response will be characterized in a similar manner as described in Section 2, Objectives.

Testing will be conducted by a Seqirus or Seqirus designated (contracted) laboratory in a blinded manner towards the treatment arm. Data will be captured and analyzed by an external CRO.

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)

Endpoints evaluating QIVc compared to a non-influenza vaccine:

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

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

8.1.1.3 Primary Immunogenicity Endpoint(s)

Not applicable.

8.1.2 Secondary Endpoint(s)

8.1.2.1 Secondary Safety Endpoint(s)

The measures for assessing safety and tolerability are as follows:

1. Percentage of subjects with solicited local and systemic AEs will be assessed for 7 days following each vaccination in the QIVc group and the comparator group.

2. Percentage of subjects with any unsolicited AEs will be assessed in the QIVc group and in the comparator group until 28 days after each vaccination.

3. Percentage of subjects with SAEs, NOCDs, AEs leading to withdrawal from the study or vaccination, and all medications associated with these events will be reported in the QIVc group and in the comparator group.

4. Percentage of subjects with medically-attended AEs within 30 days after ILI onset will be reported in the QIVc group and in the comparator group.

8.1.2.2 Secondary Efficacy Endpoint(s)

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

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

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

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

8.1.2.3 Secondary Immunogenicity Endpoint(s)

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

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

3. Geometric mean ratio (GMR): GMR is the geometric mean of the fold increase of post-vaccination HI (or MN) titer over the pre-vaccination HI (or MN) titer.

8.1.3 Exploratory Endpoint(s)

All exploratory endpoints will be further defined in the SAP.

8.2 Success Criteria

8.2.1 Success Criteria for Primary Objective(s)

The primary objective of efficacy is considered achieved if efficacy is demonstrated for at least one of the two primary efficacy endpoints.

8.2.1.1 Success Criteria for Primary Safety Objective(s)

There are no primary safety objectives in this study.

8.2.1.2 Success Criteria for Evaluation of Primary Efficacy Objective(s)

The lower limit (LL) of the two-sided 97.5% confidence interval (CI) of the estimator of absolute vaccine efficacy (aVE) of QIVc versus comparator calculated from RT-PCR confirmed influenza cases in subjects 6 months through 47 months of age is above 0%. In case an interim will be performed the 97.5% CI will be adjusted accordingly.

8.2.1.3 Success Criteria for Primary Immunogenicity Objective(s)

There are no primary immunogenicity objectives in this study.

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 and provide demographic and/or baseline screening assessments, regardless of the subject's randomization and treatment status in the study and received a Subject ID.

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 adverse reactions, solicited 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.

Overall Safety Set

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

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

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 at Secondary Immunogenicity Objectives.

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

8.3.5 Per Protocol (PP) Set Efficacy/Immunogenicity Set

All subjects in the FAS Efficacy / Immunogenicity who:

- Correctly receive the study vaccine (i.e., receive the study vaccine to which the subject is randomized and at the scheduled time points).
- Have no protocol deviations leading to exclusion (see Section 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 sub-sets of FAS and should be always defined even if the objectives do not require it.

Examples for subjects excluded due to other reasons than protocol deviations are:

- Subjects who withdrew informed consent.
- Subjects who develop an influenza infection in an influenza immunogenicity study.

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

8.3.6 Other Analysis Sets

There are no additional analysis sets for analysis.

8.3.7 Subgroups

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

- Subjects aged "6 through 23 months" and "24 through 47 months".
- Subjects "previously influenza vaccinated" and "not-previously influenza vaccinated".
- Subjects by race.

- Subjects by sex.
- Subjects by country or region.
- Subjects by season/year treated.

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

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

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

- Subjects aged "6 through 23 months" and "24 through 47 months".
- Subjects "previously vaccinated" and "not-previously vaccinated".
- Subjects by comparator (MenC or saline for injection).
- 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 Statistical Analysis Plan (SAP).

8.3.8 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 (major) protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoints, which will be specified in the Protocol Deviation Specifications to this study protocol. In some cases, exclusion of data may be due to a reason other than a protocol deviation, e.g. early termination.

