# CLINICAL STUDY PROTOCOL

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|---|---|
| **Study Number** | V118_23 |
| **Protocol Version** | FINAL VERSION 3.0, 11 JUL 2022 |
| **Study Title** | A Phase 3, Randomized, Observer-blind, Controlled, Multicenter, Clinical Study to Evaluate Immunogenicity and Safety of an MF59-adjuvanted Quadrivalent Subunit Inactivated Influenza Vaccine in Comparison with a Licensed Quadrivalent Influenza Vaccine, in Adults 50 to 64 Years of Age |
| **Study Phase** | 3 |
| **Product Name** | aQIV |
| **Regulatory Agency Identifying Number(s)** | IND 15684<br>EudraCT: 2021-001721-40 |
| **Sponsor** | Seqirus UK Limited<br>The Point, 29 Market Street, Maidenhead, UK |
| **Previous Version, if applicable** | VERSION 2.0 |
| **Date, if applicable** | 18 NOVEMBER 2021 |

## Table of Contents

## List of Tables

PROTOCOL SYNOPSIS V118_23

| **Name of Sponsor:** | **Protocol number:** | **Generic name of study vaccine(s):** |
|---|---|---|
| Seqirus UK Limited | V118_23 | MF59-adjuvanted Quadrivalent Subunit Inactivated Influenza Vaccine (aQIV)<br>Licensed comparator: nonadjuvanted Quadrivalent Influenza Vaccine (QIV) |
| **Title of Study:**<br><br>A Phase 3, Randomized, Observed-blind, Controlled, Multicenter, Clinical Study to Evaluate Immunogenicity and Safety of an MF59-adjuvanted Quadrivalent Subunit Inactivated Influenza Vaccine in Comparison with a Licensed Quadrivalent Influenza Vaccine, in Adults 50 to 64 Years of Age | | |
| **Study Period:** Approximately 9 months for each study participant. | | **Clinical Phase**: 3 |
| **Background and Rationale:** Influenza is an infectious disease caused by the influenza virus, an orthomyxovirus with two clinically relevant types (types A and B). The disease is characterized by the abrupt onset of respiratory and systemic symptoms, such as fever, myalgia, headache, severe malaise, nonproductive cough, sore throat, and rhinitis, and occurs in epidemics throughout the Northern and Southern Hemisphere winter months in temperate climates.<br><br>It has been recognized for many years that people 65 years of age and older are at greater risk of serious complications from influenza compared with young, healthy adults because human immune defences become weaker with age. However, there is also a growing recognition of a high burden of disease in adults 50-64 years of age. About one-fifth of the United States (US) population (approximately 63 million people) is between 50 and 64 years of age, and among these individuals, approximately one-third have an underlying medical condition that puts them at higher risk for influenza complications (CDC 2019). Therefore, vaccination in this age group can offer significant reduction in the burden of influenza. In the US, the estimated rate of hospitalizations due to influenza disease is 3-fold higher in adults 50-64 years of age | | |

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compared to the younger adult (18-49 years) age group (155.1 vs 48.4 per 100,000). Furthermore, the estimated number of medical visits due to influenza illnesses is even higher in the 50 to 64 years age group (3.97 million) compared to adults 65 years of age and older (1.72 million) (CDC 2018-2019). While the effect of influenza vaccination on the high rates of mortality and hospitalizations has previously been studied among those adults 65 years and older, these issues remain an unmet medical need for adults as young as 50 years.

In 2010, the Advisory Committee on Immunization Practices (ACIP) acknowledged a high burden of influenza disease in individuals 50 to 64 years of age and, as a consequence, defined the risk group for older adults as 50 years and older. In the United Kingdom (UK), the 2020/2021 national influenza vaccination program was extended to include adults 50-64 of age (NHS 2020). In addition, several national government public health agencies (Austria, Germany, Hungary, and Russia) issued recommendations for vaccination of all individuals of 60 years of age and above instead of ≥65 years of age (Lang et al. 2012).

Vaccination is considered the best approach to lower the burden of influenza disease. The efficacy in older individuals is significantly lower due to the aging of the immune system (i.e. immunosenescence) and underlying medical conditions that can both increase the risk of influenza complications as well as interfere with immune responses (Sasaki et al. 2011). Relatively low efficacy of conventional influenza vaccines in older adults provides an opportunity for vaccine improvement by stimulating stronger immune responses. Older individuals have fewer naive B and T cells, more memory cells, and an increasing number of senescent cells which are known to exert a regulatory role in vivo (Lang et al. 2012). Assuming the immune response becomes gradually weaker with age, and immune cells require a stronger stimulus, novel vaccine

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|---|---|---|
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formulations are needed to elicit an effective vaccination-mediated immunity in older individuals (Aiello et al. 2019).

One way to increase the immunogenicity of influenza vaccines is by using adjuvants, such as the squalene and water emulsion adjuvant, MF59. Fluad®, Seqirus' trivalent seasonal influenza vaccine adjuvanted with MF59 (aTIV), is licensed for use in persons 65 years of age and above in Europe since 1997 and in the US since 2015. More recently, the quadrivalent version of Fluad (aQIV including A/H1N1, A/H3N2, B/Yamagata and B/Victoria strains) is licensed in Australia (since 24 Sep 2019), the US (since 21 Feb 2020), in the European Union (EU) including Iceland, Norway and Liechtenstein (since 26 May 2020), New Zealand (since Dec 2020), and in the UK for use in adults aged 65 years and older. In multiple clinical studies, Fluad induced a significantly higher immune response compared to conventional nonadjuvanted influenza vaccines in subjects aged 65 years and older, including those with comorbidities (Frey et al. 2014).

The results of clinical studies conducted with Fluad (aTIV) in healthy individuals 50-64 years and subjects 18-60 years of age with chronic medical conditions, demonstrated similar benefits as has been seen in adults 65 years of age and older in terms of immunogenicity (Baldo et al. 2007; O'Hagan et al. 2011; Noh et al. 2016). Similar to the findings in older adults, an acceptable safety and tolerability profile was seen in adults under 65 years of age.

Apart from the medical need for improved vaccines in people aged 50 to 65 years, determining persistence beyond a typical seasonal epidemic is important, considering that influenza seasons may last for more than 6 months. Persistence of vaccine-induced

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immunity over periods longer than a typical winter season has not been widely investigated.

The aim of this study is to demonstrate both a noninferior immune response with regards to geometric mean titer (GMT) ratio and seroconversion rate (SCR) difference for each strain and a superior immune response with regards to GMT ratio for at least 2 of the 4 strains of aQIV compared with a licensed nonadjuvanted quadrivalent influenza vaccine, 3 weeks after vaccination in adults 50-64 years of age. In addition, immunogenicity, antibody persistence, reactogenicity and safety will be assessed. Data from this study will be used to expand the licensure of the quadrivalent version of Fluad for the prevention of seasonal influenza in adults 50-64 years of age.

**Disclosure Statement**: This is a randomized immunogenicity study with 2 arms that is observer-blinded.

**Study Objectives:**

**Primary Immunogenicity Objective(s):**

1a. To demonstrate immunological noninferiority of aQIV versus a nonadjuvanted quadrivalent influenza vaccine comparator (QIV) in subjects 50-64 years of age, as measured by hemagglutination inhibition (HI)[1] geometric mean titers (GMTs) and seroconversion rates (SCRs) for each vaccine strain, at 3 weeks after vaccination.

[1] In case of lack of agglutination or agglutination mediated through neuraminidase for a specific strain using HI assay, immunogenicity for that strain will be assessed as measured by microneutralization (MN) assay as an acceptable alternative.

*Success criteria:*

*Noninferiority will be demonstrated if the upper limit (UL) of the 95% confidence interval (CI) for the inter-group GMT ratio[2] (QIV/aQIV) is ≤1.5 for each vaccine strain, and the UL of the 95% CI for the difference in SCR[3] (QIV-aQIV) is ≤10% for each vaccine strain.*

1b. To demonstrate that aQIV induces a superior immune response compared with QIV in subjects 50-64 years of age as measured by HI[1] GMTs at 3 weeks after vaccination for at least 2 of the 4 vaccine strains.

*Success criteria:*

*Superior immune response will be demonstrated if the UL of the 95% CI for the inter-group GMT ratio (QIV/aQIV) is <1.0 for at least 2 of the 4 vaccine strains.*

**Secondary Immunogenicity Objective:**

2a. To demonstrate that aQIV induces a superior immune response compared with QIV in subjects 50-64 years of age as measured by HI[1] GMT for at least one vaccine strain at 3 weeks after vaccination.

*Success criteria:*

*Superior immune response will be demonstrated if the UL of the 98.73% CI for the inter-group GMT ratio (QIV/aQIV) is <0.67 for one or more vaccine strains.*

2b. To demonstrate greater persistence of the immune response for at least one vaccine strain at 6 months after vaccination with aQIV compared with QIV as measured by HI[1] in subjects 50-64 years of age.

*Success criteria:*

*Greater persistence of the immune response will be demonstrated if the UL of the 98.73% CI for inter-group GMT ratio (QIV/aQIV) <1.0 for one or more vaccine strains.*

2c. To evaluate the immunogenicity of aQIV compared with QIV as measured by HI[1] in subjects 50-64 years of age.

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**Exploratory Immunogencity Objectives:**

- To evaluate persistence of the immune response at 9 months after vaccination with aQIV compared with QIV as measured by HI1 in subjects 50-64 years of age.
- To further evaluate the immunogenicity of aQIV compared with QIV in subjects 50-64 years of age, with alternative assays, if sera permit.

**Secondary Safety Objective:**

To assess the safety and reactogenicity of aQIV and QIV in adults 50-64 years.

**Primary and Secondary Immunogenicity Endpoint(s):**

A detailed description of primary and secondary endpoints is provided in Section 8.1, Endpoints.

**Study Design:**

Experimental design: This is a Phase 3, randomized, comparator-controlled, observer-blind, multicenter study in approximately 2,018 adults 50 to ≤64 years of age.

[2] The GMT ratio is defined as the geometric mean of the postvaccination HI titer for QIV over the geometric mean of postvaccination HI titer for aQIV.

[3] The SCR is defined as the percentage of subjects with either a prevaccination HI titer <1:10 and a postvaccination HI titer ≥1:40 or a prevaccination HI titer ≥1:10 and a ≥4-fold increase in postvaccination HI titer. Difference in SCR is defined as $SCR_{QIV} - SCR_{aQIV}$.

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Duration of the study: The study duration is approximately 9 months for each subject.

Vaccination schedule: single vaccination (Day 1).

Study vaccine: aQIV vaccine.

Comparator vaccine: nonadjuvanted QIV.

Treatment groups:

aQIV group: approximately 1,009 subjects receiving one dose of aQIV at Day 1.

QIV group: approximately 1,009 subjects receiving one dose of QIV at Day 1.

Randomization: an Interactive Response Technology (IRT) will be used in the study with stratification factors for age (50-59 and 60-64 years of age) and history of any influenza vaccination within the previous 3 influenza seasons (yes/no). Subjects will be enrolled and stratified equally into two age groups (50-59 years and 60-64 years) with approximately 50% of subjects per age group and within each age group subjects will be randomized to the aQIV or QIV group according to a 1:1 ratio. Stratification for history of any influenza vaccination within the previous 3 influenza seasons (yes/no) will be applied to all subjects.

Blinding: Observer-blind study.

Blood sample schedule: Four blood samples (approximately 10 mL each) will be collected from all subjects on Days 1, 22, 181, and 271.

Data collection: electronic Diary (eDiary), electronic Case Reporting Form (eCRF).

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Study clinic visits: Four clinic visits for each subject at Days 1, 22, 181, and 271.

Safety phone call: Two safety phone calls (Day 15 and Day 91) will be conducted: on Day 15 to collect any unsolicited adverse events (AEs), including medications associated with these events and any vaccinations, and on Day 91 to collect only serious AEs (SAEs), AEs leading to withdrawal, and AEs of special interest (AESIs), and associated concomitant medications and any vaccinations.

Solicited AEs occurring on the day of study vaccination through the following 6 days (Day 1 through Day 7, or longer if the events are not resolved), will be recorded daily using an eDiary as completed by the subject.

Safety data collection: All unsolicited AEs occurring within 21 days (Day 22) after study vaccination will be collected. During the follow-up period (Days 23- 271) only SAEs, AEs leading to withdrawal, and AESIs will be collected. These data will be captured by interviewing the subject during the clinic visits and safety phone calls and by review of available medical records. Subjects will be instructed to call the site in the event of any AE which they perceive as being of concern during the entire study period.

Serological assays:

HI[1] assay for homologous vaccine strains, using egg-derived target virus, will be performed for all subjects on serum samples collected on Days 1, 22, 181, and 271.

Written informed consent will be obtained before conducting any study-specific procedures.

**Number of Subjects planned:** Approximately 2,018 subjects are planned to be enrolled into this study, randomized 1:1 to aQIV or QIV.

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**Study Population and Subject Characteristics:** The list of inclusion and exclusion criteria is included in Section 4, Selection of Study Population.

**Study Procedures:**

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

After informed consent is signed by the subject, prior to vaccination on Day 1, screening evaluations will be performed including an eligibility assessment, a review of relevant medical history, physical examination, and height and weight measurements. Once all eligibility assessments are completed and subject is confirmed as eligible, a blood sample will be collected from all subjects for influenza-specific serology testing. Subjects will be assessed for risk of complications from influenza using the standardized scoring system (Hak et al. 2004).

All eligible subjects will then be randomized and subsequently receive a single dose of 0.5 mL of study vaccine to which they were assigned. Blood samples for serology testing will be collected on Day 1 (prior to vaccination), Day 22, Day 181 and Day 271. Subjects will be followed up for safety for 270 days after vaccination (approximately 9 months).

Further details on the study procedures are presented at the end of the synopsis Table 0-1 and in Section 5, Study Procedures.

**Study Vaccines:** Regardless of the type of a vaccine assigned in the trial, subjects will receive a 0.5 mL dose.

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|---|---|---|
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Adjuvanted Quadrivalent Influenza Vaccine (*aQIV, investigational vaccine*)

An adjuvanted inactivated subunit quadrivalent influenza vaccine, administered as one 0.5 mL intramuscular dose into the deltoid muscle. The vaccine is presented in a pre-filled needleless syringe (PFS). Each 0.5 mL dose contains 15 µg hemagglutinin (HA) from each of the four influenza strains recommended by the World Health Organization for the 2021/2022 Northern Hemisphere influenza season for quadrivalent vaccines.

Licensed Comparator: nonadjuvanted Quadrivalent Influenza Vaccine

A nonadjuvanted inactivated quadrivalent influenza vaccine administered as one 0.5 mL intramuscularly into the deltoid muscle. The vaccine is presented in a pre-filled needleless syringe (PFS). Each 0.5 mL dose contains 15 µg HA from each of the four influenza strains recommended by the World Health Organization for the 2021/2022 Northern Hemisphere influenza season for quadrivalent vaccines.

**Statistical Analyses:**

The primary analysis will be conducted on the immunogenicity data collected up to Day 22.

Sample Size Estimation:

With 1:1 randomization, a sample size of 1,816 evaluable subjects is chosen so that with one-sided alpha=0.025, there will be at least 90% power to achieve the primary objectives (1a and 1b). Assuming 10% drop out, the total sample size for the study is 2,018 subjects.

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More details on the sample size calculation are provided in Section 8.5, Sample Size and Power Considerations of Primary Objectives.

aQIV will be tested against a licensed nonadjuvanted quadrivalent influenza vaccine (QIV). This study is powered to demonstrate the GMT superiority of aQIV vs QIV assessed by the four co-primary endpoints associated with primary objective 1b) at significance level of one-sided $\alpha$=0.025.

Hypothesis testing will be carried out by 1a) and 1b) sequentially. Only after the NI objectives are achieved, the superiority objectives will be tested. All tests are carried out with a one-sided alpha of 0.025 for each comparison. No adjustment for multiple endpoints for the primary objectives is necessary.

The Per Protocol Set (PPS) will be used for the noninferiority analyses, and the Full Analysis Set (FAS) will be used for superiority analyses.

Details on the statistical analysis can be found in Section 8, Statistical Considerations.

