CLINICAL STUDY PROTOCOL

Study Number	V200_10
Protocol Version	FINAL VERSION 1.0: MARCH 2020
Study Title	A Phase 2, Randomized, Stratified, Observer-Blind Clinical Study to Evaluate Safety and Immunogenicity of the MF59-Adjuvanted Quadrivalent Subunit Inactivated Cell-derived Influenza Vaccine (aQIVc) in adults ≥50 years of age
Study Phase	PHASE 2
Product Name	MF59-Adjuvanted Quadrivalent Subunit Inactivated Cell-derived Influenza Vaccine (aQIVc)
Regulatory Agency Identifying Number(s)	IND PTS #5055
Sponsor	SEQIRUS UK LIMITED. The Point, 29 Market Street, Maidenhead, UK
Previous version, if applicable	NA
Date, if applicable	NA

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PROTOCOL SYNOPSIS

Name of Sponsor:	**Protocol number:**	**Generic name of study vaccines:**
Seqirus	V200_10	MF59-adjuvanted Quadrivalent Subunit Inactivated Cell-derived Influenza Vaccine (aQIVc) Quadrivalent Subunit Inactivated Cell-derived Influenza Vaccine (QIVc) MF59-adjuvanted Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine (aQIV) Recombinant Quadrivalent influenza vaccine (QIVr)

Title of Study:

A Phase 2, Randomized, Stratified, Observer-blind Clinical Study to Evaluate Safety and Immunogenicity of the MF59-adjuvanted Quadrivalent Inactivated Subunit Cell-derived Influenza Vaccine (aQIVc) in Adults ≥50 Years of Age.

Study Period: Approximately 6 months for each study participant.	**Clinical Phase:** Phase 2

Background and Rationale:

Vaccination is the primary method for preventing influenza and its severe complications. The efficacy of the conventional influenza vaccines in the adult population is demonstrated to be high. In contrast, the efficacy in elderly 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). In view of the limitations of conventional influenza vaccines in older adults, there continues to be an unmet need for a new generation of influenza vaccines that provides more consistent and broader

coverage against all seasonal virus subtypes and variants (Wong and Webby 2013; Reber et al. 2012).

The MF59-Adjuvanted Quadrivalent Subunit Inactivated Cell-derived Influenza Vaccine (aQIVc) offers important advantages over conventional influenza vaccines. aQIVc combines the benefits of both cell-based and adjuvanted technologies to meet the unmet need of influenza in older adults. The cell-derived antigen provides a better match to circulating strains, therefore addressing mismatch due to egg adaptation (Hedge 2015; Lambert et al. 2010). The effect of inclusion of MF59 adjuvant to the vaccine is expected to enable increased magnitude of immune response by stimulating higher antibody responses at standard doses; increased breadth of immune response by expanding antibody repertoire; and increased duration of immune response with higher antibody response at 6 months after vaccination which is important in case of prolonged influenza seasons and/or late-season outbreaks (Frey et al. 2014).

The aim of this study is to perform an evaluation of the immunogenicity and safety of the MF59-adjuvanted Quadrivalent cell-based vaccine versus other influenza vaccines, such as the non-adjuvanted Quadrivalent cell-based influenza vaccine, the MF59-adjuvanted Quadrivalent egg-based vaccine, and the recombinant Quadrivalent vaccine. Immunogenicity and safety will be assessed in the overall study population (adults ≥50 years of age) and for the age subgroups 50-64 years and ≥65 years in order to assess the benefit/risk profile of aQIVc in each age population for this vaccine.

Disclosure Statement: This is a parallel-group treatment study with four arms that is observer-blinded.

Study Objectives:

Primary Objectives:

Primary Immunogenicity Objective:

1. To assess the immunogenicity of aQIVc in comparison with the QIVc, aQIV, and QIVr comparator vaccines as measured by hemagglutination inhibition (HI) assay* using *cell-derived* target viruses at 28 days after vaccination, in subjects 50-64 and ≥65 years of age and overall (adults ≥50 years of age).

[*] *In case of lack of agglutination for a specific strain, immunogenicity for that strain will be assessed as measured by microneutralizaton (MN) assay as an acceptable alternative.*

Secondary Objectives:

Secondary Immunogenicity Objectives:

1. To assess the immunogenicity of aQIVc in comparison with the QIVc, aQIV, and QIVr comparator vaccines as measured by HI assay[*] using *cell-derived* target viruses at 180 days after vaccination, in subjects 50-64 and ≥65 years of age and overall.
2. To assess the immunogenicity of aQIVc in comparison with the QIVc, aQIV, and QIVr comparator vaccines as measured by MN assay using *cell-derived* target viruses at 28 and 180 days after vaccination, in subjects 50-64 and ≥65 years of age and overall.

[*] *In case of lack of agglutination for a specific strain, immunogenicity for that strain will be assessed as measured by MN assay as an acceptable alternative.*

Secondary Safety Objectives:

1. To assess the reactogenicity of aQIVc as compared to QIVc, aQIV, and QIVr in subjects 50-64 and ≥65 years of age and overall for 7 days after vaccination.
2. To assess the safety of study vaccines in subjects 50-64 and ≥65 years of age and overall for 180 days after vaccination.

Exploratory Objectives:

Further details on exploratory objectives are provided in Section 2.3, Exploratory Objectives.

Primary and Secondary Endpoints:

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

Study Design:

Experimental design: This is a Phase 2, randomized, stratified, controlled, observer-blind, multi-center study in approximately 480 male and female adults aged 50 years and older

who are healthy or have co-morbidities which increase their risk of complications from influenza infection.

Duration of the study: The study duration is approximately 6 months for each subject. The study will be conducted in one single season.

Vaccination schedule: Single vaccination (Day 1).

Investigational Vaccine: aQIVc.

Comparator Vaccines: QIVc, aQIV and QIVr.

Treatment groups:

Enrolled subjects will be randomized to one of the four treatment groups in a 1:1:1:1 ratio.

1. aQIVc group: approximately 120 subjects receiving one dose of aQIVc on Day 1.
2. QIVc group: approximately 120 subjects receiving one dose of QIVc on Day 1.
3. aQIV group: approximately 120 subjects receiving one dose of aQIV on Day 1.
4. QIVr group: approximately 120 subjects receiving one dose of QIVr on Day 1.

Randomization: an Interactive Response Technology (IRT) will be used in the study with stratification factors for age (≥50 to 64 and ≥65 years, with about 50% of the subjects 50-64 years of age and about 50% of the subjects ≥65 years of age for each treatment group) and history of any influenza vaccination within 3 previous influenza seasons (yes/no). Approximately 40% of subjects in each age subgroup for each treatment group should not have been vaccinated with an influenza vaccine within the 3 previous influenza seasons.

Blinding: Observer-blind study.

Blood sample schedule: Three blood samples will be collected from all subjects on Day 1, Day 29 and Day 181.

Data collection: electronic Case Reporting Form (eCRF).

Study periods: The study has a treatment period and a follow-up period. Treatment period (Day 1 to Day 29) and the Follow-up Period (Day 30 to Day 181).

Study clinic visits Three clinic visits for each subject on Day 1, Day 29 and Day 181.

Safety phone call: Two safety phone calls (Day 7 and Day 91) will be conducted to collect any unsolicited Adverse Events (AEs) (on Day 7 only), Medically Attended Adverse Events (MAAEs), AEs leading to withdrawal, Serious Adverse Events (SAEs) and Adverse Event of Special Interest (AESIs), related medications and any vaccinations.

Reactogenicity data collection: Solicited AEs will be recorded daily for 7 consecutive days (or longer if the events are not resolved) following vaccination (Day 1 to Day 7) using a Subject eDiary to be completed by the subject.

Safety data collection: Unsolicited AEs will be collected for 28 days after vaccination. SAEs, MAAE, AEs leading to study withdrawal, and AESIs will be collected during the entire study period. 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 assay for homologous vaccine strains, using *cell-derived* target virus, will be performed in all subjects on serum samples collected on Days 1, 29 and 181.
- MN assay for homologous vaccine strains, using *cell-derived* target virus, will be performed in all subjects on serum samples collected on Days 1, 29 and 181.

Number of Subjects planned:

Approximately 480 subjects will be enrolled in this study, approximately 120 subjects in each treatment group.

Study Population and Subject Characteristics:

This study will enroll male and female adults aged 50 years and older who are healthy or have comorbidities that increase their risk of complications from influenza infection.

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

Study Procedures:

Written informed consent must be obtained prior to performing any study-related procedures.

On Day 1, screening evaluations will be performed and will include a review of relevant medical history, physical examination, including body temperature and an eligibility assessment.

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 29 and Day 181. Subjects will be followed up for safety for 180 days after vaccination.

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

Study Vaccines:

Regardless of the type of vaccine assigned in the trial, subjects will receive a 0.5 mL dose, administered intramuscularly into the deltoid muscle, preferably in the non-dominant arm. Haemagglutinin (HA) antigens are derived from the four influenza virus strains (A/H1N1, A/H3N2, B/Yamagata and Victoria lineage) recommended by the WHO (World Health Organization) for quadrivalent vaccines for the respective season. [redacted]

Investigational Vaccine

- Quadrivalent Subunit Inactivated Cell-derived Influenza Vaccine, which includes MF59 adjuvant.

Comparator vaccines:

- Non-adjuvanted Quadrivalent Subunit Inactivated Cell-derived Influenza Vaccine (QIVc).
- Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine, which includes MF59 adjuvant (aQIV).
- Recombinant Quadrivalent Influenza Vaccine (QIVr).

Statistical Analyses:

The primary analysis will be conducted on the immunogenicity and safety data collected up to Day 29. Exploratory comparisons of HI Geometric Mean Titer (GMTs) and MN

GMTs between treatment groups will be performed through the computation of the two-sided 95% confidence interval (CI) of the vaccine group ratio of GMTs:

GMTs aQIVc / GMTs comparator groups

To estimate the GMT ratio (adjusted analysis), a general linear model (GLM) will be fitted on log-transformed (base ten) post-vaccination HI titer as the outcome variable and terms for covariates: vaccine treatment, log 10 transformed pre-vaccination HI titer, age stratum, and vaccination history. Potential covariate interaction effects will also be examined in the fit of the GLM. From the model, an adjusted difference in the least square means (on the log scale) will be produced with 95% confidence limits. The estimated difference and the confidence limits will be back-transformed to obtain an *adjusted GMT ratio* with 95% confidence limits. Each of the four strains will be analyzed separately.