8.4 Statistical Analysis Plan

8.4.1 Analysis of Demographic and Baseline Characteristics

In general, summary descriptive statistics of continuous data will be presented as number of observations, mean, standard deviation, median, minimum and maximum. For categorical variables, statistical summaries will include counts and percentages relative to the appropriate population. Two-sided 95% (or 97.5%) confidence intervals (CI) will be provided for descriptive statistics, as warranted. The 95% or 97.5% CI for percentages will be exact CIs based upon the binomial distribution.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

The study does not have primary safety objectives.

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 Efficacy Objectives

The primary efficacy analysis will be based on the Full Analysis Set (FAS). Eligible subjects for FAS analysis are subjects who are randomized and received at least one study vaccine, and will be analyzed according to their randomized study vaccine [intent-to-treat analysis]). Absolute vaccine efficacy will only be assessed for RT-PCR confirmed influenza episodes (primary efficacy objective 1a) and culture confirmed influenza

episodes (primary efficacy objective 1b) with first onset of illness occurring at > 14 days after the last vaccination (since clinical protection is not immediate after vaccination) until the end of the influenza season. Additionally, the primary objective will be evaluated in Per-Protocol Analysis Set (PPAS).

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

$$H_0: 1 - HR \leq 0 \text{ versus } H_1: 1 - HR > 0$$

where HR is a hazard ratio of QIVc versus comparator and VE is vaccine efficacy.

Success Criteria for the Multiple Primary Efficacy Objectives:
The primary objective of efficacy is considered demonstrated if efficacy is demonstrated for at least one of the two primary efficacy endpoints, if the lower limit (LL) of the two-sided 97.5% confidence interval (CI) of VE is greater than 0% in subjects 6 months through 47 months of age.

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

Further details regarding the statistical methods and analyses are specified in the Statistical Analysis Plan (SAP).

8.4.2.2.2 Analysis Sets

The analysis population for primary vaccine efficacy analyses will be based on the Efficacy FAS and repeated on the Efficacy PPS (further details are given in Section 8.3, Analysis Sets).

8.4.2.2.3 Statistical Methods

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

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

Subjects that did not experience an event 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 97.5% overall coverage.

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

Vaccine efficacy VE = 1 – HR, that is, $1- \exp(\widehat{\beta})$ with $\hat{\beta}$ with 100(1- α) percent confidence interval as: $[1- \exp(\hat{\beta}+ Z(\text{s.e.}(\widehat{\beta})); 1- \exp(\hat{\beta}- Z(\text{s.e.}(\widehat{\beta}))]$.

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 comparator within each of the strata of interest. The term β_g is the estimate of treatment effect (or regression coefficient) between QIVc and comparator within each of the stratum.

The estimate of the hazard ratio, the respective estimate for absolute VE and pertaining two-sided 97.5% CIs will be calculated based on this model. If the study continues over several seasons, estimates will be also adjusted for the factor season(s). Factor 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 absolute VE

introduces a multiple test problem, alpha will be adjusted as described in Section 8.6, Interim Analysis via an error-spending function. For this group sequential test procedure parameters like information level and/or standard error at each stage will be calculated by the above described model and then used to calculate the actual group sequential test that compared the test statistic at each stage with the respective boundaries. Repeated CIs for each stage and also the final estimator and the respective CI can be retrieved by the group sequential test method to maintain simultaneous coverage probability.

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

Not applicable.

8.4.2.3.2 Analysis Sets

Not applicable.

8.4.2.3.3 Statistical Methods

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 vaccination will be summarized by study vaccine group.

8.4.3.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

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

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

Post-vaccination solicited adverse events reported for 7 days after each vaccination and 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. Injection-site erythema, ecchymosis and induration will be summarized according to categories based on linear measurements: Type I: none (0 mm), any (1-<10 mm, 10-25 mm, 26-50 mm, >50 mm); Type II: Grade 0 (< 10 mm), any (10-25 mm, 26-50 mm, >50 mm) (see Statistical Analysis Plan (SAP) for further details).

