CLINICAL STUDY PROTOCOL

Study Number	V89_18E1
Protocol Version	Version 2: 15-JUL-2022
Study Title	A Phase 2, Randomized, Study to Evaluate Safety and Immunogenicity of One or Two Heterologous Booster Vaccinations With an MF59-adjuvanted, Cell Culture-derived H5N6 Influenza Vaccine in Adults Primed With MF59-adjuvanted, Cell Culture-derived H5N1 Influenza Vaccine or Unprimed.
Study Phase	Phase 2
Product Name	Influenza A (H5N1) Monovalent Vaccine, Adjuvanted (Audenz™)
Regulatory Agency Identifying Number(s)	BB-IND No 13,536
Sponsor	Seqirus Inc 50 Hampshire Street, 9th floor Cambridge, MA 02139 USA
Previous Version, if applicable	Version 1
Date, if applicable	17-DEC-2021

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PROTOCOL SYNOPSIS V89_18E1

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Title of Study: A Phase 2, Randomized, Study to Evaluate Safety and Immunogenicity of One or Two Heterologous Booster Vaccinations With an MF59-adjuvanted, Cell Culture-derived H5N6 Influenza Vaccine in Adults Primed With MF59-adjuvanted, Cell Culture-derived H5N1 Influenza Vaccine or Unprimed.		
Study Period: Approximately 7 months for each study participant.		**Clinical Phase**: Phase 2

Background and Rationale:

An influenza *pandemic* is a global epidemic caused by a new influenza virus strain to which there is little or no pre-existing immunity in the human population. Pandemic influenza strains result from an *antigenic shift* (Bouvier and Palese, 2008) and may include hemagglutinin (HA) subtypes of either avian origin such as H5, H7 and H9 or swine variants of HA subtypes H1, H2 and H3 that have further acquired adaptive mutations to become infectious from human to human (Taubenberger and Kash, 2010).

Unlike seasonal influenza whereby vaccine manufacturers plan in advance of the annually occurring epidemics, pandemic influenza outbreaks are difficult to predict. Pandemic vaccines are manufactured once an official declaration by the World Health Organization (WHO) of a Public Health Emergency of International Concern (PHEIC) and a recommendation of the pandemic influenza candidate virus vaccine strain is made. Therefore, there can be a significant time delay – typically around four months – until the first batch of pandemic strain matched vaccine becomes available. This "matched pandemic vaccine response interval" was observed during the 2009 H1N1 pandemic and contributes toward part of the unmet medical need (i.e. limitations to respond rapidly in a pandemic). Seqirus recognizes the need for a viable approach to providing heterologous coverage protection to First Responders (who will be on the front line of a

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pandemic response) during the interval between the declaration of a pandemic and the availability of a strain matched vaccine. Social distancing is clearly not an option for First Responders. Furthermore, they require protection beyond what antivirals can provide. Zoonotic (formerly known as pre-pandemic) vaccines can play an important role in managing the unpredictability of a pandemic. Zoonotic vaccines are based on emerging strains of Influenza Viruses of Pandemic Potential (IVPP). Adjuvants like MF59C.1 adjuvant (MF59) have been shown to enhance the breadth of response to vaccine and provide heterologous cross-protection against non-vaccine antigen viral strains (Alberini et al. 2009; Frey et al. 2014; Nolan et al. 2014; Chanthavanich et al. 2019; Frey et al. 2019).

An influenza A/turkey/Turkey/1/2005 NIBRG-23 strain (H5N1) cell culture-derived vaccine (AUDENZ™, Seqirus Inc.) combined with MF59C.1® oil-in-water emulsion adjuvant has been approved in the United States (US) for active immunization of persons 6 months and older for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. Two doses of this MF59-adjuvanted cell culture-derived H5N1 vaccine, given at a 21-day interval, produce antibody levels against the vaccine-homologous virus that meet US regulatory criteria, as well as substantial levels of cross-reactive antibodies against viruses of other H5N1 clades (Frey et al. 2019; Chantavanich et al. 2019).

This study is designed to investigate whether two priming doses of MF59-adjuvanted A/turkey/Turkey/1/2005 (H5N1, clade 2.2) cell culture-derived vaccine (aH5N1c) followed by one or two booster vaccinations with a MF59-adjuvanted H5N6 (A/Guangdong/18SF020/2018 (H5N6)-like CDC/CNIC [clade 2.3.4.4h]) cell culture-derived vaccine (aH5N6c) 3 weeks apart elicit immune responses to the antigens used for priming (H5N1) and boosting (H5N6) after first and second heterologous booster vaccination.

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Disclosure Statement: This is a phase 2, randomized study.

Study Objectives:

Primary Objective(s):

Primary Immunogenicity Objective:

- To assess immune responses against H5N6 (contained in the booster vaccine) as measured by hemagglutination inhibition (HI)[1] assay 1 week (Day 8) and 3 weeks (Day 22) after the first heterologous aH5N6c booster vaccination, and 3 weeks (Day 43) after the second heterologous aH5N6c booster or placebo vaccination.

Secondary Objective(s):

Secondary Immunogenicity Objectives:

a. To assess immune responses against H5N1 (contained in the priming vaccine) as measured by HI[1] assay 1 week (Day 8) and 3 weeks (Day 22) after the first heterologous aH5N6c booster vaccination, and 3 weeks (Day 43) after the second heterologous aH5N6c booster or placebo vaccination.

b. To assess persistence of immune response against H5N1 (contained in the priming vaccine) as measured by HI[1] assay at Day 1 (pre-vaccination) and at Day 202, 6 months after the second heterologous aH5N6c booster or placebo vaccination.

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

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c. To assess persistence of immune response against H5N6 (contained in the booster vaccine) as measured by HI[1] assay at Day 202, 6 months after the second heterologous aH5N6c booster or placebo vaccination.

Secondary Safety Objectives:

- To assess the safety and reactogenicity of aH5N6c vaccine.

Exploratory Objective(s):

- To further evaluate immune responses to seasonal and/or homologous and/heterologous pandemic influenza strain(s), such as measured by the HI, microneutralization (MN), and single radial hemolysis (SRH) assays (depending on availability of blood samples and on assay availability).

Primary Immunogenicity Endpoints:

Immune responses to the aH5N6c vaccine in terms of HI antibody responses against the H5N6 strain contained in the booster vaccine by:

- Geometric Mean Titer (GMT): Geometric mean of HI antibodies at Day 1, Day 8, Day 22 and Day 43.
- Geometric Mean Fold Increase (GMFI): The Geometric mean of the fold increase in serum HI titers postvaccination 1 (Day 8 and Day 22) and 2 (Day 43) compared to pre-vaccination (Day 1).
- Percentages of subjects with HI titers ≥1:40 at Day 1, Day 8, Day 22 and Day 43.
- Percentage of subjects with seroconversion (defined as a ≥4-fold increase in titer postvaccination in those with pre-vaccination titer ≥1:10, or a postvaccination

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titer ≥1:40 for subjects with baseline titer <1:10) for HI antibodies at Day 8, Day 22 and Day 43.

Secondary Immunogenicity Endpoint(s):

Immune responses to the aH5N1c vaccine in terms of HI antibody responses against the H5N1 strain contained in the priming vaccine by:

- GMT: Geometric mean of HI antibodies at Day 1, Day 8, Day 22, Day 43 and Day 202.
- GMFI: The Geometric mean of the fold increase in serum HI titer postvaccination 1 (Day 8 and Day 22) and 3 weeks (Day 43) and 6 months (Day 202) after the second vaccination compared to pre-vaccination (Day 1).
- Percentages of subjects with HI titers ≥1:40 at Day 1, Day 8, Day 22, Day 43 and Day 202.
- Percentage of subjects with seroconversion (defined as a ≥4-fold increase in titer postvaccination in those with pre-vaccination titer ≥1:10, or a postvaccination titer ≥1:40 for subjects with baseline titer <1:10) for HI antibodies at Day 8, Day 22, Day 43 and Day 202.

Immune responses to the aH5N6c vaccine in terms of HI antibody responses against the H5N6 strain contained in the booster vaccine by:

- GMT: Geometric mean of HI antibodies at Day 202.
- GMFI: The Geometric mean of the fold increase in serum HI titer 6 months (Day 202) after the second vaccination compared to pre-vaccination (Day 1).

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- Percentages of subjects with HI titers ≥1:40 at Day 202.
- Percentage of subjects with seroconversion (defined as a ≥4-fold increase in titer postvaccination in those with pre-vaccination titer ≥1:10, or a postvaccination titer ≥1:40 for subjects with baseline titer <1:10) for HI antibodies at Day 202.

Safety Endpoint(s):

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

- Solicited local and systemic adverse events (AEs) for 7 consecutive days following each vaccination;
- All unsolicited AEs (including Medically Attended AEs (MAAEs)) for 3 weeks following each vaccination (Day 1 through Day 43);
- Serious AEs (SAEs), AEs leading to withdrawal, AEs of special interest (AESIs), MAAEs as collected from Day 1 through Day 202.

Exploratory Endpoint(s):

- Exploratory endpoints of seasonal and homologous and/or heterologous strain testing will be described in the Statistical Analysis Plan (SAP).

Study Design: This is a Phase 2, randomized, multi-center study in approximately 300 adults, who received 2 doses of aH5N1c or placebo[2] in and completed the parent study V89_18 in the <65 years of age cohort.

[2] In case insufficient numbers of subjects who received 2 doses of placebo in the V89_18 parent study can be included, A/H5 naïve subjects may be enrolled (i.e. did not receive an influenza H5 vaccine in the past or have a history of H5 influenza infection prior to enrollment).

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Eligible subjects, who received 2 doses of aH5N1c in the parent study V89_18 will be randomized in a 1:1 ratio to receive either two aH5N6c vaccinations, 3 weeks apart (group 1) or an aH5N6c vaccination on Day 1 and saline placebo on Day 22 (group 2). Eligible subjects, who received placebo[2] in the parent study will receive two aH5N6c vaccinations, 3 weeks apart (group 3).