**Interim Analysis:** An interim analysis is not planned for this study.

**Data Monitoring Committee**: An independent Data Monitoring Committee will not be utilized for the study.

# Schema

## Table 0-1: Time and Events Schedule

| | Visit Type | Clinic Visit | Safety Phone Call | Clinic Visit* | Safety Phone Call | Clinic Visit* | Clinic Visit* |
|---|---|---|---|---|---|---|---|
| | **Study Day** | **1** | **15** | **22** | **91** | **181** | **271** |
| | **Visit Window (Days)** | **n/a** | **-3 to +3** | **-3 to +7** | **-7 to +7** | **-14 to +14** | **-14 to +14** |
| | **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** |
| **Study Event** | **References** | | | | | | |
| **Study Treatment** | | | | | | | |
| Vaccination | Section 5.2 | X | | | | | |
| **Screening and Safety** | | | | | | | |
| Informed Consent[a] | Section 5.1.1 | X | | | | | |
| Demographics and baseline characteristics | Section 5.1.2 | X | | | | | |
| Medical History[b] | Section 5.1.2 | X | | | | | |
| Physical Exam[c] | Section 5.1.2 | X | | X | | X | X |
| Pregnancy Test[d] | Section 5.1.2 | X | | | | | |
| Exclusion/Inclusion Criteria | Section 4 | X | | | | | |
| Randomization | Section 5.1.4 | X | | | | | |
| 30 Minutes Post Injection Assessment of Unsolicited AEs | Section 5.3 | X | | | | | |
| Subject eDiary Dispensed with Training | Section 5.3 | X | | | | | |

| | Visit Type | Clinic Visit | Safety Phone Call | Clinic Visit* | Safety Phone Call | Clinic Visit* | Clinic Visit* |
|---|---|---|---|---|---|---|---|
| | **Study Day** | **1** | **15** | **22** | **91** | **181** | **271** |
| | **Visit Window (Days)** | **n/a** | **-3 to +3** | **-3 to +7** | **-7 to +7** | **-14 to +14** | **-14 to +14** |
| | **Visit Number** | **1** | **2** | **3** | **4** | **5** | **6** |
| **Study Event** | **References** | | | | | | |
| Review of eDiary data and compliance | Section 3.6.2 | Ongoing during eDiary use | | | | | |
| Assess all AEs | Section 7.1.2 | X | X | X | | | |
| Assess SAEs | Section 7.1.4 | X | X | X | X | X | X |
| Assess for AEs leading to withdrawal, and AESIs | Section 7.1.4.1 | X | X | X | X | X | X |
| Assess relevant medications and vaccinations | Section 6.5 | X | X | X | X | X | X |
| **Immunogenicity** | | | | | | | |
| Serology blood draw[e] | Section 5.1.5 | X[f] | | X | | X | X |
| **Study Completion Procedure** | | | | | | | |
| Study Completion/Early Termination[g] | Section 5.6 | | | | | | X |

| | Visit Type | Clinic Visit | Safety Phone Call | Clinic Visit* | Safety Phone Call | Clinic Visit* | Clinic Visit* |
|---|---|---|---|---|---|---|---|
| | Study Day | 1 | 15 | 22 | 91 | 181 | 271 |
| | Visit Window (Days) | n/a | -3 to +3 | -3 to +7 | -7 to +7 | -14 to +14 | -14 to +14 |
| | Visit Number | 1 | 2 | 3 | 4 | 5 | 6 |
| **Study Event** | **References** | | | | | | |

Notes: * In the exceptional case that a clinic visit is not possible, and if in line with country and site regulations with appropriate sponsor approvals, a home visit may be conducted.

[a] Consent form should be signed prior to performing any study procedures. The informed consent process may be conducted earlier, but within 10 days prior to Day 1;

[b] Medical history includes existing comorbidities;

[c] A physical examination will be based on a review of systems, i.e., a structured interview for complaints for each organ system;

[d] A pregnancy test should be done for females of childbearing potential;

[e] Subjects at selected sites may be asked to voluntarily provide extra blood samples of 50 mL at Day 1 and Day 22 (see Section 3.7, Collection of Clinical Specimens);

[f] Blood sample for serology to be taken after temperature measurement, but prior to vaccination;

[g] Subjects who terminate the study early will be requested to complete all safety-related Study Completion procedures.

## List of Abbreviations and Definition of Terms

| | |
|---|---|
| ACIP | Advisory Committee on Immunization Practices |
| AE | adverse event |
| AESI | adverse event of special interest |
| aQIV | MF59-adjuvated Quadrivalent Influenza Vaccine |
| aTIV | MF59-adjuvanted Trivalent Influenza Vaccine |
| 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 |
| CRO | Contract Research Organization |
| CSR | Clinical Study Report |
| CTAB | cetyltrimethylammonium bromide |
| DMC | Data Monitoring Committee |
| EC | Ethics Committee |
| EDC | electronic data capture |
| eCRF | electronic Case Report Form |
| EMA | European Medicines Agency |
| FAS | Full Analysis Set |
| FDA | United States Food and Drug Administration |
| GCP | Good Clinical Practice |
| GDPR | General Data Protection Regulation |
| GMFI | geometric mean fold increase |
| GMT | geometric mean titer |
| GMTr | geometric mean titer ratio |
| HA | hemagglutinin |
| HI | hemagglutination inhibition |
| ICH | The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ID | identification |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology |
| MF59 | MF59C.1 adjuvant |
| NH | Northern Hemisphere |
| PFS | pre-filled syringe |
| PPS | Per Protocol Set |
| PVRM | Pharmacovigilance and Risk Management |
| QIV | Quadrivalent Influenza Vaccine |
| SAE | serious adverse event |

| | |
|---|---|
| SAP | Statistical Analysis Plan |
| SDA | Source Document Agreement |
| SH | Southern Hemisphere |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TIV | Trivalent Influenza Vaccine |
| UL | upper limit |
| UK | United Kingdom |
| US | United States |
| WHO | World Health Organization |

| Abbreviation or Term | Definition |
|---|---|
| **Follow-up period** | The follow-up period for subjects starts at Day 23 and continues up to the study completion visit, defined as 9 months after vaccination (Day 23 – Day 271, i.e. end of study). |
| **Qualified healthcare professional** | Any **licensed** healthcare professional who is permitted by institutional policy to perform clinical interventions and assessments (as applicable to the protocol), is trained on the study procedure(s) and who is identified within the site signature and delegation log. |
| **Trained healthcare professional** | Any healthcare 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 21 days after vaccination (Days 1-22). |

# 1 BACKGROUND AND RATIONALE

## 1.1 Background

Influenza is an infectious disease caused by the influenza virus, an orthomyxovirus with two clinically relevant types (types A and B). The disease is characterized by the abrupt onset of respiratory and systemic symptoms, such as fever, myalgia, headache, severe malaise, nonproductive cough, sore throat, and rhinitis (Temte et al. 2010) and occurs in epidemics throughout the winter months in temperate climates in the Northern and Southern hemispheres. In general, influenza is resolved within 2 to 7 days, although the symptoms cough and malaise may be prolonged. However, influenza can exacerbate underlying medical conditions and/or lead to secondary viral or bacterial pneumonia for some people, notably older adults and those with chronic diseases (including pulmonary or circulatory disorders, metabolic disorders such as diabetes mellitus, renal dysfunction, or immunosuppression) (Rothberg et al. 2008; Fiore et al. 2009).

It has been recognized for many years that people 65 years and older are at greater risk of serious complications from influenza compared with young, healthy adults because human immune defenses become weaker with age. However, there is also a growing recognition of a high burden of disease in adults 50-64 years of age. About one-fifth of the United States (US) population (approximately 63 million people) is between 50 and 64 years of age, and among these individuals, approximately one-third have an underlying medical condition that puts them at higher risk for influenza complications (CDC 2019). In the US, the estimated rate of hospitalizations due to influenza disease is 3-fold higher in adults 50-64 years of age compared to the younger adult (18-49 years) age group (155.1 vs 48.4 per 100,000). Furthermore, the estimated number of medical visits due to influenza illnesses is even higher in the 50-64 years age group (3.97 million) compared to older adults (1.72 million) (CDC 2018-2019). While the effect of influenza vaccination on the high rates of mortality and hospitalizations has previously been studied among those adults 65 years and older, these issues remain an unmet medical need for adults as young as 50 years.

In 2010, the Advisory Committee on Immunization Practices (ACIP) acknowledged a high burden of influenza disease in individuals 50 to 64 years of age and as a consequence defined the risk group for older adults as 50 years and older. In the United Kingdom (UK), the 2020/2021 national influenza vaccination program was extended to include adults 50-64 of age (NHS 2020). In

addition, several national government public health agencies (Austria, Germany, Hungary, and Russia) issued recommendations for vaccination of all individuals of 60 years of age and above instead of ≥65 years of age (Lang et al. 2012).

Vaccination is considered the best approach to lower the burden of influenza disease. The efficacy in older individuals is significantly lower due to the aging of the immune system (i.e., immunosenescence) and underlying medical conditions that can both increase the risk of influenza complications as well as interfere with immune responses (Sasaki et al. 2011). Relatively low efficacy of conventional influenza vaccines in older adults provides an opportunity for vaccine improvement by stimulating stronger immune responses. Older individuals have fewer naive B and T cells, more memory cells, and an increasing number of senescent cells which are known to exert a regulatory role in vivo (Lang et al. 2012). Assuming the immune response becomes gradually weaker with age, and immune cells require a stronger stimulus, novel vaccine formulations are needed to elicit an effective vaccination-mediated immunity in older individuals (Aiello et al. 2019).

One way to increase the immunogenicity of influenza vaccines is by using adjuvants, such as the squalene and water emulsion adjuvant, MF59. Fluad®, Seqirus' trivalent seasonal influenza vaccine adjuvanted with MF59 (aTIV), is licensed for use in persons 65 years of age and above in Europe since 1997 and in the US since 2015. More recently, the quadrivalent version of Fluad (aQIV including A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains) is licensed in Australia (since 24 Sep 2019), the US (since 21 Feb 2020), in the European Union (EU) including Iceland, Norway and Liechtenstein (since 26 May 2020), New Zealand (since Dec 2020), and in the UK for use in adults aged 65 years and older. In multiple clinical studies, Fluad induced a significantly higher immune response compared to conventional nonadjuvanted influenza vaccines in subjects aged 65 years and older, including those with comorbidities (Frey et al. 2014).

The results of clinical studies conducted with Fluad (aTIV) in healthy individuals 50-64 years and subjects 18-60 years of age with chronic medical conditions demonstrated similar benefits to those observed in adults 65 years of age and older in terms of immunogenicity (Baldo et al. 2007; O'Hagan et al. 2011; Noh et al. 2016). Similar to the findings in older adults, an acceptable safety and tolerability profile was seen in adults under 65 years of age.

Apart from the medical need for improved vaccines in people aged 50 to 65 years, determining persistence beyond a typical seasonal epidemic is important, considering that influenza seasons

may last for more than 6 months. Persistence of vaccine-induced immunity over periods longer than a typical winter season has not been widely investigated.

The investigational product in this study, adjuvanted quadrivalent influenza vaccine (aQIV), is an MF59-adjuvanted egg-derived subunit inactivated quadrivalent influenza virus vaccine. A 0.5-mL dose has been formulated to contain 15 µg hemagglutinin (HA) of each influenza virus strain, including both A/H1N1 and A/H3N2 strains and strains of both B lineages.

## 1.2 Rationale

The aim of this study is to demonstrate both a noninferior immune response as assessed by geometric mean titer (GMT) ratio and seroconversion rate (SCR) difference for each strain and a superior immune response as assessed by GMT ratio for at least 2 of the 4 strains of aQIV compared with a licensed nonadjuvanted quadrivalent influenza vaccine, 3 weeks after vaccination in adults 50-64 years of age. In addition, immunogenicity, antibody persistence, reactogenicity and safety will be assessed. Data from this study will be used to expand the licensure of the quadrivalent version of Fluad for the prevention of seasonal influenza in adults 50-64 years of age.

## 1.3 Potential Risks and Benefits

Subjects will be exposed to aQIV or QIV vaccines.

As with all injectable vaccines, immediate systemic allergic reactions to vaccination can occur. The reactions for anaphylaxis are sporadic and estimated to be 1.3 per million vaccine doses administered for all vaccines (McNeil 2019). As a precautionary measure, all subjects will remain under observation at the study site for at least 30 minutes after vaccination. Vasovagal syncope (fainting) can occur before or after any vaccination, is usually triggered by the pain or anxiety caused by the injection and is not related to the substance injected; therefore, it is important that standard precautions and procedures be followed to avoid injury from fainting. Intramuscular vaccination commonly precipitates a transient and self-limiting local inflammatory reaction. This typically includes injection site pain, erythema (redness), or induration (hardness).

aQIV vaccine has been evaluated in two Phase 3 clinical studies conducted by Seqirus, which included 4,269 subjects 65 years of age and above. aQIV induced a robust immune response against all strains contained in the vaccine and showed protection against more severe and clinically

significant cases of influenza disease during mismatched influenza seasons. The immune response following aQIV was similar to the response after administration of the licensed MF59-adjuvanted trivalent influenza vaccine (aTIV). Immunogenicity was not previously determined with aQIV for subjects 50-64 years of age, but studies with aTIV showed that the MF59-adjuvanted vaccine was immunogenic in the full age range for subjects ≥50 years of age (Minutello et al. 1999).

During clinical studies with aQIV, the following side effects were very commonly reported (>1/10 subjects): injection site pain, fatigue and headache (Beran et al. 2021; Essink et al. 2020). Common side effects (>1/100 subjects but <1/10 subjects) include: loss of appetite, diarrhea, nausea, arthralgia, myalgia, erythema, induration, ecchymosis, and chills. Most of these side effects were mild or moderate and lasted for 3 days or less. A clinical immunogenicity and safety study with aTIV (Study V7P38) showed that the safety profile in the 50-64 years age group was similar to that in the ≥65 years age group; however, reactogenicity of aQIV has not been assessed in adults 50 to 64 years of age.

Based on the number of distributed doses, the cumulative exposure to aQIV up to 30 November 2020 is estimated to be around 17 million. As for all vaccines, severe allergic reactions can occur.

Please refer to the current Investigator's Brochure (IB) for aQIV for a summary of potential risks and expected benefits, and to the Product Information for [redacted] for information regarding potential risks and benefits of the nonadjuvanted QIV.

# 2 STUDY OBJECTIVES

## 2.1 Primary Objectives

### 2.1.1 Primary Immunogenicity Objectives

1a. To demonstrate immunological noninferiority of aQIV versus a nonadjuvanted quadrivalent influenza comparator (QIV) in subjects 50-64 years of age, as measured by

hemagglutination inhibition (HI)[4] geometric mean titers (GMTs) and seroconversion rates (SCRs) for each vaccine strain, at 3 weeks after vaccination.

*Success criteria:*

*Noninferiority will be demonstrated if the upper limit (UL) of the 95% confidence interval (CI) for the inter-group GMT ratio[5] (QIV/aQIV) is ≤1.5 for each vaccine strain, and the UL of the 95% CI for the difference in SCR[6] (QIV-aQIV) is ≤10% for each vaccine strain.*

1b. To demonstrate that aQIV induces a superior immune response compared with QIV in subjects 50-64 years of age as measured by HI[4] GMTs at 3 weeks after vaccination for at least 2 of the 4 vaccine strains.

*Success criteria:*

*Superior immune response will be demonstrated if the UL of the 95% CI for the inter-group GMT ratio (QIV/aQIV) is <1.0 for at least 2 of the 4 vaccine strains.*

## 2.2 Secondary Objectives

### 2.2.1 Secondary Immunogenicity Objective(s)

2a. To demonstrate that aQIV induces a superior immune response compared with QIV in subjects 50-64 years of age as measured by HI GMT for at least one vaccine strain at 3 weeks after vaccination.

*Success criteria:*

*Superior immune response will be demonstrated if the UL of the 98.73% CI for the inter-group GMT ratio (QIV/aQIV) is <0.67 for one or more vaccine strains.*

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[4] In case of lack of agglutination or agglutination mediated through neuraminidase for a specific strain using HI assay, immunogenicity for that strain will be assessed as measured by microneutralization (MN) assay as an acceptable alternative.

[5] The GMT ratio is defined as the geometric mean of the postvaccination (Day 22) HI titer for QIV over the geometric mean of postvaccination HI titer for aQIV.

[6] The SCR is defined as the percentage of subjects with either a prevaccination HI titer <1:10 and a postvaccination HI titer ≥1: 40 or a prevaccination HI titer ≥1:10 and a ≥4-fold increase in postvaccination HI titer. Difference in SCR is defined as $SCR_{QIV}$-$SCR_{aQIV}$.

2b. To demonstrate greater persistence of the immune response for at least one vaccine strain at 6 months after vaccination with aQIV compared with QIV as measured by HI assay in subjects 50-64 years of age.

*Success criteria:*

*Greater persistence of the immune response will be demonstrated if the UL of the 98.73% CI for the inter-group GMT ratio (QIV/aQIV) is <1.0 for one or more vaccine strains.*

2c. To evaluate the immunogenicity of aQIV compared with QIV as measured by HI in subjects 50-64 years of age.

### 2.2.2 Secondary Safety Objective(s)

To assess the safety and reactogenicity of aQIV and QIV in adults 50-64 years of age.