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

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

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

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

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

8.4.3.1.3 Analysis of Unsolicited Adverse Events

This analysis applies to all adverse events occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in AE eCRF, 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 adverse events in the eCRFs will be mapped to preferred terms using the MedDRA dictionary. The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

All reported adverse events, as well as adverse events 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.

When an adverse event occurs more than once for a subject, the maximal severity and strongest relationship to the study vaccine group will be counted.

Separate summaries will be produced for the following categories:

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

The analysis population for safety analyses will be based on the Safety Set (further details are given in Section 8.3, Analysis Sets).

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

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

Secondary efficacy objectives are not associated with any hypothesis testing.

8.4.3.2.2 Analysis Sets

The analysis population for all secondary efficacy objectives will be based on the Efficacy FAS and repeated on the Efficacy PPS (further details are given in Section 8.3, Analysis Sets).

8.4.3.2.3 Statistical Methods for Secondary Efficacy Objectives

The model specification 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

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

8.4.3.3.2 Analysis Sets

Secondary immunogenicity objectives will be evaluated based on the PPS Immunogenicity and FAS Immunogenicity (see Section 8.3, Analysis Sets).

8.4.3.3.3 Statistical Methods for Secondary Immunogenicity Objectives

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

Crude estimates for GMTs, GMRs and pertaining 2-sided 95% CIs will be calculated assuming log-normal distribution of the titers and will be completed by providing minimum, maximum and median titers for each study vaccine group.

Binary data (i.e., percentages of subjects with 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

The analysis of the exploratory objectives will be described in full detail in the Statistical Analysis Plan.

8.5 Sample Size and Power Considerations of Multiple Primary and Secondary Objectives

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

Statistical Considerations for Sample Size Calculations:

For the primary efficacy endpoint 1a, assuming an attack rate in the comparator group of 8% and an influenza vaccine efficacy (VE) of 40%, an estimated sample size of minimally 2,974 evaluable subjects (or 1,487 evaluable subjects per study group) with a minimum total of 191 cases are needed to have at least 90% power to reject the null hypothesis that the VE is less or equal to 0% at the significance level alpha=0.0125 and the risk of infection contained entirely within period covered by follow-up. For the primary efficacy endpoint for vaccine antigenically matched strains (1b), assuming an attack rate in the comparator groups of 4%, a VE of 50%, α=0.0125, a minimum of 3,446 evaluable subjects and a minimum number of 104 cases are needed to have at least 90% power to reject the null hypothesis that the VE is less or equal to 0% at the significance level alpha= 0.0125. These results assume that the hazard ratio is constant throughout the study and that Cox proportional hazard regression is used for the analysis. Table 8.1 summarizes the power calculations assumptions and the number of cases required to meet primary efficacy endpoints**.**

Table 8.1. Power calculation for Multiple Primary Endpoints

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

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

The study is designed to accrue a minimum of 191 RT-PCR confirmed influenza cases and a minimum of 104 culture confirmed influenza cases antigenically matched to the strains selected for the seasonal vaccine. If the overall/pooled influenza attack rate differs from the predicted and/or influenza strain circulation within a study season has drifted or shifted away from the strains selected for the seasonal vaccine, an adjustment of the prospectively specified number of cases, and number of subjects may be required. Extraneous real-life information, from (but not limited to) the influenza surveillance systems of the European Center for Disease Control (ECDC), US Center for Disease Control and Prevention (CDC) or World Health Organization (WHO) may be used to re-assess the influenza event rate.

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

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

Sample Size for Safety:

With a Safety Population of 1,723 evaluable subjects in the safety set of QIVc, AEs with population rates of 1 in 1,000 have an 82.2% probability of being detected.

Events with population rates of 1 in 575 have a 95% chance of being observed with *n*=1,723). Events with population rates of 1 in 2,000 have a 57.8% chance of being observed with *n*=1,723.

Sample size calculations were performed using PASS v12.0.2.