Treatment group	Treatment in parent Study V89_18	Treatment schedule in extension study V89_18E1		Total planned (N)
		Day 1	Day 22	
Group 1	aH5N1c	aH5N6c	aH5N6c	100
Group 2	aH5N1c	aH5N6c	Placebo	100
Group 3	Placebo[2]	aH5N6c	aH5N6c	100

Vaccine administration will be performed intramuscularly (IM) in an observer-blind manner. After each vaccination, subjects will remain under medical supervision at the study site for at least 30 minutes for observation of immediate AEs. After the second vaccine administration, subjects will be monitored for approximately 6 months for safety and antibody persistence. The total study duration will be approximately 7 months per subject.

For all subjects, study participation includes a total of 5 clinic visits[3], 2 diary completion reminder calls, and 2 safety telephone calls through the treatment and follow-up periods.

[3] In the exceptional case that a clinic visit is not possible due to the site being closed, with appropriate sponsor approvals a home visit may be considered (applicable to visits on Day 8, Day 43 and Day 202 only).

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- Treatment period (Day 1 through Day 43): 4 clinic visits and 2 diary completion reminder calls.
- Follow-up period (Day 44 through Day 202): 1 clinic visit and 2 safety telephone calls.

Immunogenicity will be measured by HI assay. Blood samples for immunogenicity assessments will be collected from each subject on Day 1 (before vaccination), Day 8, Day 22 (before vaccination), Day 43, and Day 202.

Subject diary cards will be used to collect solicited local and systemic AEs for 7 consecutive days following each vaccination. Solicited local AEs will include: injection site induration, erythema, ecchymosis and pain. Solicited systemic AEs will include: nausea, myalgia, arthralgia, headache, fatigue, chills, loss of appetite, malaise and fever (derived from measured body [preferably oral] temperature ≥38.0 °C [≥100.4 °F]). In addition, the use of analgesic/antipyretic medication for prevention or treatment will be recorded. Furthermore, during the treatment period (Day 1 through Day 43), all unsolicited AEs (including MAAEs), SAEs, all AESIs, AEs leading to study withdrawal, associated concomitant medications for any of these events, and all vaccinations will be collected. During the follow-up period (Day 44 through Day 202), only a subset of unsolicited AEs and associated medications used to treat these events, and all vaccinations will be collected in the electronic Case Report Form (eCRF): all SAEs, AESIs, AEs leading to study withdrawal, and MAAEs.

Number of Subjects planned: Approximately 300 subjects.

Study Population and Subject Characteristics:

Subjects who received 2 doses of aH5N1c vaccine or placebo[2] in and completed the parent study V89_18 in the <65 years of age cohort.

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

Study Procedures:

Written informed consent must be obtained prior to any study-related procedures. The informed consent process may be conducted up to 10 days before conducting any study-specific procedures (i.e., all of the procedures described in the protocol).

Treatment Period: Day 1 through Day 43

After informed consent is signed by the subject, prior to vaccination on Day 1, screening will be performed including an eligibility assessment: a review of relevant medical history, physical examination, and height and weight measurements. A blood sample will be collected from all eligible subjects for serology testing. All eligibility assessments need to be completed prior to blood sample collection.

aH5N1c primed subjects will be randomized in a 1:1 ratio to receive either two aH5N6c vaccinations (group 1) or an aH5N6c vaccination on Day 1 and saline placebo on Day 22 (group 2). All unprimed subjects will receive two aH5N6c vaccinations (group 3). All eligible subjects will then receive a single dose of 0.5 mL of aH5N6c vaccine administered intramuscularly in the deltoid muscle, preferably of the non-dominant arm.

After vaccination, all subjects will remain under medical supervision at the study site for at least 30 minutes to be monitored and evaluated for immediate post-vaccination AEs by qualified study personnel.

Subjects will receive a thermometer, a ruler, and a paper Diary, including instructions to ensure proper completion; subjects will note any occurrence of solicited local and systemic AEs, and record their oral temperatures, preferably in the evening, from Day 1 through Day 7 in the paper Diary. The Diary will only be used to collect solicited AEs

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and temperature measurements. On Day 4 (window: -/+ 1 day) a Diary reminder call will be performed to remind the subject on completion of the Diary.

Subjects will return to the clinic on Day 8 (window: 0/+2 days) for a symptom-directed physical examination, and to provide a serum sample for immunogenicity testing. During this visit the Subject Diary will be reviewed, all unsolicited AEs (including MAAEs) and concomitant medication use (occurring after the first vaccination between Day 1 and Day 8) will be documented in the subject's source records and captured in the eCRF.

Subjects will return to the clinic on Day 22 (window: -1/+7 days) for a symptom-directed physical examination, to provide a serum sample for immunogenicity testing, and to receive the second aH5N6c vaccination or saline placebo. aH5N1c primed subjects (group 1) will receive a second aH5N6c vaccination or saline placebo (group 2). All unprimed subjects (group 3) will receive a second aH5N6c vaccination. During this visit all unsolicited AEs (including MAAEs) and concomitant medication use (occurring after the first vaccination between Day 1 and Day 22) will be documented in the subject's source records and captured in the eCRF.

After vaccination, all subjects will remain under medical supervision at the study site for at least 30 minutes to be monitored and evaluated for immediate post-vaccination AEs by qualified study personnel.

Subjects will receive a paper Diary, including instructions to ensure proper completion; subjects will note any occurrence of solicited local and systemic AEs, and record their oral temperatures, preferably in the evening, from Day 22 through Day 28 in the paper Diary. On Day 25 (window: 0/+ 2 days) a Diary reminder call will be performed to remind the subject on completion of the Diary.

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Subjects will return to the clinic on Day 43 (window: -1/+7 days) for a symptom-directed physical examination, and to provide a serum sample for immunogenicity testing. During this visit the Subject Diary will be reviewed, all unsolicited AEs (including MAAEs) and concomitant medication use (occurring after the second vaccination between Day 22 and Day 43) will be documented in the subject's source records and captured in the eCRF.

Follow-up Period: Day 44 through Day 202

A scripted safety telephone call will be made on Day 92 (window: -/+ 7 days) and Day 142 (window: -/+ 7 days) to collect only those AEs that are: SAEs, AEs leading to study withdrawal, AESIs, MAAEs and concomitant medications associated with these events.

Subjects will return to the clinic on Day 202 (window: +/- 14 days) for a symptom-directed physical examination, and to provide a serum sample for serologic testing. During this visit the subject will be interviewed to obtain information regarding SAEs, AEs leading to study withdrawal, AESIs and MAAEs; concomitant medications associated with these events will be documented in the subject's source records and captured in the eCRF.

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

Further details on the study procedures are presented Table 0-1: Time and Events Schedule and in Section 5, Study Procedures.

Study Vaccine:

Investigational vaccine: MF59-adjuvanted cell-culture derived subunit inactivated monovalent A/H5N6 vaccine (aH5N6c) for intramuscular (IM) administration,

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containing [redacted] µg H5N6 HA (A/Guangdong/18SF020/2018 (H5N6)-like) + [redacted] mL MF59 (approximately 0.5 mL total volume). Placebo (saline solution).		
Statistical Analyses: There are no statistical (null) hypothesis associated with the immunogenicity and safety objectives, and all data will be analyzed descriptively. Statistical analyses of the immunogenicity endpoints will include point estimates and the associated 95% confidence intervals (CIs). As the decision on objectives does not involve testing procedures, adjustment for multiplicity is not applicable. Further details regarding the statistical analysis are contained in Section 8.4, Statistical Analysis Plan.		
Interim Analysis: Not applicable.		
Data Monitoring Committee: Not applicable.		

Table 0-1: Time and Events Schedule

	Visit Type	Clinic Visit	Diary Reminder Phone Call	Clinic Visit	Clinic Visit	Diary Reminder Phone Call	Clinic Visit	Phone Call	Phone Call	Clinic Visit
	Study Day[a]	1	V1+3 (Day 4)	V1+7 (Day 8)*	V1+21 (Day 22)	V3+3 (Day 25)	V3+21 (Day 43)*	V3+70 (Day 92)	V3+120 (Day 142)	V3+180 (Day 202)*
	Visit Window (Days)	n/a	-1 to+1	0 to+2	-1 to+7	-1 to+1	-1 to +7	-7 to +7	-7 to +7	-14 to +14
	Visit Number	1	n.a.	2	3	n.a.	4	5	6	7
Study Event	**References**									
Study Treatment										
Vaccination	*Section 5.2*	X			X					
Screening and Safety										
Informed Consent[b]	*Section 5.1.1*	X								
Medical History[c]	*Section 5.1.2*	X								
Physical Exam[d]	*Section 5.1.2*	X		X	X		X			X
Pregnancy Test[e]	*Section 5.1.2*	X			X					
Exclusion/Inclusion Criteria	*Section 4*	X			X					
Randomization	*Section 5.1.4*	X								
30 Minutes Post Injection Assessment	*Section 5.3*	X			X					
Subject Diary Dispensed with Training	*Section 5.3.1*	X			X					

	Visit Type	Clinic Visit	Diary Reminder Phone Call	Clinic Visit	Clinic Visit	Diary Reminder Phone Call	Clinic Visit	Phone Call	Phone Call	Clinic Visit
	Study Day[a]	1	V1+3 (Day 4)	V1+7 (Day 8)*	V1+21 (Day 22)	V3+3 (Day 25)	V3+21 (Day 43)*	V3+70 (Day 92)	V3+120 (Day 142)	V3+180 (Day 202)*
	Visit Window (Days)	n/a	-1 to+1	0 to+2	-1 to+7	-1 to+1	-1 to +7	-7 to +7	-7 to +7	-14 to +14
	Visit Number	1	n.a.	2	3	n.a.	4	5	6	7
Study Event	**References**									
Subject Diary Reminder Call	*Section 5.3.2*		X			X				
Subject Diary Reviewed and Collected	*Sections 3.6.2 and 5.4.1*			X			X			
Assess all AEs	*Section 7.1.2*	X		X	X		X			
Assess SAEs	*Section 7.1.4*	X		X	X		X	X	X	X
Assess AEs leading to withdrawal, AESIs, and MAAEs	*Section 7.1.4.1*	X		X	X		X	X	X	X
Assess relevant medications	*Section 6.5*	X		X	X		X	X	X	X
Immunogenicity										
Serology blood draw	*Section 3.7*	X[f]		X	X[f]		X			X
Study Completion Procedure										
Study Completion[g]	*Section 5.6*									X

	Visit Type	Clinic Visit	Diary Reminder Phone Call	Clinic Visit	Clinic Visit	Diary Reminder Phone Call	Clinic Visit	Phone Call	Phone Call	Clinic Visit
	Study Day[a]	1	V1+3 (Day 4)	V1+7 (Day 8)*	V1+21 (Day 22)	V3+3 (Day 25)	V3+21 (Day 43)*	V3+70 (Day 92)	V3+120 (Day 142)	V3+180 (Day 202)*
	Visit Window (Days)	n/a	-1 to+1	0 to+2	-1 to+7	-1 to+1	-1 to +7	-7 to +7	-7 to +7	-14 to +14
	Visit Number	1	n.a.	2	3	n.a.	4	5	6	7
Study Event	**References**									

Notes: *In the exceptional case that a clinic visit is not possible due to the site being closed, with appropriate sponsor approvals a home visit may be considered.