The difference in seroconversion rates (SCRs) or percentage of subjects with HI titer ≥1:40 will be presented with 95% CIs using the Miettinen and Nurminen method without and with adjustment for the age stratum. Each of the four strains will be analyzed separately.

Additionally, exploratory comparisons between groups will be performed through the computation of the two-sided 95% CI for the difference in the percentages between aQIVc vaccine and comparator groups.

Statistical Considerations for Sample Size Calculations:

A total of 480 subjects (including a 10% drop-out rate) will be enrolled in this study and are to be randomized in a 1:1:1:1 ratio to one of the four vaccine groups. Approximately one hundred twenty subjects will be enrolled in each vaccine group. More details on the sample size calculation are provided in Section 8.5.

Interim Analysis:

An interim analysis is not planned for this study.

Internal Safety Team and Data Monitoring Committee:

Because the investigational vaccine (aQIVc) has never been administered to humans, additional safety precautions have been incorporated in this study. An internal safety team (IST), independent from the clinical study, will review the safety information as soon as

data of first seven days after vaccination are available for the first 40 and 120 enrolled subjects. In addition, an independent Data Monitoring Committee (DMC) will be used for the study. See Section 3.8, Stopping/Pausing Guidelines and Section 3.9, Internal Safety Team and Data Monitoring Committee for further details.

Table 0-1: Time and Event Schedule

	Visit Type	Clinic Visit	Safety Phone Call	Clinic Visit	Safety Phone Call	Clinic Visit
	Study Day	**1**	**7**	**29**	**91**	**181**
	Visit Window (Days)	**n/a**	**-1/+3 day**	**-7/+3 days**	**+/-7 days**	**+/-7 days**
	Visit Number	**1**	**2**	**3**	**4**	**5**
Study Event	**References**					
Study Treatment						
Vaccination	Section 5.2	X				
Screening and Safety						
Informed Consent	Section 5.1.1	X[a]				
Medical History[b]	Section 5.1.2	X				
Pregnancy test[c]	Section 5.1.2	X				
Physical Exam	Section 5.1.2	X				
Targeted Physical Exam[d]	Section 5.4.1	X		X		X
Measuring body temperature	Section 5.1.2	X				
Exclusion/Inclusion Criteria	Section 4	X				
Randomization	Section 5.1.4	X				
30 Minutes Post Injection Assessment	Section 5.3	X				
Train and Dispense Subject eDiary	Section 5.3	X				
Review of eDiary data and compliance	Section 3.6.2	Ongoing during eDiary use				
Assess unsolicited AEs	Section 7.1.2	X	X	X		
Assess SAEs	Section 7.1.4	X	X	X	X	X

	Visit Type	Clinic Visit	Safety Phone Call	Clinic Visit	Safety Phone Call	Clinic Visit
	Study Day	**1**	**7**	**29**	**91**	**181**
	Visit Window (Days)	**n/a**	**-1/+3 day**	**-7/+3 days**	**+/-7 days**	**+/-7 days**
	Visit Number	**1**	**2**	**3**	**4**	**5**
Study Event	**References**					
Assess for AEs leading to withdrawal, medically attended AEs and AESIs	Section 7.1.4.1	X	X	X	X	X
Assess relevant medications and vaccinations	Section 6.5	X	X	X	X	X
Immunogenicity						
Serology blood draw	Section 5.1.5	X		X		X
Study Completion/termination	Section 5.6					X[e]

Notes: [a] Consent form(s) should be signed prior to performing any 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 pregnancy test should be done for females of childbearing potential in order to rule out any pregnancy. [d] Based on specific complaints as indicated by the subject. [e] Subjects who terminate the study early will be requested to complete all safety-related Study Completion procedures. Abbreviations: AE = adverse event; AESI = adverse event of special interest; n/a = not applicable; SAE = serious adverse event.

Definition of Terms

Term	Definition
Follow-up period	The follow-up period starts for subjects 28 days after vaccination and continues for up 180 days post-vaccination.
Previously influenza vaccinated subject	A subject that has been vaccinated at least once in the 3 previous influenza seasons.
Not-previously influenza vaccinated subject	A subject that has not been vaccinated within 3 previous influenza seasons.
Qualified healthcare professional	Any licensed health care professional who is permitted by institutional policy to perform clinical interventions and assessments such as physical examinations is trained on the study procedure(s) and who is identified within the site signature and delegation log.
Trained healthcare professionals	Any health care professional who is permitted by institutional policy, trained to perform delegated tasks, is trained on the study procedure(s) and who is identified within the site signature and delegation log.
Treatment period	The treatment period begins at the time of vaccination and ends 28 days after vaccination.
Clinic Visit	A clinic visit is a visit to the study site.
Females of non-childbearing potential	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.

List of Abbreviations

AE	Adverse event
AESI	Adverse events of special interest
aQIV	MF59-adjuvanted Quadrivalent Subunit Inactivated egg-derived Influenza Vaccine
aQIVc	MF59-adjuvanted Quadrivalent Subunit Inactivated cell-derived Influenza Vaccine
CDC	Center for Disease Control and Prevention
CHMP	Committee on Human Medicinal Products
CI	confidence interval
CRF	case report form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTAB	cetyltrimethylammonium bromide
DMC	Data Monitoring Commitee
DNA	deoxyribonucleic acid
eCRF	electronic Case Report Form
eDiaries	electronic Diaries
EC	Ethics Committee (paired with Institutional Review Board)
EDC	Electronic Data Capture
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GDPR	General Data Protection Regulation
GMFI	geometric mean fold increase
GMR	geometric mean ratio
GMT	geometric mean titer
HA	hemagglutinin
HI	hemagglutination inhibition
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Committee on Harmonization
IEC	Independent Ethics Committee
IM	intramuscular
IRB	Institutional Review Board
IRT	Interactive Response Technology
IST	Internal Safety Team
IV	Intravenous
LL	lower limit
LLOQ	Lower Limit of Quantitation
MAAEs	Medically attended Adverse Events

MCAR	Missing Completely at Random
MDCK	Madin Darby Canine Kidney
MF59	MF59C.1 adjuvant
MN	microneutralization
NA	neuraminidase
NH	Northern Hemisphere
PFS	pre-filled syringe
PO	per os, ie, by mouth
PPS	Per Protocol Set
PT	preferred term
PVRM	Pharmacovigilance and Risk Management
QIVc	Quadrivalent subunit inactivated cell-derived influenza vaccine
QIVr	Recombinant Quadrivalent influenza vaccine
RT-PCR	reverse transcription polymerase chain reaction
RTSM	Randomization and Trial Supply Management
rVE	relative vaccine efficacy
SAE	serious adverse event
SAP	Statistical analysis plan
SD	standard deviation
SCR	seroconversion rate
SDA	Source Data Agreement
SH	Southern Hemisphere
SUSAR	Suspected Unexpected Serious Adverse Reaction
US	United States
VE	Vaccine efficacy
WHO	World Health Organization

1 BACKGROUND AND RATIONALE

1.1 Background

Influenza is an infectious acute respiratory disease characterized by the abrupt onset of respiratory and systemic symptoms, such as fever, cough, sore throat and rhinitis (Temte and Prunuske 2010). Influenza occurs in annual epidemics in the northern hemisphere (NH) and southern hemisphere (SH) generally affecting individuals during the winter months in temperate climates. In tropical climates, it can occur all year round.

Influenza in humans can be caused by the influenza virus type A, B, and C, of which type A and B viruses are most clinically relevant. Type A viruses are associated with both annual epidemics and pandemics, and B viruses contribute to annual epidemics (WHO 2018). The type A viruses are further divided into different subtypes, of which the A/H3N2 and A/H1N1 viruses are the most clinically relevant for annual influenza disease burden. For influenza B, only a single type is known to exist, but 2 distinct genetic lineages are identified: Yamagata and Victoria (CDC 2019a). All influenza viruses experience some form of antigenic drift, but it is most pronounced in the influenza A virus for which new circulating variants are frequently observed over the influenza season. Such evolution of the influenza virus influences the host specificity and pathogenicity of these viruses which can differ geographically, from season to season and within a season.

Influenza is an acute and highly contagious viral infection with global circulation. Every year across the globe, there are an estimated 1 billion cases of influenza disease, of which 3 to 5 million are severe cases, resulting in 290 000 to 650 000 influenza-related respiratory deaths (WHO 2018; Iuliano et al. 2018). In the United States (US), influenza-related hospitalization rate over 15 seasons was estimated to be 309 per 100 000 in individuals 65 years and older (Zhou et al. 2012). Although the rate of hospitalization associated with influenza is lower in subjects 50 to less than 64 years of age compared to 65 years and older, the highest number of influenza illnesses and medical visits is reported for the 50 to 64 years of age cohort, which indicates also a high burden of disease in this age group (CDC 2019b).

Vaccination is the primary method for preventing influenza and its severe complications. The efficacy of the conventional influenza vaccines in the adult population is demonstrated to be high (Roshini and Miller 2019). In contrast, the efficacy in elderly individuals is significantly lower due to the aging of the immune system (ie 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).

In view of the limitations of conventional influenza vaccines in older adults, there continues to be an unmet need for a new generation of influenza vaccines that provides more consistent and broader coverage against all seasonal virus subtypes and variants (Wong and Webby 2013; Reber et al. 2012).

One approach to overcoming immunosenescence is to enhance the immune response by the addition of an adjuvant, such as the squalene and water emulsion adjuvant, MF59. The addition of MF59 increases antigen uptake, macrophage recruitment, macrophage migration, and the spectrum of antibody recognition of HA epitopes (Calabro et al. 2011; O'Hagan et al. 2012). Thus, when added to influenza vaccines, MF59 increases vaccine immunogenicity against both homologous and heterologous strains. Fluad®, Seqirus's trivalent seasonal influenza egg-based vaccine adjuvanted with MF59, has been licensed for use in Europe since 1997 and in the US since 2015. It has been shown to generate significantly higher geometric mean hemagglutination inhibition (HI) titers and rates of seroconversion than a nonadjuvanted trivalent influenza vaccine comparator in elderly subjects (Frey et al. 2014).

The investigational vaccine in this study, MF59-Adjuvanted Quadrivalent Subunit Inactivated Cell-derived Influenza Vaccine (aQIVc), combines benefits of both cell-based, and adjuvanted technologies to meet the unmet need of influenza in older adults. The cell-derived antigen provides a better match to circulating strains, therefore addressing mismatch due to egg adaptation (Hedge 2015; Lambert et al. 2010). The effect of inclusion of MF59 adjuvant to the vaccine is expected to enable increased magnitude of immune response by stimulating higher antibody responses at standard doses; increased breadth of immune response by expanding antibody repertoire, and increased duration of immune response with higher antibody response at 6 months after vaccination which is important in case of prolonged influenza seasons and/or late-season outbreaks.