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 designed to allow for analyses of interim data to enable early study termination when a statistically robust demonstration of efficacy is observed.

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

Primary Efficacy Analysis:

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

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

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

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

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

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

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

where N_{total} denotes the total number of subjects needed for further enrollment, $C_{planned}$ is the overall number of cases needed for the test, i.e 191 cases, $C_{observed}$ are the at that stage observed number of cases overall, and ER are the respective attack rates assumed for each group. A consideration of early dropout and uncertainty about assumed parameters will be accounted for number of enrolled subjects. The method of stopping rules given above is statistical and should be completed by clinical and strategic stopping rules that allow the DMC to make a decision on a broader picture of the data which includes safety endpoints and the other endpoints of the study.

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

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. eCRFs supplied by the Sponsor must be completed for each enrolled subject (see Section 8.3.1, All Enrolled Set for definition of enrolled subject). Documentation of screened but not enrolled subjects must be maintained at the site and made available for review by the site monitor. Data and documents will be checked by the Sponsor and/or monitor.

9.1 Source Documentation

Prior to the start of the study, the site staff participating in the study conduct will be instructed on what documents will be required for review as source documents. The kinds of documents that will serve as source documents will be agreed between Sponsor or delegate and investigator and designees and specified in the SDA prior to subject 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's parent(s)/LAR and date of completion and reason.

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

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

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

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to 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 specimens' 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, except for those parameters which are specifically described in Section 7, Assessment being entered directly into the EDC system.

Remote Source Data Verification may also be performed if allowed by the country and site regulations. The process of remote SDV activities will be detailed in study specific documents (e.g. Monitoring Plan) and must be conducted in full compliance with the applicable regulations, sponsor and CRO processes ensuring the protection of the subject data confidentiality.

Data verification may also be performed through a centralized / remote review of data(e.g., checking for outliers or other anomalies) (see Source Data Agreement). 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 for 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 is entered in eCRF using a secure electronic data capture (EDC) system and stored on a secure server, which is compliant with Title 21 Part 11 policies of the Code of Federal Regulations (FDA 1997). The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor 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 "read only" access.

10.2 Data Clarification

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

10.3 Data Protection

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

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

11. RECORD RETENTION

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

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

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

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

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

12. USE OF INFORMATION AND PUBLICATION

Seqirus 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, ICH E6 (R2), and Japanese Ministry of Health, Labor, and Welfare, Seqirus codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations, ICH 1997).

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after the subject's parent(s)/LAR provide written informed consent, 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 subject's parent(s)/LAR 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 or LAR of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject's parent(s)/LAR or the designee. The subject's parent(s)/LAR/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 LAR **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted up to 10 days prior to any study procedure on Visit 1. If the subject and/or LAR is unable to read and write, a witness must be present during the informed consent discussion and at the time of informed consent signature.

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

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 the integrated addendum to ICH E6: ICH Guideline for Good Clinical Practice E6(R2). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to Seqirus before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Seqirus monitors, auditors, Seqirus Clinical Quality Assurance representatives, designated agents of Seqirus, IRBs/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 qualified healthcare professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event related to the study.
- If permission to do so is given by the subject's parent(s)/LAR, ensuring that the subject's primary healthcare provider is informed of the subject's participation in the study.

The investigator should not implement any deviation from, or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/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/favourable 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.

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CLINICAL STUDY PROTOCOL AMENDMENT

Study Number: V130_14

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

Amendment Number 1

Revised Protocol version 2.0 issued on 15 NOV 18

The present amendment reflects changes to Protocol version 1.0 issued on 22 JUN 18

DESCRIPTION OF CHANGE(S) AND RATIONALE:

This document describes the change to *Neisseria meningitidis* serogroup C vaccine as comparator for all subjects to provide benefit for all subjects in all countries. Furthermore, the amended protocol describes change to the blood draw volume and administrative updates observed during operational activity of the study and some miscellaneous (typographical) errors were corrected throughout the document. Finally, the exclusion criterion 12 was updated to ensure no subjects are enrolled into the study that have had prior *N.meningitidis* serogroup C disease.