[a] Visit 1 (vaccination visit) is the baseline for calculating visits 2 and 3; Visit 3 is the baseline for calculation of all following visits

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

[c] Medical history includes existing comorbidities

[d] A physical examination will be based on a review of systems, ie, a structured interview for complaints for each organ system;

[e] A pregnancy test should be done for females of childbearing potential in order to rule out any pregnancy;

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

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

List of Abbreviations and Definition of Terms

AE	Adverse Event
AESI	Adverse Events of Special Interest
aH5N1c	MF59-adjuvanted Monovalent A/H5N1 Influenza Vaccine
CBER	Center for Biologics Evaluation and Research
CI	Confidence Interval
CRO	Contract Research Organization
CSR	Clinical Study Report
EC	Ethics Committee
EDC	Electronic Data Capture
eCRF	electronic Case Report Form
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
GMFI	Geometric Mean Fold Increase
GMT	Geometric Mean Titer
GMTr	Geometric Mean Titer ratio
HA	Hemagglutinin
HI	Hemagglutination Inhibition
HIPAA	Health Insurance Portability and Accountability Act
ICH	The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICF	Informed Consent Form
ID	Identification
IRB	Institutional Review Board
IRT	Interactive Response Technology
MAAE	Medically Attended Adverse Event
MF59	MF59C.1 adjuvant
PPS	Per Protocol Set
PVRM	Pharmacovigilance and Risk Management
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCR	Seroconversion rate
SDA	Source Document Agreement
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
US	United States
WHO	World Health Organization

Abbreviation or Term	Definition
Follow-up period	The follow-up period starts for subjects 21 days after last vaccination and continues for up to study completion visit, defined as 6 months after the second study vaccination, i.e. Day 202
Qualified healthcare professional	Any licensed healthcare 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 professional	Any healthcare professional who is permitted by institutional policy, trained to perform delegated tasks, is trained on the study procedure(s) and who is identified within the site signature and delegation log.
Treatment period	Per protocol treatment period begins at the time of vaccination and ends 21 days after last vaccination.

1 BACKGROUND AND RATIONALE

1.1 Background

An influenza pandemic is a global epidemic caused by a new influenza virus strain to which there is little or no pre-existing immunity in the human population. Pandemic influenza strains result from an antigenic shift (Bouvier and Palese, 2008) and may include hemagglutinin (HA) subtypes of either avian origin such as H5, H7 and H9 or swine variants of HA subtypes H1, H2 and H3 that have further acquired adaptive mutations to become infectious from human to human (Taubenberger and Kash, 2010).

Unlike seasonal influenza whereby vaccine manufacturers plan in advance of the annually occurring epidemics, pandemic influenza outbreaks are difficult to predict. Pandemic vaccines are manufactured once an official declaration by the World Health Organization (WHO) of a Public Health Emergency of International Concern (PHEIC) and a recommendation of the pandemic influenza candidate virus vaccine strain is made. Therefore, there can be a significant time delay - typically around four months - until the first batch of pandemic strain matched vaccine becomes available. This "matched pandemic vaccine response interval" was observed during the 2009 H1N1 pandemic and contributes toward part of the unmet medical need (i.e. limitations to respond rapidly in a pandemic). Seqirus recognizes the need for a viable approach to providing heterologous coverage protection to First Responders (who will be on the front line of a pandemic response) during the interval between the declaration of a pandemic and the availability of a strain matched vaccine. Social distancing is clearly not an option for First Responders. Furthermore, they require protection beyond what antivirals can provide. Zoonotic (formerly known as pre-pandemic) vaccines can play an important role in managing the unpredictability of a pandemic. Zoonotic vaccines are based on emerging strains of Influenza Viruses of Pandemic Potential (IVPP). Adjuvants like MF59C.1 adjuvant (MF59) have been shown to enhance the breadth of response to vaccine and provide heterologous cross-protection against non-vaccine antigen viral strains (Alberini et al. 2009; Frey et al. 2014; Nolan et al. 2014; Chanthavanich et al. 2019; Frey et al., 2019).

Currently, the geographic spread of A/H5 viruses, including A/H5N6, has increased dramatically resulting in regional outbreaks in poultry, increasing the possibility of avian-to-human transmission. As of October 2021, there have been 48 laboratory-confirmed cases of human

infection with influenza A/H5N6 virus, of which 25 had fatal outcomes (WHO, 2021). Although to date A/H5N6 has caused only sporadic human infections, no A/H5 virus has caused sustainable human-to-human transmission. However, due to the lack of immunity in humans and ongoing evolution of the virus, A/H5 viruses continuously pose a risk of causing an influenza pandemic if the ability to transmit efficiently among humans was gained. This emphasizes the need to develop vaccines against avian influenza strains with pandemic potential with the ability to elicit long-term broadly reactive antibodies that could provide at least partial protection against the emerging pandemic strains.

An influenza A/turkey/Turkey/1/2005 NIBRG-23 strain (H5N1) cell culture-derived vaccine (AUDENZ™, Seqirus Inc.) combined with MF59C.1® oil-in-water emulsion adjuvant has been approved in the United States (US) for active immunization of persons 6 months and older for the prevention of disease caused by the influenza A virus H5N1 subtype contained in the vaccine. Two doses of this MF59-adjuvanted cell culture-derived H5N1 vaccine, given at a 21-day interval, produce antibody levels against the vaccine-homologous virus that meet US regulatory criteria, as well as substantial levels of cross-reactive antibodies against viruses of other H5N1 clades (Frey et al. 2019; Chantavanich et al. 2019).

1.2 Rationale

The aim of this study is to investigate whether two priming doses of MF59-adjuvanted A/turkey/Turkey/1/2005 (H5N1, clade 2.2) cell culture-derived vaccine (aH5N1c) followed by one or two booster vaccinations with a MF59-adjuvanted H5N6 (A/Guangdong/18SF020/2018 (H5N6)-like) cell culture-derived vaccine (aH5N6c) 3 weeks apart elicit immune responses to the antigens used for priming (H5N1) and boosting (H5N6) after first and second heterologous booster vaccination.

1.3 Potential Risks and Benefits

Subjects will be exposed to aH5N6c vaccine.

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.

The aH5N6c vaccine is manufactured according to the same process as the aH5N1c vaccine, and differs only with respect to virus strain, and is expected to have a similar safety profile. Based upon clinical studies with the aH5N1c vaccine, the following local and systemic adverse events may occur after vaccination with the aH5N6c vaccine:

- Immediate hypersensitivity type reactions including anaphylaxis.
- Vaccination-related anxiety symptoms such as syncope and pre-syncope.
- Local reactions: pain at the injection site.
- Systemic reactions: fatigue, malaise, headache, arthralgia, myalgia and nausea.

Most of these reactions usually disappear within 1-2 days without treatment. As the aH5N1c vaccine has only been administered to approximately 3500 subjects, there may be other yet unforeseen adverse events or reactions that may be associated with administration of this vaccine.

The aH5N1c vaccine has a good immunogenicity and a safety profile. The benefit-risk balance for aH5N1c is positive for the prevention of infection from A/H5N1 virus.

When blood samples are taken, there is a risk of bruising at the injection site, soreness, possibly bleeding. Sometimes a person may become dizzy or faint for a short period of time. There is a rare possibility of infection or of nerve injury. Details of study procedures can be found in Section 3.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of the aH5N6c vaccine may be found in the Investigators' Brochure and the participant information leaflet.

2 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 Primary Immunogenicity Objective(s) and Endpoints

The primary immunogenicity objective is to assess immune responses against H5N6 (contained in the vaccine) as measured by hemagglutination inhibition (HI)[4] assay 1 week (Day 8) and 3 weeks (Day 22) after the first heterologous aH5N6c booster vaccination, and 3 weeks (Day 43) after the second heterologous aH5N6c booster or placebo vaccination.

2.2 Secondary Objectives

2.2.1 Secondary Immunogenicity Objectives

a. To assess immune responses against H5N1 (contained in the priming vaccine) as measured by HI[4] assay 1 week (Day 8) and 3 weeks (Day 22) after the first heterologous aH5N6c booster vaccination, and 3 weeks (Day 43) after the second heterologous aH5N6c booster or placebo vaccination.

b. To assess persistence of immune response against H5N1 (contained in the priming vaccine) as measured by HI[4] assay at Day 1 (pre-vaccination) and at Day 202, 6 months after the second heterologous aH5N6c booster or placebo vaccination.

c. To assess persistence of immune response against H5N6 (contained in the booster vaccine) as measured by HI[4] assay at Day 202, 6 months after the second heterologous aH5N6c booster or placebo vaccination.

2.2.2 Secondary Safety Objectives

To assess the safety and reactogenicity of aH5N6c vaccine.

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

2.3 Exploratory Objectives

To further evaluate immune responses to seasonal and/or homologous and/heterologous pandemic influenza strain(s), such as measured by the HI, microneutralization (MN), and single radial hemolysis (SRH) (depending on availability of blood samples and on assay availability).