## 2.3 Exploratory Objectives

To evaluate persistence of the immune response at 9 months after vaccination with aQIV compared with QIV as measured by HI1 in subjects 50-64 years of age.

To further evaluate the immunogenicity of aQIV compared with QIV in subjects 50-64 years of age, with alternative assays, if sera permit.

# 3 STUDY DESIGN

## 3.1 Overview of Study Design

Experimental design: This is a Phase 3, randomized, comparator-controlled, observer-blind, multicenter study in approximately 2,018 adults 50 to ≤64 years of age.

Duration of the study: The study duration is approximately 9 months for each subject.

Vaccination schedule: single vaccination (Day 1).

Study vaccine: aQIV vaccine.

Comparator vaccines: nonadjuvanted QIV.

Treatment groups:

aQIV group: approximately 1,009 subjects receiving one dose of aQIV at Day 1.

QIV group: approximately 1,009 subjects receiving one dose of QIV at Day 1.

Randomization: an Interactive Response Technology (IRT) system will be used in the study. Subjects will be enrolled and stratified equally into two age groups (50-≤59 years and 60-≤64 years) with approximately 50% of subjects per age group. Within each age group, subjects will be randomized to aQIV or QIV according to a 1:1 ratio. Stratification for history of any influenza vaccination within the previous 3 influenza seasons (yes/no) will be applied to all subjects.

Blinding: Observer-blind study.

Blood sample schedule: Four blood samples (approximately 10 mL each)[7] will be collected from all subjects on Days 1, 22, 181 and 271.

Data collection: electronic Diary (eDiary), electronic Case Reporting Form (eCRF).

Study clinic visits: Four clinic visits for each subject at Days 1, 22, 181, and 271.

Safety phone call: Two safety phone calls (Day 15 and Day 91) will be conducted: on Day 15 to collect any unsolicited adverse events (AEs), including associated medications and any vaccinations, and on Day 91 to collect only serious AEs (SAEs), AEs leading to withdrawal, AEs of special interest (AESIs), and concomitant medications associated with these events and any vaccinations.

Solicited AEs occurring on the day of study vaccination through the following 6 days (Day 1 through Day 7, or longer if the events are not resolved), will be recorded daily using an eDiary as completed by the subject.

[7] Subjects at selected sites may be asked to voluntarily provide extra blood samples of 50 mL at Day 1 and Day 22 that can be used for future research not directly related to this study, but with the purpose to improve the understanding of the influenza vaccines or disease.

Safety data collection: During the treatment period (Days 1-22) all unsolicited AEs occurring within 21 days (Day 22) after study vaccination will be collected. During the follow-up period (Days 23-271) only SAEs, AEs leading to withdrawal, and AESIs will be collected. These data will be captured by interviewing the subject during the clinic visits, during the safety phone calls scheduled to occur on Days 15 and 91, and by review of available medical records. Subjects will be instructed to call the site in the event of any AE which they perceive as being of concern during the entire study period.

Serological assays:

HI[8] assay for homologous vaccine strains, using egg-derived target virus, will be performed for all subjects on serum samples collected on Days 1, 22, 181, and 271.

Written informed consent will be obtained before conducting any study-specific procedures.

## 3.2 Scientific Rationale for Study Design

The design, conduct, and analysis of this study comply with international and regional standards for clinical research in humans, and for investigating the immunogenicity and safety of seasonal influenza virus vaccines.

The aim of this study is to demonstrate both a noninferior immune response with regards to GMT ratio and SCR difference for each strain and a superior immune response with regards to GMT ratio for at least 2 of the 4 strains of aQIV compared with a licensed nonadjuvanted quadrivalent influenza vaccine, 3 weeks after vaccination in adults 50-64 years of age. A superior immune response with a higher threshold (1.5-fold) for the GMT ratio for at least one vaccine strain will also be evaluated, to further demonstrate an advantage for the adjuvanted vaccine. In addition, immunogenicity, antibody persistence, reactogenicity and safety will be assessed.

As for adults of 65 years of age and older, a high burden of influenza disease has been observed in individuals 50 to 64 years of age. Assuming the high rates of hospitalization and complications associated with influenza seen in this younger age group are due to a weaker immune response

[8] In case of lack of agglutination for a specific strain or agglutination mediated through neuraminidase using HI assay, immunogenicity for that strain will be assessed as measured by microneutralization (MN) assay as an acceptable alternative.

associated with increasing age (i.e., immunosenescence), the addition of an adjuvant such as MF59 may be beneficial, and may result in a greater immune response similar to that observed in adults 65 years of age and older.

In this study we will compare an adjuvanted quadrivalent influenza vaccine (aQIV) to a standard nonadjuvanted quadrivalent influenza vaccine ([redacted] to evaluate if the addition of the adjuvant MF59 elicits an immune response as strong as a standard nonadjuvanted quadrivalent influenza vaccine, as well as resulting in a superior response for at least 2 of the 4 vaccine strains included in the vaccines. Since influenza vaccinations may be administered as early as August in the Northern Hemisphere or March in the Southern Hemisphere and influenza seasons may last beyond 6 months, immunogenicity at 6 and 9 months following vaccination with aQIV or the nonadjuvanted vaccine will be compared to determine if inclusion of MF59 results in greater duration of immune response.

Data from this study will be used to expand the licensure of the quadrivalent version of Fluad for the prevention of seasonal influenza in adults 50 to ≤64 years of age.

## 3.3 Justification for Dose

The selected dose and formulation of aQIV (15 µg of HA of each viral strain and 9.8 mg of MF59 per dose) are well tolerated as demonstrated in previous studies. aTIV induces a higher immune response and has been associated with a higher effectiveness compared to nonadjuvanted influenza vaccine (Domnich et al. 2017; Pebody et al. 2019).

## 3.4 Study Period

Each subject should expect to participate in the study for 9 months, from the time of enrollment through the last study visit.

## 3.5 Blinding Procedures

The study 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 healthcare professional will be responsible for preparing and administering the study vaccines to the subjects. They will be instructed not to reveal the identity of the study vaccines to the subject or to the investigative site personnel (i.e., blinded 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 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 IRT system.

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 an SAE, prior to completion of the study, the investigator must promptly contact the Sponsor and document the circumstances in the IRT system. 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 may be removed from an Analysis Set.

All personnel involved in the conduct of the study or in the analysis of the final study results, or who have contact with study centers, will remain blinded to the treatment codes until the clinical database has been locked, protocol deviations (except for Day 271 serum sample analysis PDs) have been assessed, and the data have been released for statistical analysis. The analysis on the primary and secondary objectives for the final CSR will be conducted on this data.

All personnel involved in processing samples and performing laboratory assays will remain blinded to the treatment codes until all Day 271 serum samples have been tested and results have been transferred. The exploratory analysis on the 9 month persistence objective will be conducted on this data and reported in a CSR addendum.

Further details are specified in a study specific Blinding Maintenance Plan.

## 3.6 Data Collection

### 3.6.1 Data Collected from Subjects

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

- Demographic Information.
- Medical History, including existing comorbidities.
- Influenza vaccination history within the previous 3 influenza seasons.
- Physical examination including temperature, height, and weight.

- Reactogenicity: Solicited AEs for 7 consecutive days (or longer if the events are not resolved) following vaccination (Day 1 through Day 7).
- Unsolicited AEs for 21 days following vaccination (Day 1 to Day 22).
- SAEs, AEs leading to withdrawal from the study, and AESIs as collected from Day 1 to Day 271.
- Concomitant medications/vaccinations (as defined in Section 6.5, Prior and Concomitant Medications and Vaccines).
- Reason for early study termination (if applicable).

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

### 3.6.2 Tools Used for Data Collection

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

**Subject Diary**

Electronic Diaries (eDiaries), hereafter referred to as Subject eDiaries will be the only source document allowed for solicited local and systemic AEs (including body temperature measurements), starting after the initial 30-minute postvaccination period at the clinic, and continuing for 7 consecutive days (or longer if the events are not resolved). Refer to the user's manual for further details.

The investigator (or delegated, Qualified HCP) will review the Subject's eDiary data during eDiary use (Day 1 through Day 7) or longer if events are not resolved (up to 14 days after vaccination). The investigator (or delegated, Trained HCP) will also monitor the Subject's eDiary status for compliance on an ongoing basis during eDiary use (Day 1 through Day 7) or longer if events are not resolved (up to 14 days after vaccination).

1. The Subject eDiary will be designed in such a way as to prevent any blank, incomplete or biologically implausible entries during eDiary completion. Subjects will be instructed to fully complete the Subject eDiary each day, as per the instructions provided.
2. Before or just after vaccination, site staff must ensure that each subject's eDiary is prepared for data capture in the ensuing postvaccination period.

3. Any new safety information reported during the site visit cannot be entered into the Subject eDiary. Such information must be described in the source notes as a verbally-reported event, and must be entered on the AE page of the eCRF.

**Electronic Case Report Forms**

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

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

## 3.7 Collection of Clinical Specimens

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

- Blood at Days 1, 22, 181, and 271.
- Urine at Day 1 for females of childbearing potential.

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

**Blood Specimens**

Approximately 10 mL sample of blood will be drawn from all subjects at Visit 1 (Day 1) before vaccination, and at Visit 3 (Day 22), Visit 5 (Day 181), and Visit 6 (Day 271). The blood volume will not exceed 10 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. See Section 7, Assessments for additional details.

The total amount of blood collected over the study period per subject will be 40 mL.

In addition, approximately 50 subjects at selected sites may be asked to voluntarily provide extra blood samples of 50 mL at Day 1 and 50 mL at Day 22 that can be used for future research not directly related to this study, but with the purpose to improve the understanding of the influenza vaccines or disease. If subject agrees to provide extra blood samples, it will be at the discretion of the investigator to decide whether the subject is eligible to provide extra blood samples.

**Urine Specimens**

Urine will be collected for pregnancy testing in females of childbearing potential. Urine will be collected at Visit 1 (Day 1) before vaccination.

## 3.8 Stopping/Pausing Guidelines

There are no predetermined stopping rules in this study. Subjects may be withdrawn from the study according to investigator discretion as described in Section 4.5, Premature Withdrawal from Study.

## 3.9 Data Monitoring Committee

Not applicable.

## 3.10 End of Study

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

Evaluation of the primary and secondary immunogenicity objectives requires the testing of biological samples from the study subjects, which can only be completed after all of the samples for these objectives are collected. The last samples for the analysis of the secondary objectives will be taken at Visit 5 (Day 181). The last clinical assessment for the secondary safety objective will be at Visit 6 (Day 271). Accordingly, for the purpose of this protocol, end of study is defined as the completion of the testing of the Visit 5 (Day 181) biological samples, to be achieved no later than 8 months after collection of the last biological sample at Visit 5 (Day 181), or the Last Subject Last Visit, whichever is later. The local end of the study is defined as the Last Subject Last Visit within the country.

# 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 50 to 64 years of age (i.e. 50 to ≤64 years) on the day of informed consent;
2. Individuals who have voluntarily given written 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[9];
4. Males, females of non-childbearing potential[10] or females of childbearing potential who are using an effective birth control method[11], at least 30 days prior to informed consent, which they intend to use for at least 2 months after the study vaccination.

## 4.2 Exclusion Criteria

In order to participate in this study, all subjects must not meet ANY of the exclusion criteria described below:

1. Females of childbearing potential who are pregnant, lactating, or who have not adhered to a specified set of contraceptive methods from at least 30 days prior to study entry and who do not plan to do so until 2 months after the study vaccination;
2. Progressive, unstable or uncontrolled clinical conditions;

[9] A subject is considered to be compliant if the investigator judges that the subject will complete the Subject eDiary, will be available for all the follow-up visits and for the telephone calls as scheduled in the study.

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

[11] The following birth control methods are considered effective: abstinence, hormonal contraception (such as oral, injection, transdermal patch, implant) if used for at least 30 days prior to informed consent, diaphragm with spermicide, tubal occlusion device, intrauterine device, tubal ligation, male partner using condom with spermicide, male partner having been vasectomized at least six months prior to informed consent.

3. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study;

4. History of any medical condition considered an AESI (see APPENDIX 2 – List of Adverse Events of Special Interest);

5. Known history of Guillain Barré syndrome or another demyelinating disease such as encephalomyelitis and transverse myelitis;

6. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws;

7. Abnormal function of the immune system resulting from:

    a. Clinical conditions;

    b. Systemic administration of corticosteroids (PO/IV/IM)[12] at a dose equivalent to ≥20 mg/day of prednisone for more than 14 consecutive 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;

8. Received immunoglobulins or any blood products within 180 days prior to informed consent;

[12] PO= by mouth; IV=intravenous; IM= intramuscular

9. Received an investigational or non-registered medicinal product within 30 days prior to informed consent, or who are unwilling to refuse participation in another clinical study at any time during the conduct of this study (notes: i. concomitant participation in a study not involving or no longer involving administration of drugs, vaccines, or medical devices, is acceptable (e.g. studies in safety follow-up phase, observational studies); ii. concomitant participation in a COVID-19 vaccine study is acceptable provided that the vaccine dosing interval mentioned in Exclusion Criterion #11 is adhered to);

10. Receipt of any influenza vaccine within 6 months prior to enrollment in this study, or plan to receive influenza vaccine during the study period;

11. Receipt of any (investigational or licensed) COVID-19 vaccine within 14 days (non-replicating vaccines) or 28 days (replicating vaccines) prior to enrollment or plan to receive any COVID-19 vaccine within 7 days from study vaccination;

12. Receipt of any inactivated non-influenza vaccine within 14 days or live-attenuated vaccine within 28 days prior to enrollment in this study or plan to receive any other non-influenza vaccine within 28 days from study vaccination;

13. Acute (severe) febrile illness (See Section 4.3, Criteria for Delay of Vaccination);

14. 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;

15. Study personnel or immediate family members or household member of study personnel.

## 4.3 Criteria for Delay of Vaccination

There may be instances when individuals meet all eligibility criteria for vaccination yet have a transient clinical circumstance, such as an infection, which may warrant delay of vaccination: body temperature elevation (≥38.0° C [≥100.4°F]) within 3 days prior to intended study vaccination], or prophylactic use of antipyretics and/or analgesic medications within 24 hours prior to vaccination. Under such circumstances, a subject may be considered eligible for study enrollment after the appropriate window for delay has passed and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

## 4.4 Criteria for Repeat Vaccination in the Study

Not applicable.

## 4.5 Premature Withdrawal from Study

Subjects may withdraw at any time or be withdrawn 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 plan or for administrative reasons. The investigator or study coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an AE.

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 wants to withdraw from the study 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 5.6.1, Early Termination Visit should be completed if possible.

Any subject who becomes pregnant during the study, despite the protocol requirement for adequate contraception, should be encouraged to continue participating in the study for safety follow-up. The site must record a confirmation of pregnancy in the eCRF and must complete a Pregnancy Reporting/Outcome Form as soon as possible after learning of pregnancy occurrence (see Section 7.1.6, Pregnancies for further details). If the pregnant subject withdraws from the study for any of the below categories except death, the site will obtain permission from the subject to continue to remain in contact with her until the outcome of the pregnancy is known, even if the outcome is not known until after the subject reaches the end of the follow-up period.

The reasons for premature withdrawal from the study include: AE, death, withdrawal of consent, lost to follow-up, 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 page by indicating "Withdrawn from study due to AE". Any ongoing AEs at the time of study withdrawal must be followed until resolution or stabilization.

**Death**

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

**Withdrawal of consent**

The subject 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 intends to withdraw consent from the study, the investigator should clarify if the subject will withdraw completely from the study or if the subject will continue study participation for safety, or a subset of other study procedures. If the subject requests complete withdrawal from the study, no further study interventions will be performed with the subject.

**Lost to Follow-Up**

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

**Other Reasons**

Examples for subjects withdrawn from the study due to an "other" reason can include: Sponsor decision to terminate the study, subject meeting a prespecified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted in the Study Completion eCRF 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 Ethics Committee (EC)/Institutional Review Board (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.

# 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 Study Procedures table (Table 5-1) and in the Time and Events Schedule (Table 0-1).

There is a potential risk of exposure to coronavirus for the subject and site staff during the study. Risk to exposure should be managed according to local/national or institutional COVID-19 guidelines.

**Table 5-1: Study Procedures**

| Visit Category | Procedures |
|---|---|
| Prevaccination Procedure(s) and Vaccination Clinic Visit | Section 5.1 describes procedures to be followed prior to study vaccination: informed consent, screening, enrolment, blood draw and randomization. Section 5.2 and Section 5.3 describe procedures to be followed during the clinic visit involving vaccination: vaccination, and postvaccination procedures |
| Postvaccination Visits | Section 5.4 describes follow-up clinic visits and safety follow-up calls |
| Study Completion/Termination Visit | Section 5.6 describes procedures to be followed at the last study visit for a subject (may include early termination visit) |

## 5.1 Prevaccination Procedures: Screening/Randomization

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

### 5.1.1 Informed Consent

Informed consent is the voluntary agreement of an individual 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 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 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 legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject and after the subject has verbally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject and that informed consent was freely given by the subject.