1.2 Rationale

The purpose of this study is to perform an evaluation of the immunogenicity and safety of the MF59-adjuvanted Quadrivalent cell-based vaccine (aQIVc) versus other influenza vaccines, such as the non-adjuvated Quadrivalent cell-based influenza vaccine (QIVc), the MF59-adjuvanted Quadrivalent egg-based vaccine (aQIV) and the Quadrivalent recombinant influenza vaccine (QIVr). Immunogenicity and safety will be assessed in the overall study population (adults ≥50 years of age

and for the age subgroups 50-64 years and ≥65 years in order to assess the benefit/risk profile in each age population for this vaccine.

1.3 Potential Risks and Benefits

Subjects will be exposed to aQIVc or QIVc or aQIV or QIVr 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 swelling (hardness).

aQIVc is expected to provide benefit over existing conventional influenza vaccines in older adults by both the inclusion of the MF59 adjuvant and the use of antigens produced in cell culture that more closely resemble the wild-type strains (Hedge 2015; Lambert et al. 2010). With the addition of MF59, aQIVc is expected to provide a robust immune response similar to the immune response elicited after vaccination with aQIV in older adults (Frey et al. 2014).

Overall, the clinical safety experience with aQIV and QIVc in older adults, in conjunction with data from the repeat dose aQIVc toxicology study are sufficient to support the initiation of a Phase 2 safety and immunogenicity study in adults 50 years and older. In the repeat-dose toxicity study, three doses of aQIVc, containing [redacted] HA/dose, were administered by intramuscular injection to male and female rabbits at 3-week intervals. The vaccine was immunogenic and there was no evidence of local or systemic toxicity. The most common local and systemic reactions observed in the adjuvanted egg-based comparator vaccine (aQIV) in older adults were injection site pain, headache, and fatigue. Most reactions were reported as mild or moderate in intensity. The most common local and systemic reactions associated with administration of the QIVc comparator vaccine in older adults included injection site pain, erythema, induration, headache, fatigue, and myalgia. Most reactions were reported as mild or moderate in intensity. For the aQIVc vaccine, similar local and systemic reactions are to be expected as for the aQIV and QIVc vaccines.

Because the investigational vaccine (aQIVc) has never been administered to humans, additional safety precautions have been incorporated in this study (see Section 3.8, Stopping/Pausing Guidelines).

Please refer to the current Investigator's Brochure (IB) for aQIVc for a summary of potential risks and benefits of aQIVc; to the Product Information for QIVc and QIVr for a summary of potential risks and benefits of QIVc and QIVr respectively, and to the current IB for aQIV for information regarding the potential risks and benefits of aQIV.

2 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 Primary Immunogenicity Objective

1. To assess the immunogenicity of aQIVc in comparison with the QIVc, aQIV, and QIVr comparator vaccines as measured by HI assay* using *cell-derived* target viruses at 28 days after vaccination, in subjects 50-64 and ≥65 years of age and overall (adults ≥50 years).

* *In case of lack of agglutination for a specific strain using HI assay, immunogenicity for that strain will be assessed as measured by microneutralization (MN) assay as an acceptable alternative.*

For primary endpoints, refer to Section 8.1.1, Primary Endpoints.

2.2 Secondary Objectives

2.2.1 Secondary Immunogenicity Objective(s)

1. To assess the immunogenicity of aQIVc in comparison with the QIVc, aQIV, and QIVr comparator vaccines as measured by HI assay* using *cell-derived* target viruses at 180 days after vaccination, in subjects 50-64 and ≥65 years of age and overall.
2. To assess the immunogenicity of aQIVc in comparison with the QIVc, aQIV, and QIVr comparator vaccines as measured by MN assay using *cell-derived* target viruses at 28 and 180 days after vaccination, in subjects 50-64 and ≥65 years of age and overall.

* *In case of lack of agglutination for a specific strain using HI assay, immunogenicity for that strain will be assessed as measured by MN assay as an acceptable alternative.*

For secondary immunogenicity endpoints, refer to Section 8.1.2.2, Secondary Immunogenicity Endpoints.

2.2.2 Secondary Safety Objectives

1. To assess the reactogenicity of aQIVc as compared to QIVc, aQIV, and QIVr in subjects 50-64 and ≥65 years of age and overall for 7 days after vaccination.
2. To assess the safety of study vaccines in subjects 50-64 and ≥65 years of age and overall for 180 days after vaccination.

For secondary safety endpoints, refer to Section 8.1.2.1, Secondary Safety Endpoints.

2.3 Exploratory Objectives

1. The immunogenicity of aQIVc in comparison with the QIVc, aQIV and QIVr comparator vaccines as measured by HI assay may be assessed using *egg-derived* target viruses at 28 days after vaccination, in subjects 50-64 and ≥65 years of age and overall.
2. Additional exploratory immunogenicity analyses may be conducted to further characterize the immune response of aQIVc.

For exploratory endpoints, refer to Section 8.1.3, Exploratory Endpoints.

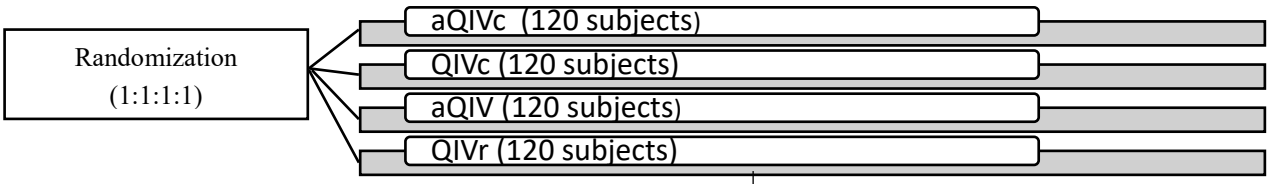
The results of these exploratory analyses may be presented in an addendum to the Clinical Study Report (CSR).

3 STUDY DESIGN

3.1 Overview of Study Design

Experimental design: Phase 2, randomized, stratified, controlled, observer-blind, multi-center study in approximately 480 male and female adults aged 50 years and older who are healthy or have co-morbidities which increase their risk of complications from influenza infection. An overview of the study design presented in Figure 3-1.

Figure 3-1: Overview of the Study



Day 1 Clinic Visit Visit 1	Day 7 Safety phone call Visit 2	Day 29 Clinic Visit Visit 3	Day 91 Safety phone call Visit 4	Day 181 Clinic Visit Visit 5
Randomization	Assessment of safety	Assessment of safety/ review of reactogenicity data	Assessment of safety[a]	Assessment of safety[a]
Serology blood draw		Serology blood draw		Serology blood draw
Vaccination				Study Completion

Notes: [a]During this call/visit, non-serious unsolicited adverse events will not be collected. Abbreviations: aQIVc= MF59-adjuvanted Quadrivalent Subunit Inactivated Cell-derived Influenza Vaccine. QIVc= Quadrivalent subunit inactivated cell-derived influenza vaccine. aQIV= MF59-adjuvanted Quadrivalent Subunit Inactivated egg-derived Influenza Vaccine. QIVr= Recombinant Quadrivalent influenza vaccine.

Duration of the study: The study duration is approximately 6 months for each subject. The study will be conducted in one single season.

Vaccination schedule: Single intramuscular injection on Day 1.

Investigational Vaccine: aQIVc.

Comparator Vaccines: QIVc, aQIV and QIVr.

Treatment groups:

Enrolled subjects will be randomized to one of the four treatment groups in a 1:1:1:1 ratio.

1. aQIVc group: approximately 120 subjects receiving one dose of aQIVc on Day 1.
2. QIVc group: approximately 120 subjects receiving one dose of QIVc on Day 1.
3. aQIV group: approximately 120 subjects receiving one dose of aQIV on Day 1.
4. QIVr group: approximately 120 subjects receiving one dose of QIVr on Day 1.

Randomization: an Interactive Response Technology (IRT) will be used in the study with stratification factors for age (≥50 to 64 and ≥65 years, with about 50% of the subjects 50-64 years of

age and about 50% of the subjects ≥65 years of age for each treatment group) and history of any influenza vaccination within 3 previous influenza seasons (yes/no). Approximately 40% of subjects in each age subgroup for each treatment group should not have been vaccinated with an influenza vaccine within the 3 previous influenza seasons.

Blinding: Observer-blind study.

Blood sample schedule: Three blood samples will be collected from all subjects on Day 1, Day 29 and Day 181.

Data collection: electronic Case Reporting Form (eCRF).

Study periods: The study has a treatment period and a follow-up period. Treatment period (Day 1 to Day 29) and Follow-up Period (Day 30 to Day 181)

Study clinic visits: Three clinic visits for each subject on Day 1, Day 29 and Day 181.

Safety phone call: Two safety phone calls (Day 7 and Day 91) will be conducted to collect any unsolicited Adverse Events (AEs) (on Day 7 only), MAAE, AEs leading to withdrawal, Serious Adverse Events (SAEs) and AESIs, related medications and any vaccinations.

Reactogenicity data collection: Solicited AEs will be recorded daily for 7 consecutive days (or longer if the events are not resolved) following vaccination (Day 1 to Day 7) using a Subject eDiary as completed by the subject.

Safety data collection: Unsolicited AEs will be collected for 28 days after vaccination. SAEs, MAAEs, AEs leading to study withdrawal, and AESIs will be collected during the entire study period. 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 assay for homologous vaccine strains, using cell-derived target virus, will be performed in all subjects on serum samples collected on Days 1, 29 and 181.
- MN assay for homologous vaccine strains, using cell-derived target virus, will be performed in all subjects on serum samples collected on Days 1, 29 and 181.

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.

Since the manufacturing process of aQIVc and QIVc is the same, with the exception of the addition of the MF59 adjuvant in aQIVc, QIVc is chosen as a comparator to assess the adjuvant effect of the addition of MF59 in aQIVc in terms of immunogenicity.

aQIV and QIVr are chosen as comparators to assess the immunogenicity and safety of aQIVc versus 'enhanced' influenza vaccines that are recommended for older adults in some regions.