3 STUDY DESIGN

3.1 Overview of Study Design

This is a Phase 2, randomized, multi-center study in approximately 300 adults who received 2 doses of aH5N1c or placebo[5] in and completed the parent study V89_18 in the <65 years of age cohort.

Eligible subjects, who received 2 doses of aH5N1c in the parent study V89_18 will be randomized in a 1:1 ratio to receive either two aH5N6c vaccinations, 3 weeks apart (group 1) or an aH5N6c vaccination on Day 1 and saline placebo on Day 22 (group 2). Eligible subjects, who received placebo[5] in the parent study will receive two aH5N6c vaccinations, 3 weeks apart (group 3), see table below.

Treatment group	Treatment in parent Study V89_18	Treatment schedule in extension study V89_18E1		Total planned (N)
		Day 1	Day 22	
Group 1	aH5N1c	aH5N6c	aH5N6c	100
Group 2	aH5N1c	aH5N6c	Placebo	100
Group 3	Placebo[5]	aH5N6c	aH5N6c	100

[5] In case insufficient numbers of subjects who received 2 doses of placebo in the V89_18 parent study can be included, A/H5 naïve subjects may be enrolled (i.e. did not receive an influenza H5 vaccine in the past or have a history of H5 influenza infection prior to enrollment).

Vaccine administration will be performed IM, in an observer-blind manner. After each vaccination, subjects will remain under medical supervision at the study site for at least 30 minutes for observation of immediate adverse events (AEs). After the second vaccine administration, subjects will be monitored for approximately 6 months for safety and antibody persistence. The total study duration will be approximately 7 months per subject.

For all subjects, study participation includes a total of 5 clinic visits[6], 2 diary completion reminder calls, and 2 safety telephone calls through the treatment and follow-up periods.

- Treatment period (Day 1 through Day 43): 4 clinic visits and 2 diary completion reminder calls.
- Follow-up period (Day 44 through Day 202): 1 clinic visit and 2 safety telephone calls.

Immunogenicity will be measured by HI assay. Blood samples for immunogenicity assessments will be collected from each subject on Day 1 (before vaccination), Day 8, Day 22 (before vaccination), Day 43, and Day 202.

Subject diary cards will be used to collect solicited local and systemic AEs for 7 consecutive days following each vaccination. Solicited local AEs will include: injection site induration, erythema, ecchymosis and pain. Solicited systemic AEs will include: nausea, myalgia, arthralgia, headache, fatigue, chills, loss of appetite, malaise and fever (derived from measured body [preferably oral] temperature ≥38.0 °C [≥100.4 °F]). In addition, the use of analgesic/antipyretic medication for prevention or treatment will be recorded. Furthermore, during the treatment period (Day 1 through Day 43), all unsolicited AEs (including medically attended AEs (MAAEs)), Serious AEs (SAEs), all AEs of special interest (AESIs), AEs leading to study withdrawal, associated concomitant medications for any of these events, and all vaccinations will be collected. During the follow-up period (Day 44 through Day 202), only a subset of unsolicited AEs and associated medications used to treat these events, and all vaccinations will be collected in the electronic Case Report Form (eCRF): all SAEs, AESIs, AEs leading to study withdrawal, MAAEs.

[6] In the exceptional case that a clinic visit is not possible due to the site being closed, with appropriate sponsor approvals a home visit may be considered (applicable to visits on Day 8, Day 43 and Day 202 only).

3.2 Scientific Rationale for Study Design

Vaccination is considered to be the most effective strategy for the mitigation of morbidity and mortality caused by influenza pandemics (Nichol and Treanor, 2006; Bernstein et al., 2008). Ensuring protection of First Responders (who will be on the front line of a pandemic response) during the interval between the declaration of a pandemic and the availability of a strain matched vaccine is paramount. The use of a pre-pandemic vaccine, containing antigens derived from a subtype strain, may improve the speed and enhance the amplitude of the response to a subsequent booster regimen matching the actual pandemic strain (Osterhaus, 2007; Jennings et al., 2008). The pre-pandemic vaccine should have the ability to induce broadly cross-reactive antibody responses against the emerging pandemic strain and provide at least partial protection.

The aim of this study is to investigate whether two priming doses of MF59-adjuvanted A/turkey/Turkey/1/2005 (H5N1, clade 2.2) cell culture-derived vaccine (aH5N1c) followed by one or two booster vaccinations with a MF59-adjuvanted H5N6 (A/Guangdong/18SF020/2018 (H5N6)-like CDC/CNIC [clade 2.3.4.4h]) cell culture-derived vaccine (aH5N6c) 3 weeks apart elicit immune responses to the antigens used for priming (H5N1) and boosting (H5N6) after first and second heterologous booster vaccination. The study will evaluate immunogenicity, antibody persistence, cross-reactive antibody responses, reactogenicity and safety of one or two aH5N6c vaccinations.

3.3 Justification for Dose

The selected dose and formulation of aHN6c ([redacted] µg HA/0.5 mL with [redacted] mL MF59 per dose) is based on the US licensed aH5N1c vaccine. The aH5N1c vaccine is safe and well tolerated as demonstrated in previous studies.

3.4 Study Period

Each subject should expect to participate in the study for 7 months, from the time of enrolment through the last study visit.

3.5 Blinding Procedures

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

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

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

- Physical examination including temperature, height, and weight.
- Medical history.
- Influenza vaccination history within the previous 2 years.
- Reactogenicity: Solicited AEs for 7 consecutive days following each vaccination.
- Unsolicited AEs (including MAAEs) for 21 days following each vaccination (Day 1 through Day 43).
- SAEs, AEs leading to withdrawal from the study, AESIs, and MAAEs as collected from Day 1 to Day 202.
- Concomitant medications/vaccinations (as defined in section Section 6.5, Prior and Concomitant Medications and Vaccines).
- Reason for early termination (if applicable).

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

3.6.2 Tools Used for Data Collection

Data will be recorded in the subject's source document, Subject Diary and collected on eCRFs.

Subject Diary

Paper Diaries, hereafter referred to as Subject Diaries will be the only source document allowed for solicited local and systemic adverse events (including body temperature measurements), starting after the initial 30-minute post-vaccination period at the clinic and continuing for 7 consecutive days following each vaccination. The following additional rules apply to documentation of safety information collected in the Subject Diary.

The Investigator or delegated staff should monitor the Subject Diary status during the treatment period of the study for compliance and should review the solicited local and systemic adverse events information reported by the subject.

The following additional rules apply to documentation of safety information collected in the diary cards:

1. No corrections or additions to the information recorded by the subject within the Subject Diary will be allowed after it is delivered to the site.

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

Electronic Case Report Forms

This study utilizes 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. Subject eCRF casebooks will be compared with the subject source records, according to the study-specific monitoring plan, by a Seqirus-approved study monitor (or designee) over the duration of the study in order to ensure data collection accuracy.

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

1. The site must enter all readable entries in the Subject Diary into the eCRF, including those values that may be biologically implausible (e.g. body temperature: 400°C).

2. Any illegible or implausible data should be reviewed with the subject. If an underlying solicited or unsolicited AE is described on review with the subject, this should be described in the source document and reported as an unsolicited AE in the Adverse Event eCRF (e.g., if the subject above confirms body temperature of 40°C on the day in which body temperature: 400°C was written into his/her Subject Diary, this fever of 40°C should be recorded in the Adverse Event eCRF).

3. Any newly described safety information (including a solicited AE) must not be written into the Subject Diary and must be described in the study file as a verbally reported AE. Any AE

reported in this fashion must be described as an unsolicited AE and therefore entered on the Adverse Event eCRF.

3.7 Collection of Clinical Specimens

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

- Blood;
- Urine

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

Blood Specimens

Approximately 10 mL sample of blood will be drawn from all subjects at Visit 1 (Day 1) before vaccination, at Visit 2 (Day 8)[7], at Visit 3 (Day 22) before vaccination, Visit 4 (Day 43)[7], and Visit 7 (Day 202)[7]. The blood volume will not exceed 10 mL at each time point in order to provide the necessary serum volume (approximately half of the blood draw volume) for the serology assays.

The blood will be used for immunological assays. See section 7, Assessments for additional details.

The total amount of blood collected over the study period per subject will be 50 mL.

Urine Specimens

Urine will be collected for pregnancy testing in females of child bearing potential. Urine will be collected at Visit 1 (Day 1) and Visit 3 (Day 22) before vaccination, and the results recorded in the source document and eCRF.

3.8 Stopping/Pausing Guidelines

There are no predetermined stopping rules other than circumstances for which subjects may not be eligible for additional study vaccinations as described in Section 4, Selection of Study Population

[7] In the exceptional case that a clinic visit is not possible due to the site being closed, with appropriate sponsor approvals a home visit may be considered.

or may be withdrawn from the study according to the best interests of the subject as described in Section 4.5, Premature Withdrawal from Study.

3.9 Data Monitoring Committee

Not applicable.

3.10 End of Study

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

Evaluation of the primary and secondary immunogenicity objectives requires the testing of biological samples from the study subjects, which can only be completed after all samples are collected. The last samples for the analysis of the primary and secondary objectives will be taken at Visit 7 (Day 202). For the purpose of this protocol, end of study is defined as the completion of the testing of such biological samples, to be achieved no later than 8 months after collection of the last biological sample Visit 7 (Day 202).

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. Subjects who received 2 doses of aH5N1c vaccine or placebo[8] in and completed the parent study V89_18 in the <65 years of age cohort.
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.

[8] In case insufficient numbers of subjects, who received 2 doses of placebo in the V89_18 parent study can be included A/H5 naïve subjects may be enrolled (i.e. did not receive an influenza H5 vaccine in the past or have a history of H5 influenza infection prior to enrollment).

3. Individuals who can comply with study procedures including follow-up[9].
4. Males, females of non-childbearing potential[10] or females of childbearing potential who are using an effective birth control method[11] which they intend to use for at least 30 days after the last study vaccination.

4.2 Exclusion Criteria

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

1. Females of childbearing potential who are pregnant, lactating, or who have not adhered to a specified set of contraceptive methods from at least 30 days prior to study entry and who do not plan to do so until at least 30 days after the last 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. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws.