### 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 which is a consecutive number assigned by the investigator. The subject's unique Screening Number will be documented in the Screening and Enrolment log only. 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.

Prior to study enrollment, demographic data will be collected from the subject, including: age, sex, race and ethnicity, and influenza vaccination history in the last 3 years.

Medical history will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for study participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem. In case a subject is recruited from outside the clinic, and the investigator despite documented effort was not able to obtain subject's medical history and associated concomitant medications, verbal recall of medical history and associated concomitant medication is acceptable.

If applicable, prior and concomitant medications or vaccinations taken prior to start of study should be collected (refer to Section 6.5, Prior and Concomitant Medications and Vaccines for further details). The use of any prophylactic systemic analgesics and/or antipyretics within 24 hours prior to vaccination is a criterion for delay of vaccination (see Section 4.3, Criteria for Delay of Vaccination).

Also, data to quantify the risk of complications from influenza will be collected. The 'Prediction Rule for Estimating the Probability of Hospitalization Due to Pneumonia or Influenza and Death Due to Any Cause' (Hak et al. 2004; see APPENDIX 1 – Prediction Rule) will be used. The risk assessment, which incorporates medical comorbidity among other baseline characteristics such as outpatient visits during previous year and previous hospitalizations due to pneumonia or influenza, is a validated predictor of risk of complications from influenza in elderly subjects. Using this prediction rule, a score of <50 is considered low risk and a score of ≥50 is considered high risk of complications from influenza in elderly subjects. Assessment of pre-existing medical conditions should be made by the investigator based on his or her clinical judgment.

Prevaccination body temperature (preferably oral) will be collected. If body temperature is ≥38.0°C/≥100.4°F at the time of screening, vaccination must be postponed until 3 days after the fever has resolved (see Section 4.3, Criteria for Delay of Vaccination). Height and weight will also be measured. For females of childbearing potential, a pregnancy test should be performed (see Section 3.7, Collection of Clinical Specimens).

Review of systems is a structured interview that queries the subject as to any complaints the subject has experienced across each organ system. This will be performed before enrolment and used to guide a physical examination.

A general physical examination is to be performed by a qualified healthcare professional, who is identified within the Study Staff Signature Log. 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 Medical History eCRF.

Prior to vaccination, approximately 10 mL of blood will be drawn from all subjects for serology, testing. Refer to Section 3.7, Collection of Clinical Specimens.

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

### 5.1.3 Enrollment

After signing the ICF, if an individual is determined to be eligible for study participation, the investigator will enroll the subject using Interactive Response Technology (IRT) system. Stratification information should be provided before randomization.

#### 5.1.4 Randomization

Enrolled subjects will be assigned a subject ID and randomized in the IRT system in a 1:1 ratio to receive either aQIV or QIV with age (50 to ≤59, and 60 to ≤64 years of age), and history of any influenza vaccination within the previous 3 influenza seasons (yes/no) as stratification factors. 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 randomization, the Screening Number ceases to be used and remains in the Screening and Enrollment Log only. The list of randomization assignments is produced by the IRT service provider 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 and the early termination study procedures must be applied. The reason for all randomization failures should be recorded in the Screening and Enrollment Log and in the source document. 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 or the subject has discontinued, the reason should be recorded in source document and in the eCRF. The information

on discontinued subjects should be kept distinct in the source documentation from randomization failures.

### 5.1.5 Blood Draw

After randomization, but prior to vaccination, approximately 10 mL of blood will be drawn from all subjects (see Section 3.7, Collection of Clinical Specimens). Additionally, an extra blood sample of 50 mL will be drawn from approximately 50 subjects at selected sites who agreed to provide an extra blood sample, for future research not related to this study.

In the exceptional situation in which a clinic visit is not possible, such as in the case when a site is not able to see study subjects at the clinic a home visit may be conducted if in line with country and site regulations. The site must get approval from the sponsor to conduct home visits. The site must also have sponsored approved SOPs/Instructions (or provided by the sponsor) for conducting home visits and the collection of blood samples in the home setting, prior to the home visit occurring. These procedures may also need to be approved by the site's IRB/EC depending on local and country regulations.

## 5.2 Vaccination Clinic Visit

Vaccination will be performed on Day 1.

Ensure the blood samples are taken **prior** to vaccination.

Prior to administration of the vaccine, it should be confirmed that the subject is eligible and does not meet any criteria for delaying the study vaccination as described in Section 4.3, Criteria for Delay of Vaccination.

After completing the prevaccination procedures on Day 1, administer the vaccine to the subject according to the procedures described in Section 6.3, Vaccine Preparation and Administration. Observe the blinding procedures described in Section 3.5, Blinding Procedures.

## 5.3 Postvaccination Procedures

The following postvaccination procedures will be performed on Day 1.

**Observation Period**

After vaccination, the subject will be observed for at least 30 minutes, including observation for immediate postvaccination AEs (unsolicited). All safety data collected during this time will be recorded in the subject's source document and in the Adverse Events eCRF.

**Subject Diary Training**

A Subject eDiary will be dispensed to subjects (provisioned device or as an app on their own device) in this study to document solicited AEs. The Subject eDiary is the primary source for collection of these data; therefore, it is critical that the subject completes the Subject eDiary correctly. The subject should be trained on how and when to complete each field of the Subject eDiary.

The subject should be trained on how to self-measure local solicited AEs and body temperature (preferably oral). The measurement of solicited local AEs is to be performed using the ruler provided by the site.

The subject 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 should check body temperature. The highest body temperature observed that day should be recorded in the Subject eDiary.

Subject eDiary training should be directed at the individual(s) who will perform the measurements of AEs and who will enter the information into the Subject eDiary. In some situations, the Subject eDiary may be completed by somebody other than the subject, e.g. caregiver, spouse, partner (except study site personnel). If a person other than the subject enters information into the Subject eDiary, the reason that the subject cannot complete their own eDiary and the person's identity and relationship to the subject must be documented in the subject's source document. Any individual who makes entries into the eDiary must receive training on completion of the eDiary at the time of the visit. This training must be documented in the subject's source document. Ideally, the same individual should complete the eDiary throughout the course of the study. Refer to the study-specific eDiary Manual for additional details on the assignment and use.

Subject Compliance: Subjects should start to complete the eDiary on the day of vaccination for 7 consecutive days after vaccination (Day 1 to Day 7). If a solicited local or systemic AE continues beyond day 7 after vaccination, recording in the Subject eDiary will be continued until the event(s) resolved or for a maximum of 14 days after vaccination. If the reaction continues to be present after

Day 14, the event and follow-up is to be captured as an unsolicited AE in the eCRF. Reminders will be sent every day via the electronic device (smartphone) and diary data should be submitted every day. Subjects must be contacted by phone if they fail to submit data on 2 or more consecutive days during the first 7 days after vaccination.

**Schedule the next study activity**

The site should schedule the next study activity with the subject. It is recommended for the site to schedule in advance the remaining upcoming study activities. Activities include clinic visits or safety phone calls.

The subject should be reminded of the next planned study activity, a safety phone call on Day 15. The subject will be reminded to contact the site if there are any questions, and to contact the site immediately if the subject has a medical condition that leads to a hospitalization or an emergency room visit (or as soon as the subject is medically stable) or to a visit to/by a doctor or is otherwise of concern.

### 5.3.1 eDiary Reminder Alerts

The subject will receive daily reminders via the Subject eDiary built-in audio-visual alarms to alert the user to complete the eDiary during the postvaccination period. From Day 1 through Day 7, the users will receive daily reminders to record any solicited AEs, and the presence of any unsolicited AEs (yes/no), and whether these AEs were medically attended ((yes/no), defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a qualified healthcare professional). In case of such events, subjects will be instructed to contact the site as soon as possible to report the event(s).

The Subject eDiary system may also allow for regular alerts to be issued via email to site staff indicating where subjects may need to be contacted for example due to:

- Non-compliance (i.e. failing to enter or transmit diary data),
- Reporting of any severe solicited reactions (one or more) that may suggest the need for medical support (as per medical judgement of the qualified healthcare professional),
- Subject experienced an unsolicited AE that was medically attended.

Sites must assess these alerts when received and contact subjects as necessary. Contact with the subject must be written down in the source document. Please refer to Section 4.5, Premature

Withdrawal from the Study and Section 7.1.3, Evaluation of Adverse Events for guidance on necessary action in the event of one of these alerts.

## 5.4 Postvaccination Visits

Postvaccination clinic visits or safety phone calls will be performed on Day 15 (Safety Phone Call), Day 22 (Clinic Visit), Day 91 (Safety Phone Call), Day 181 (Clinic Visit), and Day 271 (Clinic Visit).

### 5.4.1 Follow-up Clinic Visit(s)

Postvaccination clinic visits will be performed on Day 22 (Visit 3), Day 181 (Visit 5), and Day 271 (Visit 6) (see Section 5.6, Study Completion/Termination Visit for assessments to be performed at the study completion visit).

In the exceptional situation in which a clinic visit is not possible at Day 22 and/or Day 181, such as in the case when a site is not able to see study subjects at the clinic, a home visit may be conducted.

**Day 22 Follow-up Clinic Visit**

During the follow-up clinic visit on Day 22, the subject will be interviewed by a qualified healthcare professional to determine if any unsolicited AEs occurred, including SAEs and AESIs, and if any concomitant medications or vaccines were taken/received in the time since the last contact. The qualified healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or AEs are present. Adverse events reported by the subject 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 Assessments.

A symptom-directed physical examination will be performed, if necessary, according to symptoms the subject has reported. This physical examination will include an examination of organ systems that are relevant to the investigator based on review of the subject's reported AEs, and/or concomitant medication use. 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 and eCRF(s).

The subject will be asked to return any electronic device that was provisioned for the collection of the solicited AEs, if applicable. If the eDiary application was installed on a personal phone, it will be removed. During the visit, approximately 10 mL of blood will be drawn from all subjects (see Section 3.7, Collection of Clinical Specimens). Additionally, an extra blood sample of 50 mL will be drawn from approximately 50 subjects at selected sites who agreed to provide a blood sample, for future research not related to this study.

The site should schedule the next study activity, a safety phone call on Day 91, with the subject. The subject 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, an emergency room visit or has any other concern.

**Day 181 Follow-up Clinic Visit**

During the follow-up clinic visit on Day 181, the subject will be interviewed by a qualified healthcare professional to determine if any SAEs, AESIs, or AEs leading to withdrawal occurred and if concomitant medications associated with those events or any vaccinations were taken/received in the time since the last contact. All AEs reported by the subject at this follow-up clinic visit must be recorded in the subject's source document and only SAEs, AESIs, or AEs leading to withdrawal must be documented on an Adverse Events eCRF, as specified in Section 7.1, Safety Assessment.

A symptom-directed physical examination will be performed, if necessary, according to symptoms the subject has reported. This physical examination will include an examination of organ systems that are relevant to the investigator based on review of the subject’s reported AEs, and/or concomitant medication use. 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 and eCRF(s).

During the visit, approximately 10 mL of blood will be drawn from all subjects (see Section 3.7, Collection of Clinical Specimens).

The site should schedule the next study activity, a clinic visit on Day 271 (see Section 5.6, Study Completion/Termination Visit for assessments to be performed at the study completion visit), with the subject. The subject 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, an emergency room visit or has any other concern.

### 5.4.2 Safety Follow-up Calls

Safety follow-up calls will be performed on Day 15 and Day 91.

Safety follow-up calls are calls made to the subject by a qualified healthcare 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 will be interviewed according to the script, and information relating to the following AEs will be collected:

**Day 15 Safety Phone Call**

All unsolicited AEs, SAEs, AESIs, and AEs leading to withdrawal, concomitant medications associated with those events and any vaccinations.

The site should schedule the next study activity with the subject, a clinic visit on Day 22.

The subject 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 or has any other concern. Contact including the medical condition/event must be documented in the subject's source record.

**Day 91 Safety Follow-up Call**

All SAEs, AESIs, AEs leading to withdrawal, and concomitant medications associated with those events and any vaccinations.

Contact details including all safety information described by the subject must be written down in a designated location within the source document.

The site should schedule the next study activity with the subject, a clinic visit on Day 181.

The subject 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 has any other concern. Contact including the medical condition/event must be documented in the subject's source record.

## 5.5 Unscheduled Visits

Not applicable.

## 5.6 Study Completion/Termination Visit

The study completion visit will occur on Day 271 and will be a clinic visit.

In the exceptional situation in which a clinic visit is not possible, such as in the case when a site is not able to see study subjects at the clinic, a home visit may be conducted.

The date of completion is the date of the last contact (clinic 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 on the Study Completion eCRF page. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see Section 5.6.1, Early Termination Visit.

During the study completion visit, the subject will be interviewed by a qualified healthcare professional to determine if any SAEs, AESIs, or AEs leading to withdrawal, occurred and if concomitant medications associated with those events or any vaccinations were taken/received in the time since the last contact. Adverse events reported by the subject at this follow-up clinic visit must be recorded in the subject's source document and only SAEs, AESIs, or AEs leading to withdrawal must be documented on an Adverse Events eCRF, as specified in Section 7.1, Safety Assessment.

A symptom-directed physical examination will be performed, if necessary, according to symptoms the subject has reported. This physical examination will include an examination of organ systems that are relevant to the investigator based on review of the subject's reported AEs, and/or concomitant medication use. 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 and eCRF(s).

During the visit, approximately 10 mL of blood will be drawn from all subjects (see Section 3.7, Collection of Clinical Specimens).

The site will review with the subject 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 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.

### 5.6.1 Early Termination Visit

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures as described in Section 5.6 Study Completion/Termination Visit. 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.

The site will review with the subject 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 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.

# 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 6.6, 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 in the following sections.

**Investigational Vaccine: aQIV (Fluad Tetra/Quadrivalent)**

A 0.5 mL dose of aQIV (quadrivalent MF59C.1 adjuvanted influenza vaccine) contains nominally 15 µg of HA of each of the 2 influenza type A strains and each of the 2 influenza B strains with a total of 60 µg of HA in the vaccine. The strain composition will be that recommended by the WHO for quadrivalent influenza vaccines contemporaneous to the timing of the study. The full composition of the vaccine is reported in Table 6-1.

## Table 6-1: aQIV Vaccine (Fluad Tetra/Quadrivalent) Composition

| Names of Ingredients | Quantity per dose* | Function |
|---|---|---|
| **Active Ingredients**<br>HA and NA antigens from the influenza virus strains recommended by the WHO / CBER/ CHMP for the manufacture of influenza vaccine for season<br>A/ (H1N1)<br>A/ (H3N2)<br>B/ (Yamagata lineage)<br>B/ (Victoria lineage) | nominally 15 µg HA/strain | Active ingredient |
| **Adjuvant** | | |
| Squalene | 9.75 mg | Oil phase |
| Polysorbate 80 | 1.175 mg | Surfactant |
| Sorbitan trioleate | 1.175 mg | Surfactant |
| Sodium citrate | 0.66 mg | Buffer |
| Citric acid | 0.04 mg | Buffer |
| **Other Ingredients** | | |
| Sodium chloride | [redacted] | Isotonic aid |
| Potassium chloride | [redacted] | Buffer |
| Potassium dihydrogen phosphate | [redacted] | Buffer |
| Disodium phosphate dihydrate | [redacted] | Buffer |
| Magnesium chloride hexahydrate | [redacted] | Stabilizer |
| Calcium chloride dihydrate | [redacted] | Stabilizer |
| Water for injection | up to 0.50 mL | Diluent |
| ** | | |
| Volume of Formulation | 0.5 mL | |
| Appearance | Liquid, milky-white suspension | |
| Vaccine Presentation | Pre-filled syringe | |

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; CBER = Center for Biologics Evaluation and Research; CHMP = Committee for Medicinal Products for Human Use; HA = hemagglutinin; NA = neuraminidase; WHO = World Health Organization.
Notes:
* The quantities indicated in this table reflect the amount in a 0.5 mL dose.
** Residues of special relevance: cetyltrimethylammonium bromide (CTAB), chicken proteins, such as ovalbumin, formaldehyde, kanamycin and neomycin sulphate.

**Comparator Vaccine: [redacted] (nonadjuvanted QIV)**

A 0.5 mL dose of nonadjuvanted quadrivalent influenza vaccine contains nominally 15 µg of HA of each of the 2 influenza type A strains and each of the 2 influenza B strains with a total of 60 µg of HA in the vaccine. The strain composition will be that recommended by the WHO for quadrivalent influenza vaccines contemporaneous to the timing of the study. The full composition of the vaccine is reported in Table 6-2.