3.3 Justification for Dose

The selected dose and formulation of aQIVc ([redacted] of HA of each viral strain and [redacted] of MF59 per dose) is expected to be well tolerated and to induce a higher immune response compared to conventional influenza vaccines. [redacted] Safety profiles of aQIV and QIVc have been well characterized in both younger and older adults. No safety concerns were observed from the aQIV and QIVc clinical studies.

3.4 Study Period

Each subject should expect to participate in the study for approximately 6 months, from the time of enrolment through the last study visit.

3.5 Blinding Procedures

The study is designed as an observer-blind study. Observer-blind means that during the course of the study designated and trained unblinded nurse(s), physician(s), or other qualified health care professional(s) will be responsible for administering the study vaccines to the subjects. They will be instructed not to reveal the identity of the study vaccines either to the subject or to the investigative site personnel (i.e., investigator and study nurse) involved in the 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, data entry or data review such as safety assessments and/or collect study data after the vaccinations. Study vaccines will be assigned through an IRT system.

Details of the IRT unblinding procedures will be described in the IRT Manual. If unblinding occurs, either accidental or out of necessity, the Sponsor should be notified promptly.

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

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.
- 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 28 days following vaccination (Day 1 through Day 29).
- SAEs, MAAEs, AEs leading to withdrawal from the study, AESIs as collected from Day 1 through Day 181.
- Concomitant Medications/vaccinations (as defined in Section 6.5).
- Reason for early study termination.

All data collected must only be identified using the Sponsor 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 eDiary and collected on Case Report Forms (eCRFs).

Subject eDiary

Electronic Diaries (eDiaries), hereafter referred to as Subject eDiaries, will be the only source document allowed for solicited local and systemic adverse events (including body temperature

measurements), starting after the initial 30-minute post-vaccination period at the clinic, 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 health care staff should review the Subject's eDiary data and monitor the Subject's eDiary status for compliance on an ongoing basis during eDiary use (Day 1 to Day 7) or longer if events are not resolved.

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 post-vaccination period.
3. Any new safety information reported during the site visit (including a solicited reaction) cannot be entered into the Subject eDiary. Such information must be described in the source notes as a verbally-reported event. Any adverse reaction reported in this fashion must be described as an unsolicited reaction and therefore entered on the adverse event 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 Sponsor-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, 29, and 181.
- Urine at Day 1 for females of childbearing potential in order to rule out any pregnancy.

The processing of each specimen should be completed by a qualified site member and in accordance with the study-specific manual. See Clinical Specimen Laboratory Manual for additional details. The testing of clinical specimens (with the exception of the pregnancy test) will be performed by the Sponsor 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 on Day 1 before vaccination and at Days 29 and 181.

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 approximately 30 mL.

In addition, subjects between 50-64 years of age (maximum of 50 subjects) may be asked to voluntarily provide an extra blood sample of 50 mL at Day 29, 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. It will be at the discretion of the investigator to decide whether the subject is eligible to provide this extra blood sample.

Urine Specimens

Urine will be collected for pregnancy testing in females of childbearing potential. Urine will be collected on Day 1 before vaccination, results will be recorded in the source document and eCRF. Testing will be done on the study site.

3.8 Stopping/Pausing Guidelines

aQIVc has never been administered to humans. Therefore, additional safety precautions have been included in this study. The IST, which is independent of the clinical study team involved in the execution of the study, will review the safety information at two timepoints during the study conduct, using pause rules as provided in Table 3-1. Safety reviews by the IST will be performed as soon as a 7-day safety follow-up data are available for the first 40 and 120 enrolled subjects. In addition, ad-hoc safety reviews can be scheduled if needed. If a pause rule is met or any safety concern is identified by the IST, the enrolment into the study and study vaccination will be paused pending the independent Data Monitoring Committee (DMC) review. It is the Sponsor's responsibility to put the enrolment (or the study vaccination) on hold at all sites via the IRT. The DMC will review all available safety

data and make a recommendation to the Sponsor whether the study should be permanently stopped, modified or continue unchanged. The final decision will be made by the Sponsor in consultation with the DMC (and, if needed, the Investigators). The decision will be documented and provided in writing to the investigators.

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

Table 3-1: Pause Rules for Planned IST Review

No	Pause Rule Criteria	No. of subjects
1	Any SAE that cannot be reasonably attributed to a cause other than vaccination[a], according to the Investigator's assessment, within 28 days post-vaccination.	≥1 subject
2	Severe systemic hypersensitivity such as anaphylaxis, within 24 hours after study vaccination.	≥1 subject
3	Any Grade 3 (severe) local solicited AE lasting ≥2 consecutive days, within 7 days postvaccination	≥25% (and ≥2 subjects) in aQIVc group
4	Any Grade 3 (severe) systemic solicited AE lasting ≥2 consecutive days, within 7 days postvaccination	≥25% (and ≥2 subjects) in aQIVc group
5	Any severe unsolicited AE that cannot be reasonably attributed to a cause other than vaccination[a], within 7 days postvaccination	≥10% (and ≥2 subjects) in aQIVc group

Notes: [a] at least probably related. Abbreviations: AE = adverse event; aQIVc = MF59-adjuvanted Quadrivalent Subunit Inactivated Cell-derived Influenza Vaccine IST = internal safety team; No. = number; SAE = serious advesre event.

3.9 Internal Safety Team and Data Monitoring Committee

An IST and DMC will be established to evaluate subject safety throughout the study at a group and subject level, as appropriate. The responsibilities, roles, and procedures (including blinding) of the IST and DMC are described in the IST Charter and DMC Charter.

3.10 End of Study

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

Evaluation of the primary and/or secondary immunogenicity objectives requires the testing of biological samples from the study subjects, which can only be completed after all samples are collected. The last samples for the analysis of the primary and/or secondary objectives will be taken on Day 181. For the purpose of this protocol, the end of study is defined as the completion of the testing of such biological samples, to be achieved no later than 8 months after the collection of the last biological sample Day 181.

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 years of age and older 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[1].

[1]A Subject is considered to be compliant if the Investigator judges that the subject will complete the Subject eDiary, return for all the follow-up visits and will be available for the telephone calls as scheduled in the study. In some situations support from a caregiver is allowed for the completion of the eDiary; this is up to the judgement of the Investigator.
1

4. Males, females of non-childbearing potential or females of childbearing potential[2] who are using an effective birth control method, at least 30 days prior to informed consent,[3] 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 informed consent and who do not plan to do so until 2 months after the study vaccination.
2. Progressive, unstable or uncontrolled clinical conditions.
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 adverse event 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 administration of vaccines or blood draw.
7. Abnormal function of the immune system resulting from:
   a) Clinical conditions

[2] 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.

[3] 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.

1

b) Systemic administration of corticosteroids (PO/IV/IM)[4] at a dose of ≥ 20 mg/day of prednisone or equivalent for more than 14 consecutive days within 90 days prior to informed consent[5].

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.
9. Received an investigational or non-registered medicinal product within 30 days prior to vaccination.
10. Individuals who received any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrolment in this study or who are planning to receive any vaccine within 28 days from the study vaccines.
11. Study personnel or immediate family or household member of study personnel.
12. Receipt of any influenza vaccine within 6 months prior to vaccination in this study, or plan to receive an influenza vaccine during the study period.
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.

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 acute use of any systemic antipyretics and/or analgesic medications within 24 hours prior to vaccination. Under such circumstances, a subject may be considered eligible for study enrolment after the appropriate window for the delay has passed and inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

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

[5] Topical, inhaled and intranasal corticosteroids are permitted. Intermitted use (one dose in 30 days) of intra-articular corticosteroids are also permitted.

4.4 Criteria for Repeat Vaccination in the Study

Not applicable.

4.5 Premature Withdrawal from Study

Subjects may decide to 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 adverse event.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation and eCRF. The investigator should make every attempt to evaluate the subject's safety, including the resolution of ongoing AEs, at the time of premature withdrawal. If a subject wants to withdraw from the study before the vaccine is administered or prior to the last planned study visit, the subject will be asked to be followed for safety for the duration of the study. When a subject withdraws or is withdrawn, from the study, the procedures described in Section 5.6.1, Early Termination Visit should be completed if possible. Subjects that have been prematurely withdrawn from the study will not be replaced.

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 complete a Pregnancy Report eCRF (initial report) as soon as possible after learning of pregnancy occurrence (see Section 7.1.6, Pregnancies for further details). If the pregnant subject withdraws from the study for any of the 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; Adverse event, 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 End of Study 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 the 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. The 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., a reason other than AE). If the subject intends to withdraw consent from the study, the investigator should clarify and document 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.

If a subject withdraws consent but does not revoke the HIPAA authorization (only applicable to US sites), the Sponsor will have full access to the subject's medical records, including early termination visit information. If a subject revokes only the HIPAA authorization, the Sponsor will have full access to all of the subject's medical records prior to the date and time of written revocation.

Lost to Follow-Up

For subjects who fail to show up for the Study Completion visit, or for three consecutive 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 early 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 End of Study 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: the Sponsor's decision to terminate the study, subject meeting a pre-specified withdrawal criterion, subject discontinuation for insurance issues, moving, no time, etc. This reason should be noted at the End of

Study eCRF page and any ongoing AEs at the time of study withdrawal must be followed until resolution/stabilization. Note: If the clinical study is prematurely terminated by the Sponsor, the investigator is to promptly inform the study subjects and local EC/IRB and should assure appropriate therapy and follow up for the subjects. All procedures and requirements pertaining to the archiving of study documents should be followed. All other study materials (study medication/vaccines, etc.) must be returned to the Sponsor.

Protocol Deviation

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

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

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 both Table 0-1 and below in Table 5-1.

Table 5-1: Study Procedures

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

5.1 Pre-vaccination Procedures: Screening/Randomization

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

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 informed consent process may be conducted earlier, but within 10 days prior to Day 1. Subjects that are willing to provide an extra blood sample for research purposes should provide specific consent for this assessment. 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. Additional specifics

regarding the informed consent procedures are described in Section 13.2, Informed Consent Procedures.

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 cannot read, and who reads the informed consent form (ICF) and any other written information supplied to the subject. After the written ICF 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. The subject's unique Screening Number will be documented in the Screening and Enrolment log. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in Section 4, Selection of Study Population and evaluated during this screening procedure.

The 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 influenza vaccination in the 3 years prior to subject enrolment, concomitant medications, and previous and ongoing illnesses or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an adverse event that occurs during study participation if it represents an exacerbation of an underlying disease/pre-existing problem. In case a subject is recruited from outside the clinic, verbal recall of medical history and associated concomitant medication is acceptable if medical records are not available.