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

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

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

- Abstinence
- Hormonal contraceptive (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 (IUD)
- Tubal ligation
- Male partner using condom with spermicide
- Male partner having been vasectomized at least six months prior to informed consent

5. Abnormal function of the immune system resulting from:

    a. Clinical conditions.

    b. Systemic administration of corticosteroids (PO/IV/IM) at a dose ≥20 mg/day of prednisone (or equivalent) for more than 14 consecutive days. Topical, inhaled and intranasal corticosteroids are permitted. Intermittent use (one dose in 30 days) of intra-articular corticosteroids are also permitted.

    c. Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent.

6. History of any medical condition considered an AESI.

7. Received immunoglobulins with immunomodulating effects or any blood products within 180 days prior to informed consent.

8. Subjects, who received an influenza H5 vaccine other than in the V89_18 parent study or have a history of H5 influenza infection prior to enrollment.

9. Received an investigational or non-registered medicinal product within 30 days prior to informed consent.

10. Study personnel or immediate family or household member of study personnel.

11. 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.

12. Individuals who received any other vaccines (with the exception of COVID 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 vaccination.

13. Receipt of any (investigational or licensed) COVID-19 vaccine within 7 days prior to enrollment or plan to receive any COVID-19 vaccine within 7 days from study vaccination.

14. Acute (severe) febrile illness (see Section 4.3 Criteria for Delay of Vaccination).

15. A known history of Guillain-Barre Syndrome or other demyelinating diseases such as encephalomyelitis and transverse myelitis.

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

4.3 Criteria for Delay of Vaccination

There may be instances when individuals meet all eligibility criteria for vaccination yet have a transient clinical circumstance, such as an infection, which may warrant delay of vaccination. These situations are listed below. In the event that a subject meets a criterion for delay of vaccination, the subject may receive study vaccination once the window for delay has passed as long as the subject is otherwise eligible for study participation.

- Acute moderate or severe infection with or without fever (defined as body temperature >38.0° C (100.4° F)) within 3 days of intended study vaccination.
- Fever within 3 days of intended study vaccination.
- Administration of any vaccine not foreseen by the study protocol within 14 days prior the intended study vaccination.
- Prophylactic use of antipyretics and/or analgesic medications within 24 hours prior to vaccination.

There are also circumstances under which repeat vaccination is a contraindication in this study. These circumstances are presented in Section 4.4.

4.4 Criteria for Repeat Vaccination in the Study

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

- Has experienced any immediate allergic reaction after the previous study vaccination.

- Has experienced any SAE judged to be possibly or probably related to study vaccination, including hypersensitivity reactions.
- Has developed any clinically significant medical condition which, in the opinion of the investigator, may pose additional risk to the subject if he/she continues to participate in the study.
- Subject is pregnant.

Any subject who becomes pregnant during the study, despite the protocol requirement for adequate contraception, will not receive further vaccinations but should be encouraged to continue participating in the study for safety follow-up. The site must record a confirmation of pregnancy in the eCRF and complete a Pregnancy Reporting/Outcome Form as soon as possible after learning of pregnancy occurrence (see Section 7.1.6, Pregnancies for further details).

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

4.5 Premature Withdrawal from Study

Subjects may withdraw at any time, or be withdrawn from the study at the discretion of the investigator should any untoward effects occur and/or for safety reasons. In addition, a subject may be withdrawn by the investigator or the Sponsor if he/she violates the study plan or for administrative reasons. The investigator or study coordinator must notify the Sponsor immediately when a subject has been withdrawn due to an AE.

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal. If a subject wants to withdraw from the study before all doses are administered or prior to the last planned study visit, the subject will be asked to be followed for safety for the duration of the study. When a subject withdraws, or is withdrawn, from the study, the procedures described in section 5.6.1, Early Termination Visit should be completed if possible.

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

Death

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

Withdrawal of consent

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

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

Lost to Follow-Up

For subjects who fail to show up for final visits (clinic or telephone contacts), or for three consecutive visits, study staff are encouraged to make at least three documented attempts to contact the subject by telephone and at least one documented written attempt to contact the subject to encourage the completion of study termination procedures. These efforts to contact the subject

should be recorded in the source document. The termination date for the subject to be captured on the Study Completion eCRF page is the date of the last successful contact (clinic visit or telephone) with the subject.

Other Reasons

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

Study Terminated by Sponsor

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

5 STUDY PROCEDURES

The sections that follow provide an overview of the procedures that are to be followed in enrolling, evaluating, and following subjects who participate in this clinical study. Visits can be either clinic (or home) visits or safety follow-up telephone calls, as specified in the Study Procedures table (Table 5-1) and in the Time and Events Schedule (Table 0-1).

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

Table 5-1: Study Procedures

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

5.1 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, screening, enrolment and randomization. Visits can be either clinic or home visits or safety follow-up telephone calls, as specified in the Study Procedures table (Table 5-1) and in the Time and Events Schedule (Table 0-1).

5.1.1 Informed Consent

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

Informed consent following local IRB/EC guidance **must** be obtained before conducting any study-specific procedure (i.e., all of the procedures described in the protocol). The process of obtaining

informed consent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent.

If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. An impartial witness is defined as a person who is independent from study conduct, who cannot be unfairly influenced by those involved with the study, who attends the informed consent process if the subject 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 ICF, 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 Subject ID, which is a consecutive number created by the investigator. The subject's unique ID 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.

Prior to study enrolment, demographic data will be collected from the subject, including: gender, race, ethnicity, height, weight, and influenza vaccination history in the last 2 years.

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

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

health care practitioner. "Qualified health care practitioner" refers to any licensed health care professional who is permitted by institutional policy to perform physical examinations and who is identified within the Study Staff Signature Log.

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

Measure height and weight.

Perform pregnancy testing in women of childbearing age (refer to Section 3.7, Collection of Clinical Specimens for guidance regarding the procedure).

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 as medical history.

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

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

5.1.3 **Enrolment**

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

5.1.4 **Randomization**

Enrolled subjects will be randomized in the IRT system using the unique Subject ID. The Subject ID will be the subject's unique identification number for all eCRFs and associated study documentation that will be used for duration of the study. The list of randomization assignments is produced by the IRT service provider and approved by Seqirus according to applicable Seqirus Standard Operating Procedure (SOP).

If for any reason, after signing the 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 as specified in the Source Data Agreement (SDA). The information on subjects who are randomization failures should be kept distinct from subjects who are screen failures, as described in Section 5.1.2, Screening.

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

5.1.5 Blood Draw

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

5.2 Vaccination Clinic Visits

Vaccination will be performed on Day 1 and Day 22.

Ensure the Day 1 and Day 22 blood samples are taken **prior** to each vaccination.

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

Prior to administration of each vaccination, confirm that the subject is eligible for additional study vaccinations and does not meet any criteria for delaying additional study vaccinations as described in Section 4.3 and Section 4.4.

5.3 Post-Vaccination Procedures

The following post-vaccination procedures will be performed on Day 1 and Day 22.

After vaccination, the subject will be observed for at least 30 minutes including observation for any AEs following vaccination. Record all safety data collected during this time in the subject's source document and the eCRF.

5.3.1 Subject Diary Training

A Subject Diary will be dispensed to all subjects. A Subject Diary will be used in this study to document solicited adverse events. The Subject Diary is the only source for collection of these data; therefore, it is critical that the subject completes the Subject Diary correctly. The subject should be trained on how and when to complete each field of the Subject Diary.

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

The subject should be instructed how to perform body temperature measurement using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject should check body temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the Subject Diary.

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

The same individual should complete the Subject Diary throughout the course of the study.

Schedule the next study activity

The site should schedule the next study activity with the subject. It is recommended for the site to already schedule in advance the remaining upcoming study activities.

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

5.3.2 Diary Reminder Calls

Reminder calls are not intended to be an interview for collection of safety data. If the subject wishes to describe safety information, this information should only be collected by a healthcare

professional at the site, and the safety data described must be written down in the subject's medical chart.

Subject Diary Reminder Calls

Subject Diary reminder calls will be performed on Day 4 and Day 25. The purpose of this call is to remind the subject about completion of the Subject Diary. The call follows the Subject Diary Reminder Telephone Call Script provided to the site. The subject should be reminded to contact the site via the telephone number provided in the informed consent to discuss medical questions.

5.4 Post-Vaccination Visit(s)

Post-vaccination visits or safety follow-up calls will be performed on Day 8 (Clinic visit), Day 22 (Clinic visit), Day 43 (Clinic visit), Day 92 (Safety follow-up call), Day 142 (Safety follow-up call) and Day 202 (Clinic visit).

5.4.1 Follow-up Clinic Visit(s)

Safety follow-up clinic visits will be performed on Day 8, Day 22, Day 43, and Day 202.

During the follow-up clinic visit Day 8 and Day 43, the Subject Diary will be reviewed. No changes to the information recorded within the Subject Diary are permissible. For details on the Subject Diary see sections 3.6.2, Tools Used for Data Collection and 5.3.1, Subject Diary Training. The subject will be interviewed to determine if any unsolicited AEs (including MAAEs) occurred and if any concomitant medications or vaccines were taken/received in the time since the last clinic visit. This interview will follow a script which will facilitate the collection of relevant safety information. The qualified healthcare professional reviewing these data will discuss the symptoms (if any) reported by the subject and will determine if any additional diagnoses and/or AEs are present. Adverse events reported by the subject at this follow-up clinic visit must be recorded in the subject's source document and on an Adverse Events eCRF, as specified in section 7.1, Safety Assessment, and not written on the script used for the interview.

Perform a brief symptom-directed physical examination if necessary according to symptoms the subject has reported. This is a physical examination that will include an examination of organ systems that are relevant to the investigator based on review of the subject's reported adverse events and concomitant medication use. This assessment may include: measurement of vital signs, body temperature (specify route) and a check of general appearance. The physical assessment must be performed by the investigator or designee of the investigator, who is qualified to perform a

physical assessment in accordance with their institutional policy. Corresponding information is documented in the subject's source document and eCRF(s).

The site should schedule the next study activity with the subject.