CHANGE	LOCATION(S) OF CHANGE	RATIONALE FOR CHANGE
Each subject in the study will receive a *Neisseria meningitidis* serogroup C (MenC) vaccine as comparator to the investigational vaccine (QIVc). Children without a history of previous influenza vaccination, will be randomized to either one dose of QIVc followed by a second dose of QIVc 28 days later, or to a MenC dose followed by a placebo 28 days later. At the end of the study, at least 6 months after Visit 1, all subjects between 6 and 11 months of age will receive a dose of MenC at Visit 5.	Protocol Synopsis, Time and Event Table, Chapter 1 (Background and Rationale), Chapter 2 (Objectives), Chapter 3 (Study Design), Chapter 5 (Study Procedures), Chapter 6 (Treatment of Subjects), and Chapter 8 (Statistical Considerations).	The comparator has been adjusted to provide benefit for all subjects in all countries throughout the study and to reflect regulatory feedback. In subjects who require two doses, MenC and placebo (saline for injection) will be administered separated by 28 days. Placebo will be used as masking dose to maintain the blind in the study. Similarly, MenC will be given to all subjects between 6 and 11 months at time of enrolment to preserve the blind.

CHANGE	LOCATION(S) OF CHANGE	RATIONALE FOR CHANGE
Some subjects, aged 6 through 11 months at enrollment, enrolled in countries without a *Neisvac-C*® (MenC, Pfizer Ltd.) market authorization, will have a scheduled clinic visit (Visit 5) to assess safety of the *Neisvac-C* - vaccine given at Visit 6. Visit 6 is approximately 28 days after the MenC dose at Visit 5.	Protocol Synopsis, Time and Event Table, Chapter 1 (Background and Rationale), Chapter 3 (Study Design), and Chapter 5 (Study Procedures).	In some countries the MenC vaccine used, *Neisvac-C*® (Pfizer Ltd.) has no market authorization. In these countries, additional safety information will be collected for 28 days after MenC vaccination. The dosing schedule used in the study is according to the Summary of Product Characteristics (SPC) approved by the UK regulatory authorities. This document will serve as the MenC reference document.
One of the exclusion criteria has been modified to: "*Prior vaccination to prevent Neisseria meningitidis serogroup C disease or prior infection caused by this organism*."	Section 4.2 (Exclusion criteria).	Exclusion criterion number 12 has been updated to also prevent subjects entering the study that have documented *N. meningitidis* serogroup C disease prior to the study.

CHANGE	LOCATION(S) OF CHANGE	RATIONALE FOR CHANGE
The study includes blood sample collection at 2 time points with a maximum volume of 7 mL whole blood to be collected per time point. Blood draw volume has been lowered from 7 mL to 5 mL per blood draw.	Section 3.5 (Collection of Clinical Specimen), Section 5.1.5 (Blood draw), and Section 5.3.1 (Follow-up Clinic Visit).	To reflect feedback received from investigators and ethical committees, the current blood draw volume is lowered from 7 mL to 5 mL. This volume is sufficient to evaluate immunogenicity against all 4 homologous vaccine strains using the haemagglutination inhibition (HI) assay: 3 strains (Type A/H1N1, Type B/Yamagata and Type B/Victoria, and the microneutralization (MN) assay: 1 strain (Type A/H3N2).
Acceptable measurements of body temperature now includes: oral, axilla, ear or rectal.	Time and Event Table, List of Definitions, Chapter 2 (Objectives), Section 3.4.2 (Tools Used for Data Collection), Section 7.1.1 (Solicited Adverse Events), and Section 7.2 (Efficacy Assessment).	To accommodate feedback from investigators, the route of temperature measurement in infants has been updated to: oral, axilla, ear and rectal to allow measurement of body temperature according local practices in the participating countries.
Correction of some miscellaneous (typographical) errors and clarifications to the protocol language.	Throughout the protocol.	Observations made during operational activity of the study and some miscellaneous (typographical) errors.