**Table 6-2: [redacted] Composition**

| Names of Ingredients | Quantity per dose* |
|---|---|
| **Active Ingredients**<br>HA and NA antigens from the influenza virus strains recommended by the WHO / CBER/ CHMP for the manufacture of influenza vaccine for season<br>A/ (H1N1)<br>A/ (H3N2)<br>B/ (Yamagata lineage)<br>B/ (Victoria lineage) | nominally 15 µg HA/strain |
| **Other Ingredients**<br>Sodium chloride<br>Disodium phosphate dodecahydrate<br>Potassium dihydrogen phosphate<br>Potassium chloride<br>Magnesium chloride hexahydrate<br>Water for injection<br>Octoxynol-10 (TRITON X-100)<br>α-tocopherol hydrogen succinate<br>Polysorbate 80 (Tween 80) | <br>3.75 mg<br>1.3 mg<br>0.2 mg<br>0.1 mg<br><br><br>≤0.115 mg<br>≤0.135 mg<br>≤0.550 mg |
| * | |
| Volume of Formulation | 0.5 mL |
| Appearance | Colorless to slightly opalescent suspension |
| Vaccine Presentation | Pre-filled syringe |

* Residues of special relevance: hydrocortisone, gentamycin sulfate, ovalbumin, formaldehyde, and sodium deoxycholate.

## 6.2 Non-Study Vaccines

Non-study vaccines will not be provided by Seqirus for this study.

## 6.3 Vaccine Preparation and Administration

The investigator or designee will be responsible for oversight of the administration of vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

Detailed vaccine preparation and administration instructions will be provided to investigators prior to study start, and will also be available in the Investigator Pharmacy Manual.

Both vaccines are to be provided in pre-filled syringes, each with an injectable volume of approximately 0.5 mL. The full volume contained in the pre-filled syringes is to be administered. Vaccination will be performed intramuscularly, preferably in the deltoid muscle of the nondominant arm.

**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.

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

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

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

As with all injectable vaccines, trained medical personnel and appropriate medical treatment should be readily available in case of anaphylactic reactions following vaccine administration. For

example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

## 6.4 Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was 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 study vaccine as per dosing regimen described in Section 6.1, Study Vaccines.

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

## 6.5 Prior and Concomitant Medications and Vaccines

**Prior medications and vaccines**

The subject's influenza vaccination history from the 3 years prior to enrollment into the study is to be obtained from the subject and recorded in the subject's source records and in the eCRF. Information on whether the subject was vaccinated in the last 3 years (yes/no), including the type of vaccination (if available) should be documented. In addition, the date of the last influenza vaccination and the source of the influenza history (recall or medical source) is to be captured in the eCRF. All subjects who received at least one influenza vaccination within the previous 3 influenza seasons will be categorized as subjects with previous influenza vaccination.

All medications and vaccines as described in the inclusion and exclusion criteria or taken or received by the subject within 30 days prior to the start of the study and related to the subject's medical history are to be recorded on the Concomitant Medications eCRF. Receipt of any COVID-19 vaccine at any time prior to enrollment needs to be recorded on the Concomitant Medications eCRF.

Note that this includes all medications and vaccines described in the inclusion and exclusion criteria, including:

- Immunoglobulins or any blood products within 180 days prior to informed consent;

- Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent;
- An investigational or non-registered medicinal product within 30 days prior to informed consent;
- Systemic administration of corticosteroids (PO/IV/IM) at a dose equivalent to ≥20 mg/day of prednisone for more than 14 consecutive days within 90 days prior to informed consent;
- Any influenza vaccine within 6 months prior to vaccination in this study;
- Receipt of any inactivated non-influenza vaccine 14 days or live-attenuated vaccine 28 days prior to enrollment in this study or plan to receive any other non-influenza vaccine within 28 days from study vaccination;
- Receipt of any COVID-19 vaccine within 14 days (non-replicating vaccines) or 28 days (replicating vaccines) prior to enrollment or plan to receive any COVID-19 vaccine within 7 days from study vaccination.

Please note as a reminder that when the subject is using any of these medications or vaccines, the subject should not be enrolled in the study as per the exclusion criteria.

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 prophylactic use of antipyretics/analgesics within 24 hours prior to vaccine administration is a reason to delay study vaccination (see Section 4.3, Criteria for Delay of Vaccination).

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

**Concomitant medications and vaccines**

Concomitant medications include all medications (including vaccines) taken by/administered to the subject after study vaccination.

The following concomitant medications are to be recorded in the Concomitant Medications CRF:

- All concomitant medications from Day 1 to Day 22;

- All medications associated with SAEs, AESIs, and AEs that lead to premature withdrawal from the study, from Day 1 to study completion;
- All vaccines, including any seasonal/pandemic influenza or COVID-19 vaccines, from Day 1 to study completion;
- Any investigational and non-registered medicinal product (other than the study vaccines) during the entire study period (from Visit 1 to study completion).

In addition, the use of the following concomitant medications, for conditions reported in the medical history, from enrolment until end of the study should be documented on the Concomitant Medication eCRF page as they may have an effect on the interpretation of the study objectives and therefore if used, may be determined to be a reason for exclusion from one of the analysis sets.

- Blood, blood products or a parenteral immunoglobulin preparation;
- Oral or systemic corticosteroids;
- Other immunomodulating agents.

## 6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following:

– Supply the study vaccines.

– Appropriate labeling of all study vaccines provided that it complies 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 that the required temperature range during shipment from the Sponsor to the investigator's designated storage location has been maintained;

- 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 Investigator Pharmacy Manual;
- Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.
- Appropriate use of the study vaccines, including:
- Use only in accordance with the approved protocol.
- Proper handling, including confirmation that the vaccine has not expired or been subject to a temperature excursion 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 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. Sponsor approval is required prior to destruction of any unused vaccines.

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 Assessments

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

An 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 immediately after the subject has received the study vaccine until he or she completes the study completion visit (Day 271) or terminates the study early. Events occurring after the informed consent form is signed but prior to receiving study vaccine will be documented as medical history in the source document and medical history eCRF.

Adverse events are collected as either solicited or unsolicited AEs. Solicited events are derived from organized data collection systems, such as Subject eDiaries or interview.

### 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 for 7 consecutive days, using a pre-defined Subject eDiary. If a solicited local or systemic AE continues beyond Day 7 after vaccination, recording in the Subject eDiary will be continued until the event(s) resolved or for a maximum of 14 days after vaccination. If the reaction continues to be present after Day 14, the event and follow-up is to be captured as an unsolicited AE in the eCRF.

**Solicited Local Adverse Events**

Induration, erythema and ecchymosis will be measured by the subject and recorded directly in the Subject eDiary.

Injection site pain will be measured as follows: grade 0= absent, grade 1/mild= present but does not interfere with activity, grade 2/moderate = interferes with activity, grade 3/severe = prevents daily activity.

**Solicited Systemic Adverse Events**

The following solicited systemic AEs are included in the Subject eDiary. Each solicited systemic AE is to be assessed using the scoring system reported in Table 7-1 below:

**Table 7-1: Severity Grading for Solicited Systemic Adverse Events**

| Solicited Event | Grade 1/Mild | Grade 2/Moderate | Grade 3/Severe |
|---|---|---|---|
| Loss of appetite | Eating less than usual with no effect on normal activity | Eating less than usual /interferes with normal activity | Not eating at all |
| Nausea | No interference with daily activity | Interferes with daily activity | Prevents daily activity |
| Fatigue | No interference with daily activity | Interferes with daily activity | Prevents daily activity |
| Myalgia | No interference with daily activity | Interferes with daily activity | Prevents daily activity |
| Arthralgia | No interference with daily activity | Interferes with daily activity | Prevents daily activity |
| Headache | No interference with daily activity | Interferes with daily activity | Prevents daily activity |
| Chills | No interference with daily activity | Interferes with daily activity | Prevents daily activity |
| Vomiting | 1-2 times per 24 hours | 3-5 times per 24 hours | 6 or more times per 24 hours or requires intravenous hydration |
| Diarrhea | 2-3 loose stools per 24 hours | 4-5 loose stools per 24 hours | 6 or more loose stools per 24 hours or requires intravenous hydration |
| Fever | 38.0 – 38.4°C<br>100.4 – 101.1°F | 38.5 – 38.9°C<br>101.2 – 102.0°F | ≥39.0°C<br>≥102.1°F |

### Other Indicators of Reactogenicity

The use of analgesics/antipyretics will be captured as “absent” or “present” separately by reason “for treatment” or “for prevention”.

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

- Solicited local or systemic AE leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (AE leading to withdrawal, see Section 7.1.3, Evaluation of Adverse Events).

- Solicited local or systemic AE that otherwise meets the definition of an SAE (see Section 7.1.4, Serious Adverse Events).

### 7.1.2 Unsolicited Adverse Events

An unsolicited AE is an AE that was not solicited using a Subject eDiary and that was spontaneously communicated by a subject who was vaccinated.

Potential unsolicited AEs may be medically attended (defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a qualified healthcare professional) or were of concern to the subject. In case of such events, subjects will be instructed to contact the site as soon as possible. The detailed information about the reported unsolicited AEs will be collected by the qualified site personnel during the interview and will be documented in the subject's records. In this study, all unsolicited AEs will be collected during the treatment period (Day 1-Day 22), and only specific unsolicited AEs (SAEs, AEs leading to withdrawal and AESIs) will be collected during the follow-up period (Day 23-Day 271). In addition, any unsolicited AEs reported within 30 minutes after the study vaccination will be collected as immediate postvaccination AEs.

### 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 eCRF. 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 AE 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 an evidence that clearly indicates an alternative explanation. If the timing of the exposure to the vaccine and the onset of the AE are not

reasonably related in time, or other facts, evidence or arguments exist that reasonably suggest an alternative explanation, then the AE is not related.

2. Possibly Related

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

3. Probably Related

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

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

- Adverse events of special interest (see Section 7.1.4.1, Adverse Events of Special Interest)
- Adverse events leading to study withdrawal.

If solicited or unsolicited AEs have been reported and the subject indicated that the symptoms required medical attendance, the subject must be contacted for further information.

When the subject is contacted for any of these reasons, the contact must be documented in the subject's source documentation. All AEs to be collected in this study, 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 AEs at the time of each subject's last visit should be documented in the subject's medical chart.

### 7.1.4 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose results in one or more of the following:

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

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

It should be noted that a severe AE need not be serious in nature and that an SAE need not, by definition, be severe.

All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. The 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 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 Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

A pre-existing event or condition should be recorded on the Medical History eCRF. The worsening of a pre-existing event or condition should be reported as an AE as described in Sections 5.1.2, Screening and 7.1.2, Unsolicited Adverse Events. Worsening of a pre-existing event or condition should be reported as SAE if meets any of SAE criteria. If the onset of an event occurred before the subject entered the study (e.g., any pre-planned hospitalization for conditions like cosmetic treatments or for non-emergency routine visits for a pre-existing condition), the hospitalization would not lead to an AE being classified as serious unless, in the view of the investigator, hospitalization was prolonged as a result of participation in the clinical study or was necessary due to a worsening of the pre-existing condition.

#### 7.1.4.1 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are a predefined list of AEs that are immune-mediated medical conditions; the list of AESIs is presented in APPENDIX 2 – List of Adverse Events of Special Interest.

Subjects will be assessed at each visit for any new medical events or signs or symptoms that could possibly indicate an AESI. The subject will be asked whether any new diagnosis has been given to the subject through a review of recent medical history. Should a qualified healthcare professional who is not the investigator suspect a potential AESI, she/he should promptly inform the investigator.

A diagnosis of an AESI is to be reported in the same manner and time frame as an SAE and will be captured on the AE eCRF. If the eCRF is not available, then the study site must complete the paper AESI Report Form and send to Seqirus Pharmacovigilance and Risk Management (PVRM) (or delegate) at AE.reporting@seqirus.com. The investigator must notify Seqirus within 24 hours.

Once the eCRF is available, the AESI information should be recorded on the AE eCRF as soon as possible. The AESI diagnosis as well as any medication taken to treat the condition, will be recorded in the subject's source documents and on the AE eCRF.

### 7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

Findings regarding AEs must be reported on an AE eCRF, as specified in Section 7.1.2, Unsolicited 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**.

If the eCRF is not available, then the study site must compete the paper SAE Report Form and send to Seqirus PVRM (or delegate) at AE.reporting@seqirus.com **within 24 hours of the site becoming aware of the event**. Once the eCRF is available, the SAE information should be recorded on the AE eCRF as soon as possible.

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 delegate) will contact the investigator if it is necessary to obtain further information for assessment of the event.

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

Seqirus or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse 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/IRB or applicable regulatory authorities and other relevant authorities.

#### 7.1.5.1 Post-Study Events

Any SAE that occurs outside of the protocol-specified observation period or after the end of the study but is considered to be caused by the study vaccine will be processed by Seqirus PVRM (or delegate) and must be reported at AE.reporting@seqirus.com.

These SAEs will be considered as part of the spontaneous reporting towards the investigational study vaccine in order to ensure the safety of all subjects.

### 7.1.6 Pregnancies

If a subject becomes pregnant after vaccination, confirmation of pregnancy should be recorded in the eCRF. To ensure subjects' safety, each pregnancy in a subject after study vaccination must be reported to Seqirus PVRM (or delegate) within 72 hours of the site learning of its occurrence. The study site must complete the paper Pregnancy Reporting/Outcome Form and send it to AE.reporting@seqirus.com. If the subject agrees to submit this information, the pregnancy must be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of safety follow-up for the study has ended.

### 7.1.7 Safety Laboratory Measurements

No scheduled safety laboratory measurements are planned for this study.

## 7.2 Efficacy Assessment

There is no assessment of efficacy in this study.

## 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 immunogenicity analysis will evaluate the immunogenicity of the study vaccines, which will be measured by the HI assay by titrating antibodies against the homologous influenza strains.

For the primary and secondary immunogenicity objectives, HI antibody responses using an egg-derived target virus will be evaluated for all strains included in the study vaccines. In case of a lack of agglutination or agglutination mediated through neuraminidase for a specific strain using HI assay, immunogenicity for that strain will be assessed as measured by the MN assay.

For the exploratory objective of persistence of the immune response at 9 months after vaccination, HI antibody responses for all strains included in the study vaccines will be evaluated using an egg-derived target virus at a later stage. For this analysis, Day 1 serum samples obtained for the primary and secondary study objectives (noninferiority and superiority assessments) will be retested. Day 1 data from the exploratory assessment of persistence at 9 months will not replace data obtained for the primary and secondary endpoint analyses.

For the other exploratory immunogenicity objective, immune responses may be evaluated with additional assays, such as testing against heterologous strains or alternative assay methods (e.g., MN).

Additionally, sera samples may be tested in future research not directly related to this study, but with the purpose to improve the understanding of the influenza vaccines or disease.

Testing will be conducted by the Sponsor or designated laboratory in a blinded manner with respect to the treatment arm and the visit.

# 8 STATISTICAL CONSIDERATIONS

## 8.1 Endpoints

A complete description of the statistical analyses and methods will be available in the Statistical Analysis Plan (SAP), which will be drafted before the first subject is enrolled and finalized before the database is locked for the primary analysis. The primary analysis will be conducted on the immunogenicity data collected up to Day 22.

### 8.1.1 Primary Endpoints

The immunogenicity of the study vaccines will be assessed 21 days (ie, on Day 22) after vaccine administration by measuring HI antibody titers to the A/H1N1, A/H3N2, B/Yamagata, and B/Victoria strains included in the vaccines.

#### 8.1.1.1 Primary Efficacy Endpoint(s)

The study does not have a primary clinical efficacy endpoint.

#### 8.1.1.2 Primary Immunogenicity Endpoint(s)

Humoral immune responses in terms of HI[13] antibody response against homologous egg-derived vaccine strains (A/H1N1, A/H2N3, B/Yamagata, and B/Victoria):

- Geometric mean titer (GMT) of HI antibodies at Day 22;
- Seroconversion rate (SCR) defined as the percentage of subjects with either a prevaccination HI titer <1:10 and a postvaccination (Day 22) HI titer ≥1:40, or with either a prevaccination HI titer ≥1:10 and a ≥4-fold increase in postvaccination HI titer.

The derived variables are:

- GMT ratios (QIV/aQIV) at Day 22 for each strain;
- The inter-group differences in the SCRs (QIV - aQIV) at Day 22 for each strain.