The subject will receive a written reminder of the next planned study activity. The subject will be reminded to complete the Subject Diary 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.

5.4.2 **Safety Follow-up Calls**

Safety follow-up calls will be performed on Day 92 and Day 142.

Safety follow-up calls are calls made to the subject by a qualified healthcare professional designated on the site's roles and responsibilities log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject will be interviewed according to the script, and information relating to the following unsolicited adverse events: SAEs, AESIs, AEs leading to withdrawal, MAAEs, and concomitant medications or vaccinations associated with those events. All safety information described by the subject must be written down in a designated location within the source document and not written on the script used for the telephone call.

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

5.5 Unscheduled Visits

An unscheduled visit describes a non-routine study visit triggered by a specific event. These could include anticipated or unanticipated adverse events or interventions.

Unscheduled visits may include, but are not limited to, review of Subject Diary Card data, review of systems, symptom directed physical examination, and blood sampling for safety, and should be documented in the subject's source documentation.

5.6 Study Completion/Termination Visit

The study termination visit will occur on Day 202. The termination visit will be a clinic visit. The date of termination is the date of the last contact (clinic visit or telephone call) in which the subject's health status was assessed or, in cases where the subject does not agree to any further safety follow-up, it is the date consent is withdrawn. This date should be recorded on the Study Completion eCRF page. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see section 5.6.1, Early Termination Visit.

During the clinic visit, the following procedures will be performed: review of systems, symptom-directed physical assessment, interview of subject to collect the following unsolicited adverse events: SAEs, AEs leading to withdrawal, AESIs, MAAEs, and concomitant medications/ vaccinations associated with those events, and blood sampling for immunogenicity.

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

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

5.6.1 Discontinuation Visit

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the Sponsor and, when possible, will perform the procedures as described in Section 5.6, Study Completion/Termination Visit. The reason(s) for the early termination will be included in the subject's source documentation. If the Early Termination Visit is a telephone call, collect as much information as possible. Early Termination Visits include subjects who were randomized but not treated.

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

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

6 TREATMENT OF SUBJECTS

All vaccines associated with this study are to be stored separately from other vaccines and medications in a secure location under appropriate storage conditions with temperature monitoring. All vaccines associated with this study must be checked for expiration date and if it has experienced a temperature deviation prior to use. **Expired vaccines or those that have experienced a temperature deviation must not be administered to subjects,** as specified in Section 6.6, Vaccine Supply, Labeling, Storage and Tracking.

6.1 Study Vaccine(s)

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

The vaccine used for this study is aH5N6c vaccine, a cell culture-derived, MF59-adjuvanted, monovalent inactivated subunit H5N6 (A/Guangdong/18SF020/2018 (H5N6)-like strain) vaccine. Each dose contains [redacted] µg H5 hemagglutinin (HA) + [redacted] mL MF59, the composition of the aH5N6c vaccine is presented in Table 6-1 below.

Placebo will consist of [redacted] mL sterile saline (0.9% NaCl).

Table 6-1: aH5N6c vaccine composition

Vaccine Components	Full dose vaccine formulation (0.5 mL volume)
Influenza virus surface antigens (hemagglutinin and neuraminidase); A/Guangdong/18SF020/2018 (H5N6)-like strain	[redacted] µg (in 0.5 mL volume of vaccine formulation)
Adjuvant	MF59 content in [redacted] mL volume: Squalene ([redacted] mg) Polysorbate 80 ([redacted] mg) Sorbitan Trioleate ([redacted] mg) Sodium Citrate ([redacted] mg) Citric Acid ([redacted] mg)
Excipients	Excipients content in [redacted] mL volume: Sodium Chloride ([redacted]) Potassium Chloride ([redacted] mg) - Potassium Dihydrogen Phosphate ([redacted] mg) - Disodium Phosphate Dihydrate ([redacted] mg) Magnesium Chloride Hexahydrate ([redacted] mg)

Buffer	Up to [redacted] mL, Water for Injection
Volume of Formulation	[redacted] mL
Appearance	White homogenous liquid. Free from visible foreign particulates.
Vaccine Presentation	Prefilled Syringe, [redacted] mL total extractable volume

6.2 Non-Study Vaccines

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

6.3 Vaccine Preparation and Administration

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

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

PRECAUTIONS TO BE OBSERVED IN ADMINISTERING STUDY VACCINE:

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

Eligibility for subsequent study vaccination is determined by following the criteria outlined in Section 4.3, Criteria for Delay of Vaccination and Section 4.4, Criteria for Repeat Vaccination in the Study.

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

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

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

6.4 Vaccine Administration Error or Overdose of Vaccine

Vaccine administration error is defined as receiving a dose of study vaccine that was not reconstituted as instructed or administered by a different route from the intended route of administration. An overdose of study vaccine (whether accidental or intentional) is defined when a dosage higher than the recommended dosage is administered in one dose of study vaccine as per dosing regimen described in Section 6.1, Study Vaccines.

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

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

6.5 Prior and Concomitant Medications and Vaccines

All medications, vaccines and blood products taken or received by the subject within 30/90/180 days prior to the start of the study are to be recorded on the Concomitant Medications eCRF, as described below.

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

- Systemic administration of corticosteroids (PO/IV/IM) at a dose ≥20 mg/day of prednisone (or equivalent) for more than 14 consecutive days within 90 days prior to informed consent;
- Administration of antineoplastic and immunomodulating agents or radiotherapy within 90 days prior to informed consent;
- Immunoglobulins or any blood products within 180 days prior to informed consent;
- Receipt of an H5 vaccine other than in the V89_18 parent study;

- Receipt of an investigational or non-registered medicinal product within 30 days prior to informed consent;
- Receipt of any inactivated non-influenza vaccine 14 days or live-attenuated vaccine 28 days prior to enrollment in this study;
- Receipt of any COVID-19 vaccine 7 days prior to enrollment in this 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 prophylactic use of antipyretics/analgesics within 24 hours prior to vaccine administration is a reason to delay study vaccination (see Section 4.3, Criteria for Delay of Vaccination).

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

Concomitant medications 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 are to be recorded in the Concomitant Medications CRF:

- All concomitant medications from Day 1 through Day 43;
- All medications associated with SAEs, AESIs, and AEs that lead to premature withdrawal from the study, from Day 1 to study completion;
- All vaccines, including any seasonal/pandemic influenza or COVID-19 vaccines, from Day 1 to study completion;
- Any investigational and non-registered medicinal product (other than the study vaccines) during the entire study period Day 1 to study completion.

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

In addition, the use of the following concomitant medications, for conditions reported in the medical history, from enrolment until end of the study should be documented on the Concomitant

Medication eCRF page as they may have an effect on the interpretation of the study objectives and therefore if used, may be determined to be a reason for exclusion from one of the analysis sets:

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

6.6 Vaccine Supply, Labeling, Storage and Tracking

The Sponsor will ensure the following:

- Supply the study vaccine/saline placebo.
- Appropriate labeling of all study vaccines/saline placebo 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 that the required temperature range during shipment from the Sponsor to the investigator's designated storage location has been maintained;
  - Report any temperature deviation and do not use vaccines until further confirmation by the Sponsor or delegate that the vaccines are authorized for use;
- Proper storage of the study vaccines, including:
  - Storage in a secure, locked, temperature-controlled location;
  - Proper storage according to the instructions specified on the labels and in the Investigator Pharmacy Manual;

  - Appropriate record keeping and inventory of the study vaccines, including regular documentation of adequate storage temperature.

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

Vaccines that have been stored differently from the manufacturer's indications **must not** be used unless the Sponsor provides written authorization for use. In the event that the use cannot be

authorized, the Sponsor will make every effort to replace the vaccine supply. All vaccines used in conjunction with this protocol must be stored separately from normal hospital/practice stocks to prevent unintentional use of study vaccines outside of the clinical study setting.

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

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

7 ASSESSMENTS

7.1 Safety Assessments

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

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

The period of observation for AEs extends from the time immediately after the subject has received the study vaccine until he or she completes the study completion visit (Day 202) or terminates the study. Adverse events occurring after the informed consent form is signed but prior to receiving study vaccine/placebo will be documented as medical history in the source document and medical history eCRF.

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

7.1.1 Solicited Adverse Events

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

The solicited local and systemic AEs are included in the Subject Diary. Each AE is to be assessed according to defined severity grading scales.

The collected data will be entered into the Subject Diary. Please see Section 3.6.2, Tools Used for Data Collection for more detail.

Solicited Local Adverse Events

Injection site induration, erythema, ecchymosis and pain are included in the Subject Diary and should be recorded by the subject. Each solicited local AE is to be assessed using the scoring system reported in Table 7-1.

Solicited Systemic Adverse Events

The following solicited systemic AEs are included in the Subject Diary: nausea, myalgia, arthralgia, headache, fatigue, chills, loss of appetite, malaise and fever (derived from measured body temperature; defined as body temperature ≥38.0 °C [≥100.4 °F]).

Each solicited systemic AE is to be assessed using the scoring system reported in Table 7-1 below:

Table 7-1: Severity Grading for Solicited Local and Systemic Adverse Events[12]

Solicited Event	Grade 1/Mild	Grade 2/Moderate	Grade 3/Severe
Injection site pain	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Injection site induration / erythema / ecchymosis	2.5-5 cm	5.1-10 cm	>10 cm

[12] This toxicity grading scale is adapted from CBER 2007b to enable ease of reporting by subjects in the diary cards for 'patient reported' solicited AEs. 'Grade 4' is not listed here but will be defined in the Statistical Analysis Plan as necessary.

Solicited Event	Grade 1/Mild	Grade 2/Moderate	Grade 3/Severe
Fever	38.0–38.4°C 100.4-101.1°F	38.5–38.9°C 101.2-102°F	39.0–40°C 102.1-104°F
Nausea	Nausea present but not interfering with oral intake	Nausea leading to decreased oral intake	Nausea leading to minimal or no oral intake
Myalgia	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Arthralgia	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Headache	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Fatigue	No interference with activity	Some interference with activity	Significant, prevents daily activity
Chills	Present but does not interfere with activity	Interferes with activity	Prevents daily activity
Loss of appetite	Loss of appetite without decrease in oral intake	Decreased oral intake without weight loss	Decreased oral intake with weight loss
Malaise	No interference with activity	Some interference with activity	Significant, prevents daily activity

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 Diary as described in Section 3.6.2, Tools Used for Data Collection and Section 5.4.1, Follow-up Clinic Visit(s).