CLINICAL STUDY PROTOCOL AMENDMENT

Study Number: V130_14

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

Amendment Number 2

Revised Protocol version 3.0 issued on 03 SEP 20

The present amendment reflects changes to Protocol version 2.0 issued on 15 NOV18

DESCRIPTION OF CHANGE(S) AND RATIONALE:

This document describes an adjustment of the number of seasons over which the study is conducted and removes the requirement for a minimal number of subjects to be enrolled. Exploratory Objectives were added to include genotypic methods to characterize influenza cases and use of other assays to describe vaccine efficacy. Home visits are allowed for study assessments, in exceptional cases and remote source data verification is added as an option in view of the current pandemic situation. The amounts of residual proteins in the vaccine were corrected. Finally, administrative updates observed during operational activity of the study and some miscellaneous (typographical) errors were corrected throughout the document.

CHANGE	LOCATION(S) OF CHANGE	RATIONALE FOR CHANGE
The study is designed to accrue an approximate number of subjects and a minimum number of cases over several influenza seasons	Protocol Synopsis, Section 1.3 (Rationale), Section 3.1 (Overview of Study Design), Section 8.5 (Sample Size and Power Considerations), 8.6 (Interim Analysis).	In time-to-event outcome studies, power depends on the number of events observed and is stopped when minimum of necessary number of events is reached. We modified the protocol language to reflect this more clearly. As the attack rate is not predictable, the update omits additional constraints on a minimal number of subjects to be recruited or a minimal number of influenza seasons in which the study will be conducted.

CHANGE	LOCATION(S) OF CHANGE	RATIONALE FOR CHANGE
Added exploratory objectives: To characterize the immune response by other assays. To use genotypic methods to characterize circulating strains of influenza collected during the study.	Protocol Synopsis, Section 2.3 (Exploratory Objectives), Section 7.2 (Efficacy Assessment) and 7.3 (Immunogenicity Assessments), Section 8.1.3 (Exploratory Endpoints) and 8.4.4. (Analysis of Exploratory Objectives)	To explore next generation influenza characterization methods.
In the exceptional case where calls or clinic visits are not feasible in some countries, study site personnel may visit the subject's homes to inquire about signs and symptoms of illness in the subject, collect a NP swab specimen or perform other study assessments, when agreed upon by the Sponsor and in line with country specific requirements and/or regulations.	Protocol Synopsis, Table 1.1 and 1.2, Section 5 (Study Procedures).	To extend the possibility for home visits for other study assessments when deemed necessary e.g. in view of the current pandemic situation.
Remote Source Data Verification may be performed	Section 9.2 (Study Monitoring, Auditing and Source Data Verification)	To add the possibility when deemed necessary e.g. in view of the current pandemic situation.

CHANGE	LOCATION(S) OF CHANGE	RATIONALE FOR CHANGE
Each dose of *Flucelvax Quadrivalent/ Flucelvax Tetra* may contain residual amounts of MDCK cell protein (≤ 25.2 µg), protein other than HA (≤ 240 µg)	Section 6.1 Study Vaccine(s)	To align the protocol text with the US PI and EU SPC. The amounts of proteins other than HA in the vaccine are increased as a consequence of the use of a different antigen potency assay agreed upon by the regulatory agencies in US and Europe.
The Data Monitoring Committee may recommend to stop the study for efficacy when at least one efficacy objective met the success criteria. The CI and overall alpha for hypothesis testing for the primary objectives during the interim analysis is adjusted to meet the overall coverage of 97.5% CI and alpha is 1.25% (1-sided), respectively	Protocol Synopsis, Section 8.4.2.2.3 (Statistical Methods), Section 8.6 (Interim Analysis)	This update aligns with the success criteria described in Section 8.2.1 (Success Criteria for the Primary Objective(s)) and the statistical methods described in Section 8.4.2.2.1 (Statistical Hypotheses for Primary Efficacy Objectives)
Correction of some miscellaneous (typographical) errors and clarifications to the protocol language.	Throughout the protocol.	Observations made during operational activity of the study and some miscellaneous (typographical) errors.