If applicable, prior and concomitant medications or vaccinations should be collected (refer to Section 6.5, Prior and Concomitant Medications and Vaccines for further details). The use of any 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, on a separate eCRF, 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) found in Appendix 1, will be used. The risk assessment, which incorporates comorbidity among other baseline characteristics such as outpatient visits during the previous year and previous hospitalizations due to pneumonia or influenza, is a validated predictor of the risk of complications from influenza in elderly subjects. Using this model, a score of <50 is considered low risk and a score of ≥ 50 is considered high risk. Determination of pre-existing medical conditions should be made by the investigator based on his or her clinical judgment. The investigators will be given guidance for the completion of the eCRF.

Pre-vaccination 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. Measurements must be conducted by a trained health care professional. For women of childbearing potential, a pregnancy test should be performed (see Section 3.7, Collection of Clinical Specimens).

A general physical examination is to be performed by a qualified health care practitioner. These data will be written in the source document (see Section 9.1, Source Documentation). Should the physical assessment reveal any abnormal values or events, these must be documented in the eCRF.

In the event that the individual is determined ineligible for study participation, he/she is considered a screen failure. Re-screening with a new screening number, or further attempts to enroll or randomize the subject are not permitted. The reason for screen failure must be documented in the Screening and Enrolment log. If the individual is determined to be eligible for the study, he/she will be enrolled in the study.

5.1.3 Enrolment

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

5.1.4 Randomization

Enrolled subjects will be randomized to one of the four treatment groups in a 1:1:1:1 ratio with stratification factors for age (≥50 to 64 years and ≥65 years) and history of any influenza vaccination

within 3 previous influenza seasons (yes/no). Approximately 40% of subjects in each age subgroup for each treatment group should not have been vaccinated within the 3 previous influenza seasons.

The subject will be randomized in the IRT/RTSM system. The subject will receive a unique Subject ID that will be used for all eCRFs and associated study documentation for the duration of the study. After randomization, the Screening Number ceases to be used and remains in the Screening and Enrolment Log only. The list of randomization assignments is produced by the IRT service provider and approved by the Sponsor according to the applicable Sponsor's Standard Operating Procedure (SOP).

If for any reason, after signing the 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 Enrolment 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, the subject has to be discontinued, and the reason should be recorded at the End of Study CRF. The information on discontinued subjects should be kept distinct in the source documentation from randomization failures.

5.1.5 Blood Draw

Prior to vaccination, approximately 10 mL of blood will be drawn from subjects for the immunogenicity testing (see Section 3.7, Collection of Clinical Specimens).

5.2 Vaccination Clinic Visit

Vaccination will be performed on Day 1.

Ensure the blood sample is taken **prior** to vaccination.

After completing the pre-vaccination procedures on Day 1, the vaccine will be administered according to the procedures described in Section 6.3, Vaccine Preparation and Administration. The blinding procedures as described in Section 3.5, Blinding Procedures should be taken into account.

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

5.3 Post-Vaccination Procedures

The following post-vaccination 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 post-vaccination AE's (unsolicited adverse events). Record all safety data collected during this time in the subject's source document.

Subject eDiary Training

A Subject eDiary will be dispensed (provisioned device or their own device) in this study to document solicited adverse events. The Subject eDiary is the only source for the 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 adverse events and body temperature. The measurement of solicited local adverse events is to be performed using the ruler provided by the site.

The subject should be instructed on 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. If the subject has a fever, 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 adverse events 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. Any individual that 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. 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 (or longer if the events are not resolved). Diary data should be submitted every day.

Note: The subject 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 diary reminder alerts, clinic visits or safety phone calls.

The subject should be reminded of the next planned study activity; a safety phone call on Day 7. The subject will be reminded to complete the Subject eDiary and to contact the site if there are any questions, and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit or to a visit to/by a doctor or is otherwise of concern.

5.3.1 eDiary Reminder Alerts

The subject will receive daily reminders via the Subject eDiary device's in-built audio-visual alarms to alert the user to complete the diary during the post-vaccination period. From Day 1 through Day 7, the users will receive daily alerts through the Subject eDiary to record the presence (yes/no) of any medically attended (defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider) unsolicited AE, or any unsolicited AE of concern. In case of such events, the subject will be instructed to contact the site as soon as possible to report the event(s).

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

- Non-compliance (i.e. failing to enter or transmit diary data),
- Reporting of any severe solicited reactions.

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

5.4 Post -Vaccination Visits

Post-vaccination clinic visits or safety calls will be performed on: Day 7 (Safety Phone Call), Day 29 (Clinic Visit), Day 91 (Safety Phone Call) and Day 181 (Clinic Visit).

5.4.1 Follow-up Clinic Visit

Post-vaccination clinic visits will be performed on Day 29 (visit 3), and at Day 181 (visit 5) (see Section 5.6 for assessments to be performed at Study Completion Visit). In the event that a clinic visit is not possible, a home visit may be considered.

During the follow-up clinic visit on Day 29, the subject will be interviewed to determine if any unsolicited AEs occurred including SAEs, AESIs, MAAEs, and if any concomitant medications or vaccines were taken/received in the time since the last clinic visit. 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 adverse events 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 AE eCRF, as specified in Section 7.1, Safety Assessments.

If applicable, a qualified healthcare professional will perform a targeted physical examination if necessary based on specific complaints indicated by the subject.

The subject will be asked to return any electronic device that was provisioned for the collection of the solicited AEs, if applicable.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 subjects (maximum of 50 subjects) who agreed to provide a blood sample, for future research not related to this study.

In addition, 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 hospitalization or an emergency room visit or has any other concern.

5.4.2 Safety Follow-up Calls

Safety follow-up calls will be performed on Days 7 and 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 as guidance, which will facilitate the collection of relevant safety information. The subject will be interviewed, and information relating to unsolicited adverse events. The following unsolicited adverse events will be collected:

Day 7 Safety Follow-up Call

- All unsolicited adverse events
- SAEs, AESIs, MAAEs, and AEs leading to withdrawal
- Concomitant medication or vaccinations associated with the events above.

Day 91 Safety Follow-up Call

- SAEs, AESIs, MAAEs, and AEs leading to withdrawal
- Concomitant medication or vaccinations associated with the events above.

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

In addition, the site should schedule the next study activity 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 hospitalization or an emergency room visit or has any other concern.

5.5 Unscheduled Visits

Not applicable to this study.

5.6 Study Completion Visit

The study completion visit will occur on Day 181 and will be a clinic visit. The date of study 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 at the end of the Study 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 clinic visit, the subject will be interviewed to determine if any SAEs, AESIs or medically attended adverse events occurred and if any associated concomitant medications

or vaccines were taken/received in the time since the last safety assessment. 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 adverse events 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.

If applicable, a qualified healthcare professional will perform a targeted physical examination based on specific complaints indicated by the subject. This is a physical examination that will include an examination of organ systems that are relevant to the investigator based on a review of the subject's reported influenza complications and the use of medication to treat these complications.

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 end of the Study 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 discontinues the study, the investigator will perform the safety assessment procedures during study completion (see Section 5.6, Study Completion 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 and subjects who were eligible and enrolled but failed to be randomized.

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 end of the Study 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 and in the Investigators Manual.

6.1 Study Vaccine(s)

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

Investigational Vaccine: aQIVc

Quadrivalent Subunit Inactivated Cell-derived Influenza Vaccine, which includes MF59 adjuvant. HA antigens are derived from the four influenza virus strains (A/H1N1, A/H3N2, B/Yamagata and Victoria lineage) recommended by the WHO (World Health Organization) for quadrivalent vaccines for the respective season. [redacted] of each HA antigen is present in 0.5 mL of the vaccine, which is formulated in a pre-filled syringe (PFS). The full composition of the vaccine is reported in Table 6-1.

Table 6-1: aQIVc Vaccine Composition

Name of Ingredients	Final Quantity per 0.5mL dose	Function
Active Ingredients HA and NA antigens from the influenza virus strains recommended by the WHO for the respective season • Strain A1 (H1N1 subtype) • Strain A2 (H3N2 subtype) • Strain B1 (B/Victoria lineage) • Strain B2 (B/Yamagata lineage)	[redacted] HA (per strain)	HA Antigen (active ingredient)
Adjuvant		
Squalene	[redacted]	Oil phase
Polysorbate 80	[redacted]	Surfactant
Sorbitan trioleate	[redacted]	Surfactant
Sodium citrate	[redacted]	Buffer
Citric acid	[redacted]	Buffer
Other Ingredients		
Phosphate-buffered saline		
Sodium chloride	[redacted]	Isotonic acid
Potassium chloride	[redacted]	Isotonic acid
Magnesium chloride hexahydrate	[redacted]	Stabilizer
Disodium phosphate dihydrate	[redacted]	Buffer
Potassium dihydrogen phosphate	[redacted]	Buffer
Water for injection	Up to 0.50 mL	Diluent
*		

Notes:* residues of special relevance are MDCK cell protein ([redacted]), protein other than HA ([redacted]), MDCK cell deoxyribonucleic acid (DNA) ([redacted]), cetyltrimethlyammonium bromide (CTAB) ([redacted]), beta-propiolactone ([redacted]), polysorbate 80 ([redacted]), and sorbitan trioleate ([redacted]). Abbreviations: aQIVc = MF59- adjuvanted Quadrivalent Subunit inactivated cell-derived Influenza Vaccine; CTAB = cetyltrimethlyammonium bromide; DNA = deoxyribonucleic acid; HA = hemagglutinin; MDCK = Madin-Darby Canine Kidney; NA = neuraminidase; WHO = World Health Organization.

Comparator vaccine: aQIV

Quadrivalent Subunit Inactivated Egg-derived Influenza Vaccine, which includes MF59 adjuvant. HA antigens are derived from the four influenza virus strains (A/H1N1, A/H3N2, B/Yamagata and Victoria lineage) recommended by the WHO for quadrivalent vaccines for the respective season. Fifteen (15) µg of each HA antigen is present in 0.5 mL of the vaccine, which is formulated in a PFS. The full composition of the vaccine is reported in Table 6-2.