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 Adverse Event eCRF:

- Solicited local or systemic AE that continues beyond day 7 after vaccination.
- Solicited local or systemic AE leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (adverse event leading to withdrawal, see Section 7.1.3, Evaluation of Adverse Events).
- Solicited local or systemic AE that otherwise meets the definition of a SAE (see Section 7.1.4, Serious Adverse Events).

7.1.2 Unsolicited Adverse Events

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

Potential unsolicited AEs may be medically attended (defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a 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. The detailed information about the reported unsolicited AEs will be collected by the qualified site personnel during the interview and will be documented in the subject's records. In this study, all unsolicited AEs (including MAAEs) will be collected during the treatment period (Day 1 through Day 43) and only specific unsolicited AEs (SAEs, AEs leading to withdrawal, AESIs, and MAAEs) will be collected during the follow-up period (Day 44 through Day 202). In addition, any AEs reported within 30 minutes after the study vaccination will be collected as immediate post-vaccination AEs.

7.1.3 Evaluation of Adverse Events

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

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

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

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

1. Not Related

The AE is not related to an investigational vaccine if there is evidence that clearly indicates an alternative explanation. If the timing of the exposure to the vaccine and the onset of the AE are not

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

2. Possibly Related

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

3. Probably Related

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

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

Note: solicited AEs will not be evaluated for relationship to study treatment. Grading for severity of solicited local and systemic AEs is described in Section 7.1.1, Solicited Adverse Events.

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

- AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal;
- AESIs: Please see Appendix 2 for the full list of AESIs;
- MAAEs: AEs that lead to an unscheduled visit to/by a healthcare professional.

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

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

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

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

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

All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the Sponsor as related/suspected events.

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

1. Related/suspected

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

2. Not Related

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

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

In addition, SAEs will be evaluated by the Sponsor or designee for "expectedness." An unexpected AE is one that is not listed in the aH5N1c Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

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

7.1.4.1 Adverse Events of Special Interest

Adverse events of special interest (AESIs) are a predefined list of AEs that are potentially immune-mediated medical conditions that theoretically have the potential for association with novel vaccines. The list of AESIs is presented in Appendix 2.

Subjects will be assessed at each visit for any new medical events or signs or symptoms that could possibly indicate an AESI. The subject will be asked whether any new diagnosis has been given to the subject through a review of recent medical history. Should a qualified 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 a SAE and will be captured on the AE eCRF. If the eCRF is not available, then the study site must complete the paper Adverse Event of Special Interest Report Form and send to Seqirus Pharmacovigilance and Risk Management (PVRM) (or delegate) at AE.reporting@seqirus.com. The investigator must notify Seqirus within 24 hours. Once the eCRF is available, the AESI should be documented on the AE

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

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

Findings regarding Adverse Events must be reported on the AE eCRF, as specified in Section 7.1.2, Unsolicited Adverse Events, which is part of the Investigator Site File. All findings in subjects experiencing AEs must be reported also in the subject's source document.

All SAEs which occur during the course of the study, whether considered to be associated with the study vaccination or not, must be 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 Serious Adverse Event Report Form and send to Seqirus 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 SAE will be recorded on the appropriate eCRF(s) in addition to the outcome of the SAE.

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

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

Seqirus (or delegate) must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse reactions (also known as SUSARs) to the regulatory authority(ies) and the IRB/EC. If a SUSAR is reported to Seqirus (or delegate), 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 in accordance with country specific regulatory requirements.

7.1.5.1 Post-Study Events

Any SAE that occurs after the end of the study but is considered to be causally related to the study vaccine by the investigator must be reported to Seqirus PVRM (or delegate) at AE.reporting@seqirus.com.

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

7.1.6 Pregnancies

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

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 vaccines, which will be measured by the HI assay by titrating antibodies against the influenza strains contained in the vaccines (H5N6 and H5N1).

For the primary and secondary immunogenicity objectives, HI antibody responses will be evaluated for the strains included in the study vaccine (H5N6). For the secondary objectives the HI responses are evaluated for the strain included in the priming vaccine (H5N1). In case of a lack of agglutination or agglutination mediated through neuraminidase for a specific strain using HI assay, immunogenicity for that strain will be assessed as measured by the MN assay.

For the exploratory immunogenicity objective, immune responses may be evaluated with additional assays, such as testing against heterologous strains or alternative assay methods (e.g., MN). Additionally, sera samples may be tested in future research not directly related to this study, but with the purpose to improve the understanding of the influenza vaccines or disease.

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

8 STATISTICAL CONSIDERATIONS

8.1 Endpoints

8.1.1 Primary Endpoint(s)

A complete description of the statistical analyses and methods will be available in the Statistical Analysis Plan (SAP), which will be drafted before the first subject is enrolled and finalized before the database is locked for the primary analysis. The primary analysis will be conducted on the immunogenicity data collected up to Day 43.

8.1.1.1 Primary Efficacy Endpoint(s)

The study does not have a primary efficacy endpoint.

8.1.1.2 Primary Immunogenicity Endpoint(s)

The primary immunogenicity endpoints are the humoral immune responses in terms of HI antibody response against the booster vaccine strain (A/H5N6):

- Geometric mean titer (GMT) of HI antibodies on Day 1, Day 8, Day 22, and Day 43;

- Geometric mean fold increase (GMFI): The geometric mean of the fold increase of postvaccination HI titers over the prevaccination HI titer (Day 8/Day 1, Day 22/Day 1, Day 43/Day 1).

- Seroconversion rate (SCR) defined as the percentage of subjects with either a prevaccination HI titer <1:10 and a postvaccination HI titer ≥1:40, or with either a prevaccination HI titer ≥1:10 and a ≥4-fold increase in postvaccination HI titer on Day 8, Day 22 and Day 43;

- The percentage of subjects with a titer ≥1:40 on Day 1, Day 8, Day 22, and Day 43.

The derived variables are:

- Geometric mean titer ratios (GMTr) of HI antibodies between vaccine arms on Day 1, Day 8, Day 22, and Day 43 for A/H5N6;

- The inter-group differences in the SCRs at Day 8, Day 22, and Day 43 for A/H5N6.

- The inter-group differences in the percentage of subjects with a titer ≥1:40 on Day 1, Day 8, Day 22, and Day 43 for A/H5N6.

8.1.1.3 Primary Safety Endpoint(s)

The study does not have a primary safety endpoint.

8.1.2 Secondary Endpoint(s)

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

8.1.2.1 Secondary Safety Endpoint(s)

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

- Solicited local and systemic AEs for 7 days following each vaccination (Day 1 through Day 7; and Day 22 through Day 28);

- All unsolicited AEs (including MAAEs) for 21 days following each vaccination (Day 1 through Day 43);
- SAEs, AEs leading to withdrawal from the study, AESIs, MAAEs as collected from Day 1 through Day 202.

8.1.2.2 Secondary Efficacy Endpoint(s)

The study does not have a secondary efficacy endpoint.

8.1.2.3 Secondary Immunogenicity Endpoint(s)

The secondary immunogenicity endpoints are the immune responses to the aH5N1c vaccine in terms of HI antibody responses against the H5N1 strain contained in the priming vaccine by:

- GMT of HI antibodies on Day 1, Day 8, Day 22, Day 43 and Day 202;
- GMFI: The geometric mean of the fold increase of postvaccination HI titers over the prevaccination HI titer against H5N1 (Day 8/Day 1, Day 22/Day 1, Day 43/Day 1, Day 202/Day 1).
- SCR defined as the percentage of subjects with either a prevaccination HI titer <1:10 and a postvaccination HI titer ≥1:40, or with either a prevaccination HI titer ≥1:10 and a ≥4-fold increase in postvaccination HI titer against H5N1 on Day 8, Day 22, Day 43, and Day 202;
- The percentage of subjects with a titer ≥1:40 against H5N1 on Day 1, Day 8, Day 22, Day 43, and Day 202.

Immune responses to the aH5N6c vaccine in terms of HI antibody responses against the H5N6 strain contained in the vaccine by:

- GMT: Geometric mean of HI antibodies at Day 202.
- GMFI: The Geometric mean of the fold increase in serum HI titer 6 months (Day 202) after the second vaccination compared to pre-vaccination (Day 1).
- Percentages of subjects with HI titers ≥1:40 at Day 202.
- Percentage of subjects with seroconversion (defined as a ≥4-fold increase in titer postvaccination in those with pre-vaccination titer ≥1:10, or a postvaccination titer ≥1:40 for subjects with baseline titer <1:10) for HI antibodies at Day 202.

The derived variables are:

- GMTr of HI antibodies between vaccine arms on Day 1, Day 8, Day 22, Day 43 and Day 202 for A/H5N1, and on Day 202 for A/H5N6;
- The inter-group differences in the SCRs at Day 8, Day 22, Day 43, and Day 202 for A/H5N1, and at Day 202 for A/H5N6.
- The inter-group differences in the percentage of subjects with a titer ≥1:40 on Day 1, Day 8, Day 22, Day 43, and Day 202 for A/H5N1, and Day 202 for A/H5N6.

8.1.3 Exploratory Endpoint(s)

8.1.3.1 Exploratory Safety Endpoint(s)

The study does not have an exploratory safety endpoint.

8.1.3.2 Exploratory Efficacy Endpoint(s)

The study does not have an exploratory efficacy endpoint.

8.1.3.3 Exploratory Immunogenicity Endpoint(s)

Exploratory immunogenicity endpoints that may be assessed in the study include immune responses to seasonal and/or homologous and/heterologous pandemic influenza strain(s), such as measured by the HI, MN, and SRH (depending on availability of blood samples and on assay availability). Details will be described in the SAP.

8.2 Success Criteria

There are no pre-defined success criteria in this study.

8.2.1 Success Criteria for Primary Objective(s)

8.2.1.1 Success Criteria for Primary Safety Objective(s)

The study does not have a primary safety objective.