To evaluate the primary immunogenicity objectives 1a and 1b, the following derived variables of GMT ratios and SCR differences will be assessed at Day 22:

1a. Noninferiority of aQIV compared to QIV will be assessed for the eight primary endpoints of HI GMT and SCR for each virus strain included in the vaccines as follows:

- The GMT ratio (QIV/aQIV) for the A/H1N1 strain;
- The GMT ratio (QIV/aQIV) for the A/H3N2 strain;
- The GMT ratio (QIV/aQIV) for the B strain (Yamagata lineage);
- The GMT ratio (QIV/aQIV) for the B strain (Victoria lineage);

[13] In case of lack of agglutination or agglutination mediated through neuraminidase for a specific strain using HI assay, immunogenicity for that strain will be assessed as measured by microneutralization (MN) assay as an acceptable alternative.

- The difference between the SCR (QIV-aQIV) for the A/H1N1 strain;
- The difference between the SCR (QIV-aQIV) for the A/H3N2 strain;
- The difference between the SCR (QIV-aQIV) for the B strain (Yamagata lineage);
- The difference between the SCR (QIV-aQIV) for the B strain (Victoria lineage).

1b. A superior immune response of aQIV compared to QIV will be assessed for the endpoints of HI GMT for each virus strain included in the vaccines as follows:

- The GMT ratio (QIV/aQIV) for the A/H1N1 strain;
- The GMT ratio (QIV/aQIV) for the A/H3N2 strain;
- The GMT ratio (QIV/aQIV) for the B strain (Yamagata lineage);
- The GMT ratio (QIV/aQIV) for the B strain (Victoria lineage);

#### 8.1.1.3 Primary Safety Endpoint(s)

The study does not have a primary safety endpoint.

### 8.1.2 Secondary Endpoint(s)

Secondary endpoints assessed in the study include immunogenicity and safety endpoints of solicited and unsolicited AEs.

#### 8.1.2.1 Secondary Safety Endpoint(s)

Safety and reactogenicity will be assessed by the frequency and severity of:

- Solicited local and systemic AEs for 7 days following vaccination (Day 1 through Day 7);
- All unsolicited AEs for 21 days following vaccination (Day 1 through Day 22);
- SAEs, AEs leading to withdrawal from the study, AESIs as collected from Day 1 through Day 271.

#### 8.1.2.2 Secondary Efficacy Endpoint(s)

The study does not have a secondary clinical efficacy endpoint.

#### 8.1.2.3 Secondary Immunogenicity Endpoint(s)

Humoral immune response in terms of HI antibody response against homologous egg-derived vaccine strains (A/H1N1, A/H2N3, B/Yamagata, and B/Victoria):

- GMT of HI antibodies at Day 22 and Day 181.

To evaluate the secondary immunogenicity objectives 2a and 2b, the following derived variables of GMT ratios will be assessed:

2a. Superior immune response of aQIV compared to QIV will be assessed for HI GMT for the strains included in the vaccines as follows:

- The GMT ratio (QIV/aQIV) at Day 22.

2b. Greater persistence of the immune response of aQIV compared to QIV will be assessed for HI GMT for the strains included in the vaccines as follows:

- The GMT ratio (QIV/aQIV) at Day 181.

2c. To evaluate the immunogenicity of aQIV compared with QIV as measured by HI in subjects 50-64 years of age as follows:

- GMT of HI antibodies on Day 1, Day 22 and Day 181.
- Geometric mean fold increase (GMFI): The geometric mean of the fold increase of postvaccination HI titer over the prevaccination HI titer (Day 22/Day 1, Day 181/Day 1).
- The percentage of subjects with a titer ≥1:40 at Day 1, Day 22, and Day 181.
- SCR: the percentage of subjects with either a prevaccination HI titer <1:10 and a postvaccination HI titer ≥1:40 or a prevaccination titer ≥1:10 and a ≥4-fold increase in postvaccination titer on Day 22, and Day 181.

### 8.1.3 Exploratory Endpoint(s)

#### 8.1.3.1 Exploratory Safety Endpoint(s)

Not applicable.

#### 8.1.3.2 Exploratory Efficacy Endpoint(s)

Not applicable.

#### 8.1.3.3 Exploratory Immunogenicity Endpoint(s)

Persistence of the immune response of aQIV compared to QIV at Day 271 will be assessed for HI GMT for all strains included in the vaccines through the same descriptive immune response parameters as presented for secondary objective 2c, and further explored through the GMT ratio (QIV/aQIV). For this analysis, Day 1 serum samples obtained for the primary and secondary study objectives (noninferiority and superiority assessments) will be retested. Day 1 data from the exploratory assessment of persistence at 9 months will not replace data obtained for the primary and secondary endpoint analyses.

Additional exploratory immunogenicity endpoints that may be assessed in the study include the measures of immunogenicity of aQIV and QIV as determined by the HI or MN assay against homologous or heterologous strains at Day 1, Day 22, Day 181, and Day 271 (depending on availability of adequate sera and on assay availability). Details will be described in the SAP.

## 8.2 Success Criteria

### 8.2.1 Success Criteria for Primary Objective(s)

#### 8.2.1.1 Success Criteria for Primary Safety Objective(s)

The study does not have primary safety objectives.

#### 8.2.1.2 Success Criteria for Primary Efficacy Objective(s)

The study does not have primary efficacy objectives.

#### 8.2.1.3 Success Criteria for Primary Immunogenicity Objective(s)

Success criterion for primary immunogenicity objective 1a is defined as:

Noninferiority of the aQIV immune response will be demonstrated if the UL of the 95% CI for the inter-group Day 22 GMT ratio (QIV/aQIV) is ≤1.5 for each vaccine strain, and the UL of the 95% CI for the difference in SCR (QIV - aQIV) is ≤10% for each vaccine strain.

Success criterion for primary immunogenicity objective 1b is defined as:

Superiority of the aQIV immune response will be demonstrated if the UL of the 95% CI for the inter-group Day 22 GMT ratio (QIV/aQIV) is <1.0 for at least 2 of the 4 vaccine strains.

The study is considered successful if primary objective 1a is achieved.

### 8.2.2 Success Criteria for Secondary Objective(s)

#### 8.2.2.1 Success Criteria for Secondary Safety Objective(s)

No success criteria for secondary safety objectives are prespecified.

#### 8.2.2.2 Success Criteria for Secondary Efficacy Objective(s)

The study does not have secondary efficacy objectives.

#### 8.2.2.3 Success Criteria for Secondary Immunogenicity Objective(s)

Success criterion for secondary immunogenicity objective 2a is defined as:

Superior immune response will be demonstrated if the UL of the 98.73% CI for the inter-group GMT ratio (QIV/aQIV) is <0.67 for one or more vaccine strains.

Success criterion for secondary immunogenicity objective 2b is defined as:

Greater persistence of the immune response will be demonstrated if the UL of the 98.73% CI for the inter-group GMT ratio (QIV/aQIV) <1.0 for one or more vaccine strains at 6 months.

For secondary immunogenicity objective 2c, no success criteria are prespecified; 95% CI bounds will be used for statistical descriptions.

## 8.3 Analysis Sets

### 8.3.1 All Enrolled Set

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

### 8.3.2 All Exposed Set

All subjects in the All Enrolled Set who receive a study vaccination.

### 8.3.3 Safety Set

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

**Solicited Safety Set**

All subjects in the All Exposed Set with any solicited AE data including temperature measurements or use of analgesics/antipyretics.

**Unsolicited Safety Set**

All subjects in the Exposed Set who provided unsolicited AE data.

**Overall Safety Set**

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

### 8.3.4 Full Analysis Set (FAS) Immunogenicity

**Full Analysis Set Immunogenicity**

All subjects in the All Enrolled Set who are randomized, received study vaccination and provide immunogenicity data at any time point.

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

The FAS Immunogenicity will be used for immunogenicity superiority comparisons.

### 8.3.5 Per Protocol Set (PPS) Immunogenicity

All subjects in the FAS Immunogenicity who:

- Have both Day 1 and Day 22 immunogenicity assessment.
- Correctly receive the vaccine (i.e., receive the vaccine to which the subjects are 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)

The PPS Immunogenicity will be used for immunogenicity noninferiority comparisons.

### 8.3.6 Other Analysis Set(s)

Not applicable.

### 8.3.7 Subgroup(s)

Primary and secondary analyses of immunogenicity and safety endpoints will be done for the total population and by age subgroup (50-59 and 60-64 years of age).

Additional subgroup analysis will be conducted by:

- previous vaccination history
- sex
- race
- ethnicity
- comorbidity risk score (<50 and ≥50)

Refer to the SAP for further details.

### 8.3.8 Protocol Deviation(s)

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

## 8.4 Statistical Analysis Plan

### 8.4.1 Analysis of Demographic and Baseline Characteristics

Descriptive statistics (mean, standard deviation, median, minimum, and maximum) for age, height, weight, body mass index, and comorbidity risk score at enrollment will be calculated overall and by treatment group.

Distributions of subjects by sex, age, ethnic origin (race, ethnicity), previous vaccination history, and comorbidity risk (low/high defined as assessment score <50 or ≥50 based on scale described in Section 5.1.2, Screening) will be summarized overall, by treatment group, and by age group.

### 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.

#### 8.4.2.2 Analysis of Primary Efficacy Objective(s)

The study does not have primary efficacy objectives.

#### 8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

The primary immunogenicity objectives are:

1a. To demonstrate immunological noninferiority of aQIV versus QIV in subjects 50-64 years of age, as measured by hemagglutination inhibition (HI) geometric mean titers (GMTs) and seroconversion rates (SCRs) for each vaccine strain, at 3 weeks after vaccination.

1b. To demonstrate that aQIV induces a superior immune response compared to QIV in subjects 50-64 years of age as measured by HI GMTs at 3 weeks after vaccination for at least 2 of the 4 vaccine strains.

#### 8.4.2.3.1 Statistical Hypothesis

*Noninferiority of aQIV to QIV (Objective 1a)*

To demonstrate that vaccination with aQIV elicits an immune response that is not inferior to that of QIV containing the same virus strains among adults 50-64 years of age, aQIV will be considered to be noninferior to QIV if, for each of the four strains, the following statistical criteria are met:

- The UL of the two-sided 95% CI for the ratio of the Day 22 GMTs (GMTr) does not exceed 1.5. The GMTr will be calculated by $GMT_{QIV}/GMT_{aQIV}$
- The UL of the two-sided 95% CI for the difference between the SCRs does not exceed 10%. The difference in SCR will be calculated by $SCR_{QIV} - SCR_{aQIV}$

The statistical hypotheses to be tested for the primary immunogenicity objective 1a correspond to:

$H_0$: *GMTri* >1.5, for any strain

$H_a$: *GMTri* ≤1.5, for all strains

and

$H_0$: *Di* >10%, for any strain

$H_a$: *Di* ≤10%, for all strains

where *GMTri* (*i*=1,2,3,4) is any of the 4 strain-specific Day 22 GMT ratios, namely,

- $GMTr_1 = GMT_{QIV}/GMT_{aQIV}$ for A/H1N1 strain
- $GMTr_2 = GMT_{QIV}/GMT_{aQIV}$ for A/H3N2 strain
- $GMTr_3 = GMT_{QIV}/GMT_{aQIV}$ for B/Yamagata strain
- $GMTr_4 = GMT_{QIV}/GMT_{aQIV}$ for B/Victoria strain

and *Di* (*i*=1,2,3,4) is the 4 strain-specific Day 22 SCR differences ($\boldsymbol{\pi}_{QIV,i}$-$\boldsymbol{\pi}_{aQIV,i}$), namely,

- $D_1$=$\boldsymbol{\pi}_{QIV,1} - \boldsymbol{\pi}_{aQIV,1}$ for A/H1N1 strain
- $D_2$=$\boldsymbol{\pi}_{QIV,2} - \boldsymbol{\pi}_{aQIV,2}$ for A/H3N2 strain
- $D_3$= $\boldsymbol{\pi}_{QIV,3} - \boldsymbol{\pi}_{aQIV,3}$ for B/Yamagata strain
- $D_4$= $\boldsymbol{\pi}_{QIV,4} - \boldsymbol{\pi}_{aQIV,4}$ for B/Victoria strain

where $\boldsymbol{\pi}_{QIV,i}$, $\boldsymbol{\pi}_{aQIV,i}$ (*i*=1,2,3,4) denotes the SCRs for the 4 strains in QIV and aQIV respectively.

*Superiority of aQIV to QIV (Objective 1b)*

To demonstrate that aQIV induces a superior immune response compared to QIV in subjects 50-64 years of age as measured by HI GMTs at 3 weeks after vaccination for at least 2 of the 4 vaccine strains, aQIV will be considered to be superior to QIV if the following statistical criteria are met:

The UL of the 95% CI for the inter-group GMT ratio (QIV/aQIV) is <1.0 for at least 2 of the 4 vaccine strains.

The statistical hypotheses to be tested for the primary immunogenicity objective 1b correspond to:

$H_0$: *GMTri* ≥1, for at least 3 of the 4 vaccine strains at Day 22

$H_a$: *GMTri* <1, for at least 2 of the 4 vaccine strains at Day 22

where *GMTri* (*i*=1,2,3,4) are defined as above.

#### 8.4.2.3.2 Analysis Sets

The PPS Immunogenicity will be used for the primary immunogenicity noninferiority analysis 1a, and a supporting analysis will be performed using the FAS Immunogenicity. The FAS Immunogenicity will be used for the primary immunogenicity superiority analysis 1b, and a supporting analysis will be performed using the PPS Immunogenicity.

#### 8.4.2.3.3 Statistical Methods

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

Reverse cumulative distribution curves will be derived by time-point and strain.

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

The analysis model for the HI GMT will use a general linear model on log-transformed (base 10) Day 22 titers as the outcome variable and as covariates: treatment groups (aQIV, and QIV), prevaccination titer ($log_{10}$ transformed), age stratum, gender, and history of any influenza vaccination within the 3 previous influenza seasons. From this model, adjusted differences in the least square means (on the $log_{10}$ scale) will be produced with 95% confidence limits for QIV versus aQIV. The estimated difference and the confidence limits will be back-transformed to obtain *adjusted GMT ratios* with 95% confidence limits. The adjusted GMT ratio will be the result for which the assessment of the HI GMT primary endpoint will be based on. Each of the 4 strains will be analyzed separately.

Potential covariate interaction effects will also be examined in the fit of the GLM, as well as the other co-variates such as age taken as a continuous factor.

The differences of binary endpoints (i.e. seroconversion or titer ≥1:40) will be compared using the Miettinen and Nurminen method (Miettinen and Nurminen 1985). Additional supportive analyses might be done using generalized linear models with factors for treatment group, age subgroup, prevaccination titer ($log_{10}$ transformed) as well as vaccination history. Adjusted differences between treatment groups with 2-sided 95% CI will be calculated based on the model and potential interaction effects will be examined.

No multiplicity adjustment to the CI levels will be implemented for the primary objectives. For the secondary endpoints, alpha was adjusted to 0.0127 for 1 out of 4 strain success for objective 2a and 2b so that the overall type I error is less than 0.05. The statistical hypotheses will be tested sequentially according to the order of the objectives. Details of the hypothesis testing procedure will be specified in the SAP.

*Handling of missing values for immunogenicity data:*

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

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

### 8.4.3 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 vaccinated will be presented by treatment group.

##### 8.4.3.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

Solicited AEs are reported daily from Day 1 up to and including Day 7 postvaccination. If a solicited AE continues beyond Day 7 after vaccination, recording in the Subject eDiary will be continued until the event(s) resolved or for a maximum of 14 days after vaccination. If the reaction continues to be present after Day 14, the event and follow-up is to be captured as an unsolicited AE in the eCRF. A solicited AE will be defined as “present” or at least mild on any of the recorded days to be counted. This will be summarized as total and for local, systemic and the category of other indicators of reactogenicity separately. The same tables will be created at each time point.

Frequencies and percentages of subjects experiencing each AE will be presented overall and for each maximum symptom severity and by treatment group. Postvaccination solicited AEs reported from Day 1 to Day 7 will also be summarized for the intervals Day 1-3 and Day 4-7 overall and for each maximal severity and by treatment group. Injection-site erythema, ecchymosis and induration

will be summarized according to categories based on linear measurements. Please refer to the SAP for definitions of categories.

Each solicited local and systemic AE will also be further summarized as "Present" versus "Absent". "Present" will include measurements with a diameter of at least 25 mm.

The use of antipyretics and analgesics will be summarized by type of use (prophylactic versus treatment) as the number and percentage of subjects reporting use.

Body temperature will be summarized by 0.5°C increments from 36.0°C up to ≥40°C.

#### 8.4.3.1.3 Analysis of Unsolicited Adverse Events

This analysis applies to all AEs occurring during the study, judged either as probably related, possibly related, or not related to vaccination by the investigator, recorded in the AE eCRF, with a start date on or after the date of vaccination. The original verbatim terms used by investigators to identify AEs in the eCRFs will be mapped to preferred terms using the MedDRA dictionary. The AEs will then be grouped by MedDRA preferred terms into frequency tables according to system organ class (SOC).