Table 6-2: aQIV Vaccine Composition

Names of Ingredients	Quantity per 0.5 mL dose	Function
Active Ingredients HA and NA antigens from the influenza virus strains recommended by the WHO for the manufacture of influenza vaccine for the season A/ (H1N1) A/ (H3N2) B/ (Yamagata lineage) B/ (Victoria lineage)	15 µg HA (per 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 Buffer		
Sodium chloride	[redacted]	Isotonic aid
Potassium chloride	[redacted]	Buffer
Potassium dihydrogen phosphate	[redacted]	Buffer
Disodium phosphate dihydrate	[redacted]	Buffer
Magnesium chloride hexahydrate	[redacted]	Stabiliser
Calcium chloride dihydrate	[redacted]	Stabiliser
Water for injection	up to 0.50 mL	Diluent
*		

Notes: *residues of special relevance are cetyltrimethlyammonium bromide (CTAB), chicken proteins such as ovalbumin, formaldehyde, kanamycin and neomycin sulphate. Abbreviations: aQIV = MF59-adjuvanted Quadrivalent Subunit Inactivated egg-derived Influenza Vaccine; CTAB = cetyltrimethlyammonium bromide; HA = hemagglutinin; NA = neuraminidase; WHO = World Health Organization

Comparator vaccine: QIVc

Non-adjuvanted Quadrivalent Subunit Inactivated Cell-derived Influenza Vaccine. HA antigens are derived from the four influenza virus strains (A/H1N1, A/H3N2, B/Yamagata and Victoria lineage) recommended by the WHO for quadrivalent vaccines for the respective season. Fifteen (15) µg of each HA antigen is present in 0.5 mL of the vaccine, which is formulated in a PFS. The full composition of the vaccine is reported in Table 6-3.

Table 6-3: QIVc Vaccine Composition

Names of Ingredients	Quantity per 0.5 mL dose	Function
Active Ingredients HA and NA antigens from the influenza virus strains recommended by the WHO for the manufacture of influenza vaccine for the season A/ (H1N1) A/ (H3N2) B/ (Yamagata lineage) B/ (Victoria lineage)	15 µg HA (per strain)	Active ingredient
Other Ingredients		
Buffer M (PBS) pH 7.2		
Sodium chloride	[redacted]	Isotonic aid
Potassium chloride	[redacted]	Buffer
Magnesium chloride hexahydrate	[redacted]	Stabilizer
Disodium hydrogen phosphate dihydrate	[redacted]	Buffer
Potassium dihydrogen phosphate	[redacted]	Buffer
Water for injection	Up to 0.5 mL	Diluent
*		

Notes: * residues of special relevance are cetyltrimethlyammonium bromide (CTAB), polysorbate 80, and β-propiolactone.
Abbreviations: CTAB = cetyltrimethlyammonium bromide; HA = hemagglutinin; NA = neuraminidase; QIVc = Quadrivalent Subunit Inactivated Cell-derived Influenza Vaccine; WHO = World Health Organization.

Comparator vaccine: QIVr

Recombinant Quadrivalent Influenza Vaccine HA antigens are derived from the four influenza virus strains (A/H1N1, A/H3N2, B/Yamagata and Victoria lineage) recommended by the WHO for quadrivalent vaccines for the respective season. Forty-five (45) µg of each HA antigen is present in

0.5 mL of the vaccine, which is formulated in a PFS. The full composition of the vaccine is reported in Table 6-4.

Table 6-4: QIVr Vaccine Composition

Names of Ingredients	Quantity per 0.5 mL dose	Function
Active Ingredients HA antigens from the influenza virus strains recommended by the WHO for the manufacture of influenza vaccine for the season A/ (H1N1) A/ (H3N2) B/ (Yamagata lineage) B/ (Victoria lineage)	45 µg HA (per strain)	Active ingredient
Other Ingredients		
Sodium Chloride	4.4 mg	Isotonic Acid
Monobasic sodium phosphate	0.195 mg	Inorganic salt
Dibasic sodium phosphate	1.3 mg	Buffer
Polysorbate 20	27.5 µg	Solubilizing agent
Triton X-100	≤ 100 µg	Detergent
*		

Notes:* residues of special relevance are baculovirus and Spodoptera frugiperda cell proteins (≤ 19 µg), baculovirus and cellular DNA (≤ 10 ng), and Triton X-100 (≤ 100 µg). Abbreviations: DNA = deoxyribonucleic acid; HA = hemagglutinin; QIVr = Recombinant Quadrivalent Influenza Vaccine; WHO = World Health Organization.

6.2 Non-Study Vaccines

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

6.3 Vaccine Preparation and Administration

The investigator or designee will be responsible for oversight of the administration of the vaccine to subjects enrolled in the study according to the procedures stipulated in this study protocol. Refer to the Investigator's Manual for additional details. 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.

All vaccines are to be provided in PFS, each with an injectable volume of approximately 0.5 mL. The full volume contained in the PFS is to be administered.

Vaccination will be performed intramuscularly, preferably in the deltoid muscle of the non-dominant arm. Detailed administration instructions will be provided to investigators prior to the study start.

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

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

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 the vaccine, the vaccination site is to be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. **DO NOT inject intravascularly.**

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

6.4 Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was 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 the 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 adverse event and as a Protocol Deviation. If the vaccine administration error or overdose is associated with a serious adverse event (SAE), it must be reported as such within 24 hours to the Sponsor.

6.5 Prior and Concomitant Medications and Vaccines

Prior medications and vaccines

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

All medications and vaccines 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 and Non-Study Vaccinations eCRF.

In addition, all medications and vaccines described in the inclusion and exclusion criteria are considered prior medications for this protocol, 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 of ≥20 mg/day of prednisone or equivalent 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.

Please note that when the subject is using any of these medications or vaccines, the subject should not be enrolled in the study.

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

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

Concomitant medications and vaccines

Concomitant medications include all medications (including vaccines) taken by/administered to the subject at and after enrolment and must be documented on the Concomitant Medications eCRF.

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

- All concomitant medications from Day 1 to Day 29.
- All medications associated with SAEs, MAAEs, AESIs, and AEs that lead to premature withdrawal from the study, from Day 1 to study completion.
- All vaccines, including any seasonal or pandemic influenza 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 after enrolment until end Day 181 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 of vaccines.
- Appropriate labeling of all study vaccines provided, that 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 to the Sponsor of the temperature range during shipment from the Sponsor to the investigator's designated storage location in the correct range (2°C to 8°C/ 36°F to 46°F)
  - Report any temperature deviation and do not use vaccines until further confirmation by the Sponsor or delegate that the vaccines are authorized for use.
- Proper storage of the study vaccines, including:
  - Storage in a secure, locked, temperature-controlled location.
  - Proper storage according to the instructions specified on the labels and in the Investigators Manual.
  - Appropriate record-keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.
- Appropriate use of the study vaccines, including:
  - Not use of vaccines prior to receipt of authorization for use from the Sponsor.
  - Use only in accordance with the approved protocol.
  - Proper handling, including confirmation that the vaccine has not expired prior to administration.
  - Appropriate documentation of the 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 the destruction of study vaccines.
- Complete record keeping of vaccine use, wastage, return or destruction, including documentation of:
  - Copy of the site's procedure for the destruction of hazardous material.

– The number of doses destroyed, date of destruction, destruction code (if available), method of destruction, and name of individual performing destruction.

Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the Sponsor provides written authorization for use. In the event that their 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 the 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 adverse events routinely monitored in vaccine studies as indicators of reactogenicity.

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

The period of observation for AEs extends from the time the subject signs informed consent until he or she completes the specified safety follow-up period of 180 days or terminates early (whichever comes first). AEs occurring after the informed consent form is signed but prior to receiving the study vaccine will be documented as an adverse event and recorded within the source document. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from "treatment-emergent" AEs (AEs occurring after administration of the study vaccine). Adverse events are

collected as either solicited or unsolicited adverse events. Solicited events are derived from organized data collection systems, such as Subject Diaries or interviews.

7.1.1 Solicited Adverse Events

The term "reactogenicity" refers to solicited signs and symptoms ("solicited adverse events") occurring in the hours and days following vaccination, to be collected by the subject for 7 consecutive days (Day 1 to Day 7), using a pre-defined Subject eDiary. If a solicited local or systemic adverse event continues beyond day 7 after vaccination, it will continue to be recorded in the Subject eDiary.

Each solicited AE is to be assessed according to a defined severity grading scale; see specifics of the solicited event and grading system below in Table 7-1.

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

Solicited Event	Grade 1/Mild	Grade 2/Moderate	Grade 3/Severe
Injection site pain	No interference with daily activity	Interferes with daily activity	Prevents daily activity
Erythema	25-50 mm	51-100 mm	> 100 mm
Induration	25-50 mm	51-100 mm	> 100 mm
Loss of appetite	Eating less than usual with no effect on normal activity	Eating less than usual /interfered 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
Fever	38.0 - 38.4 °C 100.4 – 101.1 °F	38.5 – 38.9 °C 101.2 – 102.0 °F	≥39.0 °C ≥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".

The study staff must review the data entered into the Subject eDiary as described in Section 3.6.2, Tools Used for Data Collection and Section 5.4, Post-vaccination Visits.

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 that leads to an unscheduled visit to a healthcare provider (MAAE, see Section 7.1.3, Evaluation of Adverse Events).
- 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 a serious AE (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 has signed the informed consent.

Potential unsolicited AEs may be medically attended (defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider), or were of concern to the subject. In case of such events, subjects will be instructed to contact the site as soon as possible to report the event(s). The detailed information about the reported unsolicited AEs will be collected by the qualified site personnel during the interview and will be documented in the subject's records.

The period of observation for AEs extends from the time of informed consent until the subject either completes the specified safety follow-up period (Day 181) or at early study termination.

All unsolicited AEs that start during the treatment period (Day 1 to Day 29) will be recorded in the eCRF. During the follow-up (Day 30 to Day 181), unsolicited AEs that meet any reporting criterion (an SAE, AESI, AE leading to withdrawal or a MAAE) are to be recorded in the eCRF.

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 on the AE page. In other words, the practice of reporting only symptoms (e.g., "cough" or "ear pain") are better reported according to the underlying cause (e.g., "asthma exacerbation" or "otitis media").

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

Mild: transient with no limitation in normal daily activity.

Moderate: some limitations in normal daily activity.

Severe: unable to perform normal daily activity.

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

1. Not Related

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

2. Possibly Related

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

3. Probably Related

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

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

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

- Medically attended adverse event: An AE that leads to a visit to a healthcare provider.
- AESI see Section 7.1.4.1, Adverse Events of Special Interest.

- AEs leading to withdrawal: adverse events leading to study withdrawal.

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

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

It should be noted that a severe AEs 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 the relationship of the event to the study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the Sponsor as related/suspected events.