All reported AEs, as well as AEs judged by the investigator as at least possibly related to study vaccine, will be summarized according to SOC and preferred term within SOC. These summaries will be presented by treatment group and by interval of study observation. When an AE occurs more than once for a subject, the maximal severity and strongest relationship to the treatment group will be counted.

Separate summaries will be produced for the following categories:

- Unsolicited AEs during the 30 minutes postvaccination;
- AEs
- SAEs;
- Unsolicited AEs that are possibly or probably related to vaccine;
- AESIs;
- AEs leading to withdrawal.

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

No imputation of missing unsolicited AEs will be used.

#### 8.4.3.1.4 Statistical Hypotheses

No statistical hypotheses will be tested.

#### 8.4.3.1.5 Analysis Sets

The Solicited Safety Set for the solicited AEs and the Unsolicited Safety Set for all unsolicited AEs.

#### 8.4.3.1.6 Statistical Methods

Only descriptive statistics will be calculated and presented.

### 8.4.3.2 Analysis of Secondary Efficacy Objective(s)

Not applicable

#### 8.4.3.2.1 Statistical Hypotheses

Not applicable.

#### 8.4.3.2.2 Analysis Sets

Not applicable.

#### 8.4.3.2.3 Statistical Methods

Not applicable.

### 8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

#### 8.4.3.3.1 Statistical Hypotheses

*Superiority of aQIV vs QIV (higher threshold) (Objective 2a)*

To demonstrate that aQIV induces a superior immune response compared to QIV in subjects 50-64 years of age as measured by HI GMT for at least one of the vaccine strains at 3 weeks after

vaccination, aQIV will be considered to be superior to QIV if, for at least one of the vaccine strains at Day 22, the following statistical criteria are met:

- *Superior immune response will be demonstrated if the UL of the 98.73% CI for the inter-group GMT ratio (QIV/aQIV) is <0.67 for one or more vaccine strains.*

The statistical hypotheses to be tested for the secondary immunogenicity 2a correspond to:

- $H_0$: *GMTr* ≥0.67, for all four vaccine strains at Day 22
- $H_a$: *GMTr* <0.67, for one or more vaccine strains at Day 22

where *GMTr* is the Day 22 GMT ratios of $GMT_{QIV}/GMT_{aQIV}$ for that vaccine strain.

*Persistence of immune response of aQIV compared to QIV (Objective 2b)*

To demonstrate greater persistence of the immune response for at least one of the vaccine strains at 6 months after vaccination with aQIV compared with QIV as measured by HI assay in subjects 50-64 years of age, the statistical hypotheses to be tested for the secondary immunogenicity 2b correspond to:

$H_0$: *GMTr* ≥1, for all four vaccine strains at Day 181

$H_a$: *GMTr* <1, for one or more vaccine strains at Day 181

where *GMTr* is 6-month GMT ratio of $GMT_{QIV}/GMT_{aQIV}$ for that strain.

*Greater persistence of the immune response will be demonstrated if the UL of the two-sided 98.73% CI for inter-group GMT ratio (QIV/aQIV) <1.0 for one or more vaccine strains.*

#### 8.4.3.3.2 Analysis Sets

The FAS Immunogenicity will be used for the secondary endpoint analyses. The PPS Immunogenicity will be used for supporting analyses.

#### 8.4.3.3.3 Statistical Methods

The statistical analysis methods are the same as the primary immunogenicity analysis for GMT ratio analysis.

### 8.4.4 Analysis of Other Objective(s)

Not applicable.

#### 8.4.4.1 Analysis of Other Safety Objective(s)

Not applicable.

#### 8.4.4.2 Analysis of Other Efficacy Objective(s)

Not applicable.

#### 8.4.4.3 Analysis of Other Immunogenicity Objective(s)

The analysis of the exploratory objectives will be described in full detail in the SAP.

## 8.5 Sample Size and Power Considerations of Primary Objectives

aQIV will be tested against QIV. The randomization ratio is 1:1 (aQIV:QIV). The study is designed to have at least 90% power to achieve the primary objectives: to demonstrate the noninferiority of GMT and SCR of aQIV vs QIV for all 4 strains, and the superiority (superiority margin of 1) of GMT of aQIV vs QIV for at least 2 of the 4 strains with one-sided significance level $\alpha$=0.025.

The results of a previous clinical study with aTIV and TIV vaccine in subjects 50-64 years of age (Study V7P38) was used to generate assumptions for vaccine effect and sample size.

It is assumed that the differences of $\log_{10}$(GMT) of A/H1N1 is 0.07, with standard deviation of 0.46 for both treatment arms, 1,816 evaluable subjects will provide at least 90% of power to demonstrate a superiority of aQIV vs QIV for the A/H1N1 strain. The table below shows the power of each comparison based on GMT ratio and SCR data from Study V7P38:

| Strain | $\log_{10}$(GMT) Differences (SD) | Sample Size (Evaluable Subjects) for 90% Power | Power with Sample size of 2,018 for superiority (GMTr margin of 1) (1,816 Evaluable Subjects) | Power with Sample size of 2,018 for NI (Margin of 0.67) |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| A/H1N1 | 0.07 (0.46) | 2,018 (1,816 evaluable subjects) | 90% | ~100% |
| A/H3N2 | 0.26 (0.61) | 260 (234 evaluable subjects) | ~100% | ~100% |
| B | 0.14 (0.48) | 552 (496 evaluable subjects) | ~100% | ~100% |

| Strain | SCR in aQIV group | SCR in Comparator group | Power with Sample size of 2,018 (1,816 evaluables) for NI (margin -10%) |
|---|---|---|---|
| A/H1N1 | 86% | 76% | ~100% |
| A/H3N2 | 87% | 77% | ~100% |
| B | 82% | 80% | ~100% |

Abbreviations: aQIV = adjuvanted Quadrivalent Influenza Vaccine; GMT = geometric mean titer; NI = noninferiority; SCR = seroconversion rate; SD = standard deviation.

Thus with 1:1 randomization, 1,816 evaluable subjects will provide an overall power of 90% to demonstrate the primary objectives of noninferiority and superiority of aQIV vs QIV with one-sided alpha=0.025. Assuming a 10% drop out rate, the total sample size for the study needed is 2,018 subjects.

Further details of the sample size calculation will be fully described in the SAP.

Hypothesis testing will be carried out by 1a) and 1b) sequentially. Only after the noninferiority objectives are achieved, the superiority objectives will be tested. Only after the primary objectives are reached, secondary objective will be tested sequentially. All primary endpoint analyses will be carried out with a one-sided alpha of 0.025 for each comparison. No adjustment for multiple endpoints for the primary objectives is necessary.

## 8.6 Interim Analysis

No interim analysis is planned for this study.

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

Prior to enrollment of the first study subject, Seqirus or delegate will train investigators and/or their study staff on the study protocol, all applicable study procedures, documentation practices, and all electronic systems. 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 Source Document Agreement (SDA prior to subject enrollment.

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

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

All safety data reported by subjects must be written down in source documents prior to entry of the data into eCRFs. If there are multiple sources of information (e.g., Subject eDiary, verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an AE, 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 on the AE eCRF.

The Subject eDiary source data is hosted by a vendor engaged for this study, on behalf of the study investigators. In case the Subject eDiary data cannot be integrated into electronic data capture (EDC), each investigator will be provided with a certified archive copy of all diary data relating to subjects at that site and must confirm it is readable.

### 9.2 Study Monitoring, Auditing and Source Data Verification

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

- the rights and well-being of human subjects are protected,
- the reported study data are accurate, complete, and verifiable from the source documents, and
- the conduct of the study is in compliance with the current approved protocol/amendment(s), Good Clinical Practice (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 directly into the EDC system (e.g. when an electronic Diary is being used by the subject.

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

The investigator and/or site staff must make source documents of subjects enrolled in this study available for inspection by Seqirus or its representative at the time of each monitoring visit and Sponsor audits, when applicable. These documents must also be available for inspection, verification and copying, as required by regulations, by officials of the regulatory health authorities (e.g., FDA, EMA and others) and/or ECs/IRBs. The investigator and study site staff must comply

with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

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

# 10 DATA MANAGEMENT

## 10.1 Data Entry and Management

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

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

## 10.2 Data Clarification

As part of the conduct of the trial, the Sponsor 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 to GDPR in all stages of Data Management.

## 11 RECORD RETENTION

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

The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an 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 agrees that samples will be retained for use limited to additional analyses related to this study. If the subject also agrees to have the his/her 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 3.10, End of Study.

In accordance with standard editorial, ethical practices and current guidelines of Good Publication Practice (Battisti et al. 2015), 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 (ICH E6(R2), with applicable local regulations European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare, Seqirus codes on protection of human rights, and

with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations, ICH 1997).

### 13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written informed consent or assent, as described in Section 5.1.1, Informed Consent. Before the start of the study, the investigator will have the informed consent and any other materials that will be provided to the subjects reviewed and approved by the IRB/EC. This review and approval will be documented and stored with other study documents. The investigator or designee must fully inform the subject of all pertinent aspects of the study. A copy of the written informed consent will be given to the subject. The subject 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 **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent process may be conducted up to 10 days prior to vaccination on Day 1. If the subject 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.

Women of childbearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements indicated in the protocol for the duration of the study. If case of doubts on the ability of a subject to adhere to these requirements, that subject should not be allowed in the study.

### 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 appropriately trained healthcare professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any AE related to the study.
- If permission to do so is given by the subject, 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/EC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)). In addition, the investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favorable opinion. As soon

as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) to the IRB/EC for review and approval/favorable opinion,

(b) to the Sponsor for agreement and, if required,

(c) to the regulatory authority(ies).

### 13.4 Protocol Amendments

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

## 14 REFERENCE LIST

Aiello A, Farzaneh F, Candore G, Caruso C, et al. Immunosenescence and its hallmarks: how to oppose aging strategically? A review of potential options for therapeutic intervention. Front Immunol. 2019;10:2247.

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# APPENDIX 1 – PREDICTION RULE

**Prediction rule for estimating the probability of hospitalization due to pneumonia or influenza and death due to any cause (Hak et al. 2004).**

| Characteristic | Score[a] |
|---|---|
| **Age, years** | |
| <70 | 0 |
| 70-74 | 14 |
| 75-79 | 28 |
| 80-89 | 42 |
| ≥90 | 56 |
| **Sex** | |
| Female | 0 |
| Male | 9 |
| **Outpatient visits during the previous year** | |
| 0 | 0 |
| 1-6 | 11 |
| 7-12 | 22 |
| >13 | 33 |
| **Previous hospitalization due to pneumonia or influenza** | |
| No | 0 |
| Yes | 63 |
| **Comorbidity[b]** | |
| Pulmonary disease | 18 |
| Heart disease | 6 |
| Renal disease or renal transplant | 12 |
| Dementia or stroke | 22 |
| Non-hematological and hematological cancer | 48 |
| **Subject total score** | |

**Notes:**

a. The prognostic score for a given subject can be obtained by adding the scores for each applicable characteristic.

b. Pre-existing medical conditions of eligible subjects will be scored following a judgment by the investigator.

# APPENDIX 2 – LIST OF ADVERSE EVENTS OF SPECIAL INTEREST

Gastrointestinal disorders
- Celiac disease
- Crohn's disease
- Ulcerative colitis
- Ulcerative proctitis

Liver disorders
- Autoimmune cholangitis
- Autoimmune hepatitis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis

Metabolic diseases
- Addison's disease
- Autoimmune thyroiditis (including Hashimoto thyroiditis)
- Diabetes mellitus type I
- Grave's or Basedow's disease

Musculoskeletal disorders
- Antisynthetase syndrome
- Dermatomyositis
- Juvenile chronic arthritis (including Still's disease)
- Mixed connective tissue disorder
- Polymyalgia rheumatic
- Polymyositis
- Psoriatic arthropathy
- Relapsing polychondritis
- Rheumatoid arthritis
- Scleroderma, including diffuse systemic form and CREST syndrome
- Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis
- Systemic lupus erythematosus
- Systemic sclerosis

Neuroinflammatory disorders
- Acute disseminated encephalomyelitis, including site-specific variants (e.g., non-infectious encephalitis, encephalomyelitis, myelitis, radiculomyelitis)
- Cranial nerve disorders, including paralyses/paresis (e.g., Bell's palsy)
- Guillain-Barré syndrome, including Miller Fisher syndrome and other variants

- Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy
- Multiple sclerosis
- Narcolepsy
- Optic neuritis
- Transverse myelitis
- Myasthenia gravis, including Eaton-Lambert syndrome

Skin disorders
- Alopecia areata
- Autoimmune bullous skin diseases, including pemphigus, pemphigoid and dermatitis herpetiformis
- Cutaneous lupus erythematosus
- Erythema nodosum
- Morphoea
- Lichen planus
- Psoriasis
- Sweet's syndrome
- Vitiligo

Vasculitides
- Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis
- Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease thromboangiitis obliterans, necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch- Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis

Others
- Antiphospholipid syndrome
- Autoimmune hemolytic anemia
- Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis)
- Autoimmune myocarditis/cardiomyopathy
- Autoimmune thrombocytopenia
- Goodpasture syndrome
- Idiopathic pulmonary fibrosis
- Pernicious anemia
- Raynaud's phenomenon

- Sarcoidosis
- Sjögren's syndrome
- Stevens-Johnson syndrome
- Uveitis

# APPENDIX 3 – SPONSOR AND INVESTIGATOR SIGNATURE PAGES

SIGNATURE ON BEHALF OF SPONSOR

I have read the protocol entitled "**A Phase 3, Randomized, Observer-blind, Controlled, Multicenter, Clinical Study to Evaluate Immunogenicity and Safety of an MF59-adjuvanted Quadrivalent Subunit Inactivated Influenza Vaccine in Comparison with a Licensed Quadrivalent Influenza Vaccine, in Adults 50 to 64 Years of Age**" and confirm that, to the best of my knowledge; the protocol accurately describes the design and conduct of the study.

Signature: [redacted] Date: 11 July 2022
(DD MMM YYYY)

Name and qualifications: [redacted]

Role: Clinical Program Director - FLUAD

SIGNATURE OF INVESTIGATOR

I have read the protocol entitled "**A Phase 3, Randomized, Observer-blind, Controlled, Multicenter, Clinical Study to Evaluate Immunogenicity and Safety of an MF59-adjuvanted Quadrivalent Subunit Inactivated Influenza Vaccine in Comparison with a Licensed Quadrivalent Influenza Vaccine, in Adults 50 to 64 Years of Age**", I agree to conduct the clinical study, after approval by an Institutional Review Board or Independent Ethics Committee (as appropriate), in accordance with the protocol, the principles of the Declaration of Helsinki, the standards of Good Clinical Practice (as defined by the International Conference on Harmonisation) and applicable regulatory requirements.

Changes to the protocol will only be implemented after written approval is received from the sponsor (Seqirus) and the Institutional Review Board or Independent Ethics Committee (as appropriate), with the exception of medical emergencies.

I will ensure that study staff fully understand and follow the protocol.

Signature: ……...…… Date: ……
(DD MMM YYYY)

Affiliation and qualifications: ……

Address of Investigator: ……

# STUDY PROTOCOL V118_23

**Amendment Number 1**

**Amendment Date: 18 NOV 2021**

## A Phase 3, Randomized, Observer-blind, Controlled, Multicenter, Clinical Study to Evaluate Immunogenicity and Safety of an MF59-adjuvanted Quadrivalent Subunit Inactivated Influenza Vaccine in Comparison with a Licensed Quadrivalent Influenza Vaccine, in Adults 50 to 64 Years of Age

**The present amendment introduces changes to the study protocol since the version 1, dated 15 April 2021 of the protocol. These changes are reflected into the revised protocol associated to this amendment.**

## RATIONALE AND DESCRIPTION OF CHANGE(S)

This Amendment includes a change to address a request from CBER, as well as some further corrections to the statistical definition of success criteria. Furthermore, updates have been made in several sections to clarify the protocol language and/or to better reflect current status.

Rationale for major changes:

1. The Confidence Interval (CI) for the secondary objective 2a (*To demonstrate that aQIV induces a superior immune response compared with QIV in subjects 50-64 years of age as measured by HI GMT for at least one vaccine strain at 3 weeks after vaccination*) has been updated to reflect correct alpha.

Changes:

| Section(s) | Previous text: | Amended text: |
|---|---|---|
| Synopsis, Section 2.2.1, Section 8.2.2.3, Section 8.4.3.3.1 | Success criteria:<br>Superior immune response will be demonstrated if the UL of the 95% CI for the inter-group GMT ratio (QIV/aQIV) is <0.67 for one or more vaccine strains. | Success criteria:<br>Superior immune response will be demonstrated if the UL of the 98.73% CI for the inter-group GMT ratio (QIV/aQIV) is <0.67 for one or more vaccine strains. |
| Section 8.4.2.3.3 | No multiplicity adjustment to the CI levels will be implemented. | No multiplicity adjustment to the CI levels will be implemented for the primary objectives. For the secondary endpoints, alpha was adjusted to 0.0127 for 1 out of 4 strain success for objective 2a and 2b so that the overall type I error is less than 0.05. The statistical hypotheses will be testing sequentially according to the order of the objectives. Details of the hypothesis testing procedure will be specified in the SAP. |

2. The Confidence Interval (CI) for the secondary objective 2b (*To demonstrate greater persistence of the immune response for at least one vaccine strain at 6 and 9 months after vaccination with aQIV compared with QIV as measured by HI in subjects 50-64 years of age*) has been updated to reflect correct alpha.

Changes:

| Section(s) | Previous text: | Amended text: |
|---|---|---|
| Synopsis, Section 2.2.1, Section 8.2.2.3, Section 8.4.3.3.1 | Success criteria:<br><br>Greater persistence of the immune response will be demonstrated if the UL of the 95% CI for inter-group GMT ratio (QIV/aQIV) <1.0 for one or more vaccine strains. | Success criteria:<br><br>Greater persistence of the immune response will be demonstrated if the UL of the 98.73% CI for inter-group GMT ratio (QIV/aQIV) <1.0 for one or more vaccine strains. |
| Section 8.4.2.3.3 | No multiplicity adjustment to the CI levels will be implemented. | No multiplicity adjustment to the CI levels will be implemented for the primary objectives. For the secondary endpoints, alpha was adjusted to 0.0127 for 1 out of 4 strain success for objective 2a and 2b so that the overall type I error is less than 0.05. The statistical hypotheses will be testing sequentially according to the order of the objectives. Details of the hypothesis testing procedure will be specified in the SAP. |

3. To allow expedited CSR reporting, database lock and unblinding will be conducted in two stages. A Blinding Maintenance Plan is prepared to ensure blinding of relevant laboratory and statistical personnel is maintained until their activities have been completed.

Changes:

| Section | Previous text: | Amended text: |
|---|---|---|
| Section 3.5 | All personnel involved in processing samples and performing laboratory assays and other personnel who are directly involved in the conduct of the study or in the analysis of the final study results, or have contact with study centers, will remain blinded to the treatment codes until the | All personnel involved in the conduct of the study or in the analysis of the final study results, or have contact with study centers, will remain blinded to the treatment codes until the clinical database has been soft-locked and protocol deviations have been assessed. |

| | | |
|---|---|---|
| | database has been locked for final analysis. | All personnel involved in processing samples and performing laboratory assays will remain blinded to the treatment codes until the clinical database has been locked for final analysis.<br><br>Further details are specified in a study specific Blinding Maintenance Plan. |

4. Clarifications on several exclusion criteria have been implemented consequent to Estonian EC response and questions raised during study initiation phase

Changes:

| Section(s) | Previous text: | Amended text: |
|---|---|---|
| Section 4.2 | 7. Abnormal function of the immune system resulting from:<br>a. Clinical conditions;<br>b. Systemic administration of corticosteroids (PO/IV/IM)[1] at a dose ≥20 mg/day of prednisone for more than 14 consecutive 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 | 7. Abnormal function of the immune system resulting from:<br>a. Clinical conditions;<br>b. Systemic administration of corticosteroids (PO/IV/IM)[1] at a dose equivalent to ≥20 mg/day of prednisone for more than 14 consecutive 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; |

[1] PO= by mouth; IV=intravenous; IM= intramuscular

| | | |
|---|---|---|
| | permitted;<br>c. Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent; | c. Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent; |
| | 9. Received an investigational or non-registered medicinal product within 30 days prior to informed consent, or who are unwilling to refuse participation in another clinical study at any time during the conduct of this study (note: concomitant participation in an observational study not involving drugs, vaccines, or medical devices, is acceptable); | 9. Received an investigational or non-registered medicinal product within 30 days prior to informed consent, or who are unwilling to refuse participation in another clinical study at any time during the conduct of this study (notes: i. concomitant participation in a study not involving or no longer involving administration of drugs, vaccines, or medical devices, is acceptable (e.g. studies in safety follow-up phase, observational studies); ii. concomitant participation in a COVID-19 vaccine study is acceptable provided that the vaccine dosing interval mentioned in Exclusion Criterion #11 is adhered to); |

5. Clarifications on reporting requirements for solicited AEs that start during day 1-7 and continue beyond Day 14

| Section(s) | Previous text: | Amended text: |
|---|---|---|
| Section 5.3<br>Section 7.1.1,<br>Section 8.4.3.1.2 | If a solicited local or systemic AE continues beyond day 7 after vaccination, recording in the Subject eDiary will be continued until the event(s) resolved or for a maximum of 14 days after vaccination. | If a solicited local or systemic AE continues beyond day 7 after vaccination, recording in the Subject eDiary will be continued until the event(s) resolved or for a maximum of 14 days after vaccination. If the reaction continues to be present after Day 14, the event and follow-up is to be captured as an unsolicited AE in the eCRF. |

6. Correction how Full Analysis Set will be analyzed in case of vaccination errors, consequent to CBER advice.

Changes:

| Section(s) | Previous text: | Amended text: |
|---|---|---|
| Section 8.3.4 | In case of vaccination error, subjects in the FAS sets will be analyzed “as treated” (i.e., according to the vaccine the subject actually received, rather than the vaccine the subject may have been randomized). | In case of vaccination error, subjects in the FAS sets will be analyzed “as randomized” (i.e., according to the vaccine the subject was designated to receive, which may be different from the vaccine the subject actually received). |

7. Update on the analysis model for the HI GMT to include relevant covariates.

Changes:

| Section(s) | Previous text: | Amended text: |
|---|---|---|
| Section | The analysis model for the HI | The analysis model for the HI |

| | | |
|---|---|---|
| 8.4.2.3.3 | GMT will use a general linear model on log-transformed (base 10) Day 22 titers as the outcome variable and as covariates: treatment groups (aQIV, and QIV), prevaccination titer ($log_{10}$ transformed), age stratum, gender. From this model, adjusted differences in the least square means (on the $log_{10}$ scale) will be produced with 95% confidence limits for aQIV versus QIV. The estimated difference and the confidence limits will be back-transformed to obtain *adjusted GMT ratios* with 95% confidence limits. The adjusted GMT ratio will be the result for which the assessment of the HI GMT primary endpoint will be based on. Each of the 4 strains will be analyzed separately.<br><br>Potential covariate interaction effects will also be examined in the fit of the GLM, as well as the other co-variates such as previous vaccination history and age were taken as a continuous factor. | GMT will use a general linear model on log-transformed (base 10) Day 22 titers as the outcome variable and as covariates: treatment groups (aQIV, and QIV), prevaccination titer ($log_{10}$ transformed), age stratum, gender, and history of any influenza vaccination within the 3 previous years. From this model, adjusted differences in the least square means (on the log10 scale) will be produced with 95% confidence limits for QIV versus aQIV. The estimated difference and the confidence limits will be back-transformed to obtain *adjusted GMT ratios* with 95% confidence limits. The adjusted GMT ratio will be the result for which the assessment of the HI GMT primary endpoint will be based on. Each of the 4 strains will be analyzed separately.<br><br>Potential covariate interaction effects will also be examined in the fit of the GLM, as well as the other co-variates such as age taken as a continuous factor. |

Summary of minor changes:

Clarification of age range boundaries, details on number of subjects who can provide extra blood samples, typographical errors, minor edits and textual clarifications have been implemented throughout.

# STUDY PROTOCOL V118_23

**Amendment Number 2**

**Amendment Date: 11 JUL 2022**

**A Phase 3, Randomized, Observer-blind, Controlled, Multicenter, Clinical Study to Evaluate Immunogenicity and Safety of an MF59-adjuvanted Quadrivalent Subunit Inactivated Influenza Vaccine in Comparison with a Licensed Quadrivalent Influenza Vaccine, in Adults 50 to 64 Years of Age**

**The present amendment introduces changes to the study protocol since the version 2, dated 18 Nov 2021 of the protocol. These changes are reflected into the revised protocol associated to this amendment.**

## RATIONALE AND DESCRIPTION OF CHANGE(S)

This Amendment includes a reclassification of one of the secondary objectives regarding 9 months persistence to become an exploratory objective, a correction of an inconsistency in the analysis of local solicited reactions and an improvement in the definition of previous influenza vaccination.

Rationale for major changes:

To expedite the primary and secondary immunogenicity results and to report them with the complete safety data to support timely license applications in different regions, the analyses of immunogenicity persistence at 9 months after vaccination with aQIV has been removed from a secondary objective and added as an exploratory objective. Otherwise, the study design and objectives remain the same, including the secondary objective and analyses for persistence of immune response at 6 months after vaccination.

The protocol language regarding the serum antibody testing strategy and end of study definition has been adjusted accordingly. The impact on the serum antibody testing strategy will be that the 9 month samples will be assayed at a later time, and that those later runs of the 9 month sera will include repeat assays of the baseline sera (Day 1) in the same testing. These repeat Day 1 results will be used only for the Day 271 statistical analyses (e.g. seroconversion rates, modeling covariates, etc.), as described in the SAP.

Changes:

| Section(s) | Previous text: | Amended text: |
|---|---|---|
| Synopsis, Section 2.2.1, Section 8.4.3.3.1 | To demonstrate greater persistence of the immune response for at least one vaccine strain at 6 and 9 months after vaccination with aQIV compared with QIV as measured by HI in subjects 50-64 years of age. | To demonstrate greater persistence of the immune response for at least one vaccine strain at 6 months after vaccination with aQIV compared with QIV as measured by HI in subjects 50-64 years of age. |
| Synopsis, Section 2.3 | Exploratory Immunogenicity Objective:<br>- To further evaluate the immunogenicity of aQIV compared with QIV in subjects 50-64 years of age, with alternative assays, if sera permit. | Exploratory Immunogenicity Objectives:<br>- To evaluate persistence of the immune response at 9 months after vaccination with aQIV compared with QIV as measured by HI in subjects 50-64 years of age.<br><br>- To further evaluate the |

| | | |
|---|---|---|
| | | immunogenicity of aQIV compared with QIV in subjects 50-64 years of age, with alternative assays, if sera permit. |
| Section 3.5 | All personnel involved in the conduct of the study or in the analysis of the final study results, or have contact with study centers, will remain blinded to the treatment codes until the clinical database has been soft-locked and protocol deviations have been assessed.<br><br>All personnel involved in processing samples and performing laboratory assays will remain blinded to the treatment codes until the clinical database has been locked for final analysis.<br><br>Further details are specified in a study specific Blinding Maintenance Plan. | All personnel involved in the conduct of the study or in the analysis of the final study results, or who have contact with study centers, will remain blinded to the treatment codes until the clinical database has been locked, protocol deviations (except for Day 271 serum sample analysis PDs) have been assessed, and the data have been released for statistical analysis. The analysis on the primary and secondary objectives for the final CSR will be conducted on this data.<br><br>All personnel involved in processing samples and performing laboratory assays will remain blinded to the treatment codes until all Day 271 serum samples have been tested and results have been transferred. The exploratory analysis on the 9 month persistence objective will be conducted on this data and reported in a CSR addendum.<br><br>Further details are specified in a study specific Blinding Maintenance Plan. |
| Section 3.10 | Evaluation of the primary and secondary immunogenicity objectives requires the testing of biological samples from the study subjects, which can only be completed after all samples are | Evaluation of the primary and secondary immunogenicity objectives requires the testing of biological samples from the study subjects, which can only be completed after all of the samples |

| | | |
|---|---|---|
| | collected. The last samples for the analysis of the secondary objectives will be taken at Visit 6 (Day 271). 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 collection of the last biological sample at 6 (Day 271). | for these objectives are collected. The last samples for the analysis of the secondary objectives will be taken at Visit 5 (Day 181). The last clinical assessment for the secondary safety objective will be at Visit 6 (Day 271). Accordingly, for the purpose of this protocol, end of study is defined as the completion of the testing of the Visit 5 (Day 181) biological samples, to be achieved no later than 8 months after collection of the last biological sample at Visit 5 (Day 181) or the Last Subject Last Visit, whichever is later. The local end of the study is defined as the Last Subject Last Visit within the country. |
| Section 7.3 | (*No prior statement*)<br><br>For the exploratory immunogenicity objective, immune responses may be evaluated with additional assays, such as testing against heterologous strains or alternative | For the exploratory objective of persistence of the immune response at 9 months after vaccination, HI antibody responses for all strains included in the study vaccines will be evaluated using an egg-derived target virus at a later stage. For this analysis, Day 1 serum samples obtained for the primary and secondary study objectives (noninferiority and superiority assessments) will be retested. Day 1 data from the exploratory assessment of persistence at 9 months will not replace data obtained for the primary and secondary endpoint analyses.<br><br>For the other exploratory immunogenicity objective, immune responses may be evaluated with additional assays, such as testing against |

| | | |
|---|---|---|
| | assay methods (e.g., MN). | heterologous strains or alternative assay methods (e.g., MN). |
| Section 8.1.2.3 | 2b. Greater persistence of the immune response of aQIV compared to QIV will be assessed for HI GMT for the strains included in the vaccines as follows:<br>• The GMT ratio (QIV/aQIV) at Days 181 and 271. | 2b. Greater persistence of the immune response of aQIV compared to QIV will be assessed for HI GMT for the strains included in the vaccines as follows:<br>• The GMT ratio (QIV/aQIV) at Day 181. |
| Section 8.1.3.3 | (*No prior statement*)<br><br>Exploratory immunogenicity endpoints that may be assessed in the study include the measures of immunogenicity of aQIV and QIV as determined by the HI or MN assay against homologous or heterologous strains at Day 1, Day 22, Day 181, and Day 271 (depending on availability of | Persistence of the immune response of aQIV compared to QIV at Day 271 will be assessed for HI GMT for all strains included in the vaccines through the same descriptive immune response parameters as presented for secondary objective 2c, and further explored through the GMT ratio (QIV/aQIV). For this analysis, Day 1 serum samples obtained for the primary and secondary study objectives (noninferiority and superiority assessments) will be retested. Day 1 data from the exploratory assessment of persistence at 9 months will not replace data obtained for the primary and secondary endpoint analyses.<br><br>Additional exploratory immunogenicity endpoints that may be assessed in the study include the measures of immunogenicity of aQIV and QIV as determined by the HI or MN assay against homologous or heterologous strains at Day 1, Day 22, Day 181, and Day 271 (depending on availability of |

| | | |
|---|---|---|
| | adequate sera and on assay availability). Details will be described in the SAP. | adequate sera and on assay availability). Details will be described in the SAP. |
| Section 8.2.2.3 | Greater persistence of the immune response will be demonstrated if the UL of the 98.73% CI for the inter-group GMT ratio (QIV/aQIV) <1.0 for one or more vaccine strains at 6 months and subsequently at 9 months | Greater persistence of the immune response will be demonstrated if the UL of the 98.73% CI for the inter-group GMT ratio (QIV/aQIV) <1.0 for one or more vaccine strains at 6 months |

To acknowledge variability in timing of the annual influenza vaccination campaigns, the stratification factor definition has been improved to consider subjects who have received an influenza vaccination within the previous 3 influenza seasons as previously vaccinated subjects (Yes). The original text was meant not to be literally 3 times 365 days prior to the randomization date, but the 3 prior influenza years/seasons, and was implemented as such.

Changes:

| Section(s) | Previous text: | Amended text: |
|---|---|---|
| Synopsis, Section 3.6.1, Section 6.5, Section 8.4.2.3.3 | Stratification for history of any influenza vaccination within the previous 3 influenza years (yes/no) will be applied to all subjects. | Stratification for history of any influenza vaccination within the previous 3 influenza seasons (yes/no) will be applied to all subjects. |

To ensure consistency with the approved labelling information for aQIV (Fluad Quadrivalent/Quad/Tetra), assessment and reporting of solicited local reactions has been updated to consider local events as being present if measured ≥25 mm.

Changes:

| Section(s) | Previous text: | Amended text: |
|---|---|---|
| Section 8.4.3.1.2 | Each solicited local and systemic AE will also be further summarized as “none” versus “any”. “Any” will include measurements with a diameter of | Each solicited local and systemic AE will also be further summarized as “Present” versus “Absent”. “Present” will include measurements with a diameter of |

| | | |
|---|---|---|
| | at least 1 mm. | at least 25 mm. |

Summary of minor changes:

Typographical errors and minor edits have been implemented throughout.