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

1. Related/suspected

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

2. Not Related

The SAE is not related if exposure to the study vaccine has not occurred, **or** the occurrence of the SAE is not reasonably related in time, **or** the SAE is considered unlikely to be related to using 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 Product Information or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

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

7.1.4.1 Adverse Events of Special Interest

Adverse events of Special Interest (AESI)s are a pre-defined list of adverse events that are of potential immune-mediated medical conditions; the list can be found in Appendix 2.

Subjects will be assessed at each clinic visit and safety phone call 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 health care 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 SAE Report Form send to the Sponsor's Pharmacovigilance and Risk Management (PVRM) (or delegate) at AE.reporting@Seqirus.com. The investigator must notify the Sponsor within 24 hours. The AESI diagnosis, as well as if any medication is 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 documented on the AE eCRF **within 24 hours of the site becoming aware of the event.**

If the eCRF is not available, then the study site must complete the paper SAE Report Form and send it to the Sponsor's PVRM (or delegate) at AE.reporting@Seqirus.com **within 24 hours of becoming aware.** Once the eCRF is available, the SAE should be documented 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 the Sponsor or its designee will contact the investigator if it is necessary to obtain further information for an 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.

Sponsor or its designee must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (SUSARs) to the regulatory

authority(ies) and the IRB/EC. If a SUSAR or other safety signal relating to the use of one of the study vaccines is reported to the Sponsor 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 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 the Sponsor PVRM (or delegate) and must be reported using the email address: 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 the Sponsor's 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.

Any pregnancy outcome meeting the definition of a SAE (see Section 7.1.4, Serious Adverse Events) must also be reported on the AE eCRF.

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 vaccine, which will be measured by the HI and MN assay by titrating antibodies against the homologous influenza strains.

For the primary immunogenicity objectives, HI antibody responses using a cell-derived target virus will be evaluated for all strains. In case of a lack of agglutination for a specific strain using HI assay, immunogenicity for that strain will be assessed as measured by the MN assay.

For the secondary immunogenicity objectives, HI and MN antibody responses using cell-derived target virus will be evaluated for all strains. In case of a lack of agglutination for a specific strain using HI assay, immunogenicity for that strain will be assessed as measured by the MN assay.

For the exploratory immunogenicity evaluation, HI antibody responses may be evaluated for all strain using egg-derived target viruses.

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

8 STATISTICAL CONSIDERATIONS

A complete description of the statistical analyses and methods will be available in the Statistical Analysis Plan, which will be finalized before the database is locked for the primary analysis. The primary analysis will be conducted on the immunogenicity and safety data collected up to Day 29.

8.1 Endpoints

8.1.1 Primary Endpoint(s)

The primary objective of the study is to assess the immunogenicity of aQIVc compared to QIVc, aQIV, and QIVr as measured by HI assay using *cell-derived* target viruses. The primary endpoints are therefore the set of immunogenicity endpoints routinely applied for studies with such objectives.

8.1.1.1 Primary Immunogenicity Endpoints

Humoral immune response in terms of HI antibody response against homologous *cell-derived* vaccine strains (A/H1N1, A/H3N2, B/Yamagata and B/Victoria):

- Geometric Mean Titer (GMT): Geometric mean of HI antibodies at Day 29;
- Geometric Mean Fold Increase (GMFI): The Geometric mean of the fold increase in serum HI GMTs post-vaccination (Day 29) compared to pre-vaccination (Day 1);
- Percentages of subjects with HI titers ≥ 1:40 at Day 29;
- Percentage of subjects with seroconversion (defined as a ≥ 4-fold increase in titer post-vaccination in those with pre-vaccination titer above the LLOQ (1:10), or a post-vaccination titer ≥ 1:40 for subjects with baseline titer below the LLOQ (1:10) for HI antibodies at Day 29).

Note that the HI assay could be replaced by the MN assay due to a lack of agglutination.

8.1.1.2 Primary Safety Endpoints

No primary safety endpoints have been defined.

8.1.2 Secondary Endpoints

Secondary endpoints assessed in the study include the safety endpoints of solicited and unsolicited adverse events, the immunogenicity endpoints measured by the HI assay assessed at Day 181 and in addition the immunogenicity endpoints measured by the MN assay both at Day 29 and day 181.

8.1.2.1 Secondary Safety Endpoints

The secondary safety endpoints include the proportion of subjects reporting solicited and unsolicited adverse events:

- Percentage of subjects reporting a local and/or systemic adverse event for the 7 days following the vaccination (Day 1 to Day 7)
- Percentage of subjects reporting unsolicited adverse events for 28 days following vaccination (Day 1 to Day 29).
- Percentage of subjects reporting serious AEs, MA AEs, AEs leading to withdrawal or AESIs as collected during the study (Day 1 to End of Study).

8.1.2.2 Secondary Immunogenicity Endpoints

Humoral immune response in terms of HI antibody response against homologous *cell-derived* vaccine strains (A/H1N1, A/H3N2, B/Yamagata and B/Victoria) at Day 181:

- GMT: Geometric mean of HI antibodies at Day 181;
- GMFI: The Geometric mean of the fold increase in serum HI GMTs post-vaccination (Day 181) compared to pre-vaccination (Day 1);
- Percentages of subjects with HI titers ≥ 1:40 on Day 181.

In addition, the humoral immune response in terms of MN antibody response against homologous *cell-derived* vaccine strains (A/H1N1, A/H3N2, B/Yamagata and B/Victoria) at Days 29 and 181:

- GMT: Geometric mean of MN antibodies at Days 29 and 181;
- GMFI: The Geometric mean of the fold increase in serum MN GMTs post-vaccination (Day 29 and Day 181) compared to pre-vaccination (Day 1);
- Percentages of subjects with seroconversion (defined as ≥ 4-fold increase for subjects with pre-vaccination MN titers ≥ Lower Limit of Quantitation (LLOQ) or as ≥ 4LLOQ for subjects with pre-vaccination MN titer <LLOQ) at Day 29.

8.1.3 Exploratory Endpoints

Exploratory endpoints that may be assessed in the study include the immunogenicity endpoints as measured by HI assay using *egg-derived* target viruses on Day 29, 28 days after vaccination. Refer to the SAP for more details.

8.1.3.1 Exploratory Safety Endpoints

No exploratory safety endpoints were defined.

8.1.3.2 Exploratory Immunogenicity Endpoints

Humoral immune response in terms of HI antibody response against homologous *egg-derived* vaccine strains (A/H1N1, A/H3N2, B/Yamagata and B/Victoria):

- GMT: Geometric mean of HI antibodies at Day 29;
- GMFI: The Geometric mean of the fold increase in serum HI GMTs post-vaccination (Day 29) compared to pre-vaccination (Day 1);
- Percentages of subjects with HI titers ≥ 1:40 at Day 29;

- Percentage of subjects with seroconversion for HI antibodies on Day 29.

The results of these exploratory analyses may be presented in an addendum to the Clinical Study Report (CSR)

8.2 Success Criteria

This study is a Phase 2 study to explore the immunogenicity of aQIVc versus comparator vaccines (QIVc, aQIV, and QIVr). No success criteria are pre-specified.

8.3 Analysis Sets

8.3.1 All Enrolled Set

All screened subjects who provide informed consent, receive 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 are randomized and received study vaccination.

8.3.3 Safety Set

Solicited Safety Set

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

Unsolicited Safety Set (unsolicited adverse events)

All subjects in the Exposed Set with unsolicited adverse event data.

Overall Safety Set

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

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 provided immunogenicity data on Day 1 and Day 29 assessment.

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).

8.3.5 Per Protocol Set (PPS) Immunogenicity

All subjects in the FAS Immunogenicity who:

- Correctly receive the vaccine (i.e., receive the vaccine to which the subject is randomized and at the scheduled time point).
- 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, including subjects who withdrew informed consent prior to Day 28.

8.3.6 Other Analysis Sets

Not applicable

8.3.7 Subgroups

Primary and secondary analyses of immunogenicity and safety endpoints will be done for the total population and by age subgroup (50 – 64 years and ≥ 65 years).

Additional subgroup analysis will be conducted for previous vaccination history. Refer to the SAP for further details.

8.3.8 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures of a study protocol. A protocol deviation may be a reason to remove data from an analysis set at the time of analysis. CSR-reportable protocol deviations will be defined as exclusionary from the analysis according to protocol objectives and endpoints, which will be specified in the statistical

analysis plan. In some cases, exclusion of data may be due to a reason other than a protocol deviation, e.g. early termination.

8.4 Statistical Analysis Plan

8.4.1 Analysis of Demographic and Baseline Characteristics

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

Distributions of subjects by sex, race and ethnic origin, prior vaccination status and site will be summarized overall and by vaccine group.

Demographic and baseline characteristics will also be presented by the age subgroup.

8.4.2 Analysis of Primary Objectives

8.4.2.1 Analysis of Primary Safety Objectives

Not applicable.

8.4.2.2 Analysis of Primary Immunogenicity Objectives

The primary objective is to assess the immunogenicity assessed using the HI assay at Day 29.

8.4.2.2.1 Statistical Hypothesis

No statistical testing will be performed for the immunogenicity objectives.

8.4.2.2.2 Analysis Sets

All immunogenicity objectives will be evaluated based on the PPS Immunogenicity. Only in case, more than 5% of subjects are excluded, additional analysis based on the FAS Immunogenicity will be conducted.

8.4.2.2.3 Statistical Methods

All statistical analyses for HI (and MN) 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 vaccine group. Binary data (i.e., percentages of subjects with seroconversion and with titer ≥ 1:40) will be summarized for each group using crude estimates and will be reported together with 2-sided 95% CIs calculated according to Clopper Pearson's method. No multiplicity adjustment to the CI levels will be implemented.

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

The analysis model for the HI GMT will be done using a general linear model on log-transformed (base 10) Day 29 titers as the outcome variable and as covariates: treatment groups (aQIVc, QIVc, aQIV, and QIVr), pre-vaccination titer, age stratum. From this model, adjusted differences in the least square means (on the log scale) will be produced with 95% confidence limits for aQIVc versus QIVc, for aQIVc versus aQIV and for aQIVc versus QIVr. The estimated difference and the confidence limits will be back-transformed to obtain an *adjusted GMT ratio* with 95% confidence limits. Each of the four strains will be analyzed separately.

Potential interaction between age stratum and treatment effect will be examined, as well as the other co-variates such as previous vaccination history and age were taken as a continuous factor.

A similar model will be used for the GMFI on Day 29.

The binary endpoints (i.e. seroconversion or titer ≥1:40) will be compared using the Miettinen and Nurminen method without adjustment for the age stratum. The results will be presented as the difference in the percentage of subjects with 95% confidence intervals. Additional supportive analyses will be done using generalized linear models with factors for vaccine group, age subgroup, pre-vaccination titer as well as history of vaccination. Adjusted differences between vaccine groups with 2-sided 95% CI will be calculated based on the model and potential interaction effects will be examined.

8.4.3 Analysis of Secondary Objectives

8.4.3.1 Analysis of Secondary Safety Objectives

8.4.3.1.1 Analysis of Extent of Exposure

The number of subjects vaccinated will be presented by the vaccine group.

8.4.3.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

Solicited adverse events are reported daily from Day 1 up to and including Day 7 post-vaccination. A solicited adverse event 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 other category separately. The same tables will be created at each timepoint.

Frequencies and percentages of subjects experiencing each adverse event will be presented overall and for each maximum symptom severity and by vaccine group. Post-vaccination solicited adverse events reported from Day 1 to Day 7 will also be summarized for the interval's Day 1-3 and Day 4-7 overall and for each maximal severity and by vaccine group.

The severity of solicited local adverse events will be summarized according to the grading. For the categories based on linear measurement for local AEs erythema and induration: 25-50 mm is mild, 51-100 mm is moderate and >100 mm is severe. Solicited local adverse events measuring less than 25 mm will not be considered as an adverse event. For temperature: any fever is ≥ 38 °C and severe is ≥ 39 °C.

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 AE's 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. AE starting prior to study vaccination will only be listed. The original verbatim terms used by investigators to identify adverse events in the eCRFs will be mapped to preferred terms using the MedDRA dictionary.

The adverse events will then be grouped by MedDRA preferred terms into frequency tables according to system organ class. All reported AEs, as well as AEs judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and the preferred term within system organ class. These summaries will be presented by the vaccination group and by the interval of study observation (Day 1 to Day 29, Day 30 to end of study). When an AE occurs more than once for a subject, the maximal severity and strongest relationship to the vaccine group will be counted.

Separate summaries will be produced for the following categories

- AEs
- SAEs
- AEs that are possibly or probably related to the vaccine
- SAEs that are possibly or probably related to the vaccine
- AESIs
- MAAEs
- AEs leading to withdrawal

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

8.4.3.1.4 Statistical Hypotheses

No statistical hypotheses will be tested

8.4.3.1.5 Analysis Sets

Where applicable, the safety set will be used for the safety analysis. The solicited safety set for the solicited adverse events and the unsolicited safety set for all unsolicited adverse events.

8.4.3.1.6 Statistical Methods

Only descriptive statistics will be calculated and presented.

8.4.3.2 Analysis of Secondary Immunogenicity Objective(s)

The analysis of the secondary immunogenicity endpoints will be conducted in the same way as described for the primary immunogenicity endpoints.

8.4.3.2.1 Statistical Hypotheses

No statistical hypotheses will be tested.

8.4.3.2.2 Analysis Sets

All secondary immunogenicity objectives will be evaluated based on the PPS Immunogenicity. Note that the PPS for the Day 181 analysis may exclude additional subjects in case of major protocol deviations related to the use of concomitant medication interfering with the immunogenicity assessment. Only in case, more than 10% of subjects are excluded, additional analysis based on the FAS Immunogenicity will be conducted.

8.4.3.2.3 Statistical Methods

The statistical methods will follow the same methods as described for the primary endpoints in Section 8.4.2.2.3.

8.4.4 Analysis of Other Objectives

The exploratory analysis may be done based on the immunogenicity endpoints by the HI assay using the egg-derived target viruses. Results from these analyses will be reported separately.

8.4.4.1 Analysis of Other Safety Objectives

No exploratory safety analysis was defined.

8.4.4.2 Analysis of Other Immunogenicity Objectives

The exploratory endpoints will be evaluated using the same methods as described above in Section 8.4.2.2.3.

8.5 Sample Size and Power Considerations of Primary Objectives

This study is an exploratory Phase 2 study without any formal inferential analysis. The total sample size of 480 subjects has been determined by the feasibility of conducting the study in one season.

This sample size – including around 10% of exclusions – is enough to obtain preliminary immunogenicity data. Table 8-1 illustrates the effects which can be detected depending (80% power and the two-sided significance level of 0.05) on different values for the inter-subject variation, as well as the size of the 95% two-sided confidence interval indicating the accuracy of the estimates.

Table 8-1: Detectable GMT ratios

SD #	Log10 GMT Differences that can be detected	GMT ratios can be detected	95% confidence interval (times the GMT ratio)
0.45	0.172	1.49	0.76 to 1.32
0.50	0.191	1.55	0.73 to 1.36
0.55	0.211	1.62	0.71 to 1.40
0.60	0.230	1.70	0.69 to 1.45
0.65	0.250	1.77	0.67 to 1.49
0.7	0.268	1.85	0.65 to 1.54
0.75	0.287	1.94	0.63 to 1.59
0.80	0.306	2.02	0.61 to 1.64

Notes: # range of values based on studies V7P38 and V70P3. Abbreviations: GMT= geometric mean titer. SD = Standard deviation.

8.6 Interim Analysis

No interim analysis of data from this study is planned.

Two final analyses will be performed stepwise as follows:

1. A final analysis including all immunogenicity and safety data collected from Visit 1 to Visit 3 (Day 29) and associated primary and secondary objectives will be conducted on cleaned and locked data. No individual listings and unblinding data will be generated at this stage. Access to information about study groups will be limited by a biostatistician in charge of statistical analysis.

2. The analysis of immunogenicity and safety data collected between Visit 3 and Visit 5 will be performed after all data is available. The results of this analysis will cover the entire study duration. All results will be presented in the clinical study report and will include individual data listings and unblinded information.

9 SOURCE DOCUMENTATION, STUDY MONITORING, AND AUDITING

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

Prior to the enrolment of the first study subject, the Sponsor 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 the definition of the 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 the Sponsor or delegate and investigator and designees and specified in the SDA prior to subject enrolment.

In addition, source documentation **must** include all of the following: subject identification (on each page), eligibility and participation, proper informed consent procedures, dates of visits, adherence to protocol procedures, adequate reporting and follow-up of adverse events, documentation of prior/concomitant medication/vaccines, study vaccine receipt/dispensing/return records, study vaccine administration information, any data collected by a telephone conversation with the subject and 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 adverse event, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be justified and written in the source documents, and this diagnosis must be captured in the Adverse Event eCRF (AE eCRF).

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

9.2 Study Monitoring, Auditing and Source Data Verification

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

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

Contact details for the Sponsor's team or its designee involved in study monitoring will be provided to the investigator. Study data recorded on eCRFs will be verified by checking the eCRF entries against source documents in order to ensure data completeness and accuracy as required by study protocol except for those parameters which are specifically described in Section 7, Assessments being entered directly into the EDC system.

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 an emergency.

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

10 DATA MANAGEMENT

10.1 Data Entry and Management

In this study, all clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, and physical assessments) and blood sampling 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 electronic data capture (EDC) system, which is compliant with Title 21 Part 11 policies of the Code of Federal Regulations (FDA 1997). The data system includes password protection and internal quality checks. The EDC system will be designed and validated by the Sponsor prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the eCRFs to verify their accuracy.

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

10.2 Data Clarification

As part of the conduct of the trial, the Sponsor 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

The sponsor 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 the Sponsor and by the applicable regulations in a secure and safe facility. The investigator must consult the Sponsor's 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 Sponsor's or Sponsor's- 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 subject's samples stored for future testing (not related to this study) after the study is completed, this can be indicated on the ICF.

12 USE OF INFORMATION AND PUBLICATION

The Sponsor 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.

The Sponsor 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 the study as defined in Section 3.10, End of Study.

In accordance with standard editorial, ethical practices and current guidelines of Good Publication Practice (Graf 2009), the Sponsor 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 the International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which the contribution of the Sponsor's personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor's personnel.

The Sponsor must be notified of any intent to publish data collected from the study and prior approval from the Sponsor 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 including European Directive 2001/20/EC and US Code of Federal Regulations Title 21, Sponsor's 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, as described in Section 5.1.1, Informed Consent. Before the start of the study, the investigator will have 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, the Sponsor will provide 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 the Sponsor before submission to the IRB/EC and a copy of the approved version must be provided to the Sponsor 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 the 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 the case of doubts on the ability of a subject to adhering to these requirements, that subject should not be allowed in the study

13.3 Responsibilities of the Investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before the 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 the Sponsor 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 the Sponsor's monitors, auditors, Sponsor's Clinical Quality Assurance representatives, designated agents of the Sponsor, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the Sponsor immediately that this request has been made.

The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.

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

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

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

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

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

(c) to the regulatory authority(ies).

13.4 Protocol Amendments

An amendment is a written description of change(s) to or formal clarification of a study protocol which may impact on the conduct of the clinical study, potential benefit of the clinical study, or may

affect subject safety, including changes of study objectives, study design, subject population, sample sizes, study procedures, or significant administrative aspects. An administrative change of a study protocol is a minor correction or clarification that has no significant impact on the way the clinical study is to be conducted and no effect on subject safety (e.g., change of telephone number(s), logistical changes). Protocol amendments must be approved by the Sponsor, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject's safety urgently, 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, the Sponsor 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

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APPENDIX 1 – HAK SCORE

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.

[a] 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 the SPONSOR

I have read the protocol entitled "A Phase 2, Randomized, Stratified, Observer-Blind Clinical Study to Evaluate Safety and Immunogenicity of the MF59-Adjuvanted Quadrivalent Inactivated Subunit Cell-derived Influenza Vaccine (aQIVc) in adults ≥50 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: 30-MAR-2020
(DD MMM YYYY)

Name and qualifications: [redacted]

Role: [redacted]

SIGNATURE OF INVESTIGATOR

I have read the protocol entitled "A Phase 2, Randomized, Stratified, Observer-Blind Clinical Study to Evaluate Safety and Immunogenicity of the MF59-Adjuvanted Quadrivalent Inactivated Subunit Cell-derived Influenza Vaccine (aQIVc) in adults ≥50 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 and the Institutional Review Board or Independent Ethics Committee (as appropriate), with the exception of medical emergencies.

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

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

Affiliation and qualifications: ……

Address of Investigator: ……

Electronic Signatures

User	Date	Justification
[redacted]	30-Mar-2020 12:42:26	Manager Approval