8.2.1.2 Success Criteria for Primary Efficacy Objective(s)

The study does not have a primary efficacy objective.

8.2.1.3 Success Criteria for Primary Immunogenicity Objective(s)

No success criteria for the primary immunogenicity objectives are prespecified. There are no statistical (null) hypotheses associated with the primary immunogenicity objectives, and all data will be analyzed descriptively. Statistical analyses of the immunogenicity endpoints will include point estimates and the associated two-sided 95% confidence intervals (CIs).

8.2.2 Success Criteria for Secondary Objective(s)

8.2.2.1 Success Criteria for Secondary Safety Objective(s)

No success criteria for the secondary safety objective are prespecified.

8.2.2.2 Success Criteria for Secondary Efficacy Objective(s)

The study does not have a secondary efficacy objective.

8.2.2.3 Success Criteria for Secondary Immunogenicity Objective(s)

No success criteria for the secondary immunogenicity objectives are prespecified. There are no statistical (null) hypotheses associated with the secondary immunogenicity objectives, and all data will be analyzed descriptively. Statistical analyses of the immunogenicity endpoints will include point estimates and the associated two-sided 95% CIs.

8.3 Analysis Sets

8.3.1 All Enrolled Set

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

8.3.2 All Exposed Set

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

8.3.3 Safety Set

Solicited Safety Set

All subjects in the Exposed Set with any solicited AE data and/or indicators of solicited AEs (e.g., use of analgesics/antipyretics).

Unsolicited Safety Set (unsolicited adverse events)

All subjects in the Exposed Set with unsolicited AE data.

Overall Safety Set

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

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

8.3.4 Full Analysis Set (FAS) Immunogenicity Set

Full Analysis Set Immunogenicity

All subjects in the All Enrolled Set who are randomized, receive at least one study vaccination and provide at least one evaluable serum sample at relevant timepoints. FAS will be defined by timepoint and objective. More details will be provided in the statistical analysis plan.

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

8.3.5 Per Protocol (PP) Immunogenicity Set

All subjects in the FAS Immunogenicity who:

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

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

Similar, to FAS, PPS will also be defined per objective and timepoint. Exclusions need to be considered by objective/time point, i.e., sometimes not all data of a subject but only part of the subject's data will be removed from the PPS analysis.

8.3.6 **Other Analysis Set(s)**

Not applicable.

8.3.7 **Subgroup(s)**

Primary and secondary analyses of immunogenicity and safety endpoints will be done for the total population.

Additional subgroup analysis will be conducted by as appropriate for immunogenicity or safety parameters:

- subjects stratified by baseline HI titer <1:10 or ≥1:10;
- subjects with and without seasonal influenza vaccine in the last 12 months;
- subjects by age (18 to <50 and ≥50 years of age);
- gender;
- race and ethnicity;
- center

Refer to the SAP for further details.

8.3.8 **Protocol Deviation(s)**

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

Distributions of subjects by sex, ethnicity, race and previous influenza vaccination (in the past 12 months) will be summarized overall and by study group.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

The study does not have a primary safety objective.

8.4.2.2 Analysis of Primary Efficacy Objective(s)

The study does not have a primary efficacy objective.

8.4.2.3 Analysis of Primary Immunogenicity Objective

The primary immunogenicity objective is:

- To assess immune responses against H5N6 (contained in the vaccine) as measured by HI[13] assay 1 week (Day 8) and 3 weeks (Day 22) after the first heterologous aH5N6c booster vaccination, and 3 weeks (Day 43) after the second heterologous aH5N6c booster or placebo vaccination.

8.4.2.3.1 Statistical Hypothesis

No formal statistical hypothesis testing will be performed for the primary immunogenicity objective.

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

8.4.2.3.2 Analysis Sets

All immunogenicity objectives will be evaluated based on the PPS Immunogenicity. In the case that there is >5% difference in the total number of subjects between the PPS Immunogenicity and the FAS Immunogenicity, additional analysis based on the FAS Immunogenicity will be conducted for sensitivity analysis.

8.4.2.3.3 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 of HI (and MN) titers will be presented graphically by time-point and strain.

Adjusted GMTs will be calculated based on the $\log_{10}$-transformed antibody titers at Day 8, Day 22, Day 43, and Day 202 using an Analysis of Covariance (ANCOVA) model which includes the vaccine group (G1, G2, G3), $\log_{10}$-transformed pre-vaccination antibody titer, and gender. GMT ratios between groups and pertaining 2-sided CIs will be calculated based on these models.

Unadjusted 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 study group.

The number and proportion of subjects achieving the binary endpoints (percentage of subjects with seroconversion) will be summarized by assessment (Day 8, Day 22, Day 43 and Day 202) and vaccine group. These summaries will be reported together with the associated two-sided 95% CIs for the proportion according to Clopper-Pearson.

The binary endpoints (percentage of subjects with seroconversion) at Day 8, Day 22, Day 43 and Day 202 will be compared between treatment groups by the differences of proportions with 95% CI using the Miettinen and Nurminen method without adjustment for covariate.

In addition, SCRs and the percentages of subjects achieving HI antibody titer ≥ 1:40 results collected at Day 8, Day 22, and Day 43 will also be evaluated against the age appropriate Center for Biologics Evaluation and Research (CBER) criteria, CBER Guidance Clinical Data Needed to

Support the Licensure of Pandemic Influenza Vaccines (United States Food and Drug Administration (FDA), 2007):

- The lower bound of the two-sided 95% confidence interval for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 30% for adults ≥65 years of age and 40% for adults <65 years of age.
- The lower bound of the two-sided 95% confidence interval for the percentage of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 60% for adults ≥65 years of age and 70% for adults <65 years of age.

Additional supportive analyses for binary endpoints might be done using generalized linear models with a qualitative factor for vaccine group, $\log_{10}$-transformed pre-vaccination antibody titer, and gender. Adjusted differences and pertaining 2-sided 95% CI between vaccine groups will be calculated based on the model. For immunogenicity data, it may be reasonable to consider missing immunogenicity values as missing completely at random (MCAR), i.e., not informative. Therefore, the immunogenicity analysis will comprise a complete case analysis only, without introducing any bias. Imputation methods will not be used.

8.4.3 Analysis of Secondary Objective(s)

8.4.3.1 Analysis of Secondary Safety Objective(s)

The secondary safety objective is:

- To assess the safety and reactogenicity of aH5N6c vaccine.

8.4.3.1.1 Analysis of Extent of Exposure

The number of subjects actually receiving the first and the second vaccination will be summarized by study group.

8.4.3.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

Solicited AEs are reported daily for 7 consecutive days following each vaccination. A solicited AE will be defined as “present” or at least mild on any of the recorded days to be counted. This will be summarized as total and for local, systemic and the “other” category separately. The same tables will be created at each timepoint.

Frequencies and percentages of subjects experiencing each AE will be presented overall and for each maximum symptom severity and by treatment group. Post-vaccination solicited AEs reported for 7 consecutive days following each vaccination will be summarized for the intervals 1-3, 4-7, 1-7 days post-vaccination by maximal severity and by study group, excluding the 30 minute measurement, which will be summarized separately. Injection-site erythema, ecchymosis and induration will be summarized according to categories based on linear measurements. Please refer to the SAP for definitions of categories.

Each solicited local and systemic AE will also be further summarized as “none” versus “any”.

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.

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

8.4.3.1.3 Analysis of Unsolicited Adverse Events

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

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

Separate summaries will be produced for the following categories:

- Serious adverse events.
- Adverse events that are possibly or probably related to vaccine.

- Adverse events of special interest.
- Adverse event leading to withdrawal.
- Medically attended adverse events.

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

During the follow-up period (Day 44 to Day 202), only AEs that meet the reporting criterion (an SAE, AESI, AE leading to withdrawal, or MAAE) are to be recorded in the eCRF. Any recorded AE that starts during the follow-up period but does not meet any of the reporting criteria will be listed but will not be included in summary tables.

8.4.3.1.4 Statistical Hypotheses

No statistical hypotheses will be tested.

8.4.3.1.5 Analysis Sets

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

8.4.3.1.6 Statistical Methods

Only descriptive statistics will be calculated and presented.

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

Not applicable.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

The secondary immunogenicity objectives are:

- To assess immune responses against H5N1 (contained in the priming vaccine) as measured by HI assay 1 week (Day 8) and 3 weeks (Day 22) after the first heterologous aH5N6c booster vaccination, and 3 weeks (Day 43) after the second heterologous aH5N6c booster or placebo vaccination.

- To assess persistence of immune response against H5N1 (contained in the priming vaccine) as measured by HI assay at Day 1 (pre-vaccination) and at Day 202, 6 months after the second heterologous aH5N6c booster or placebo vaccination.

- To assess persistence of immune response against H5N6 (contained in the booster vaccine) as measured by HI assay at Day 202, 6 months after the second heterologous aH5N6c booster or placebo vaccination.

8.4.3.3.1 Statistical Hypotheses

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

8.4.3.3.2 Analysis Sets

All immunogenicity objectives will be evaluated based on the PPS Immunogenicity. In the case that there is >5% difference in the total number of subjects between the PPS Immunogenicity and the FAS Immunogenicity, additional analysis based on the FAS Immunogenicity will be conducted.

8.4.3.3.3 Statistical Methods

Secondary immunogenicity analysis will be carried out in a similar fashion as the primary immunogenicity analysis.

Details of the analysis will be fully described by SAP.

8.4.4 Analysis of Other Objective(s)

8.4.4.1 Analysis of Other Safety Objective(s)

This study does not have other safety objectives.

8.4.4.2 Analysis of Other Efficacy Objective(s)

This study does not have other efficacy objectives.

8.4.4.3 Analysis of Other Immunogenicity Objective(s)

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

8.5 Sample Size and Power Considerations of Primary Objective

Sample size consideration

The sample size was chosen to provide sufficient power to enable reliable descriptive statistics and detection of differences between treatment groups. No formal power calculations were performed for these analyses.

The table below shows the statistical power to demonstrate the GMT ratio superiority (margin of 1) assuming that the true GMT ratios between two groups are 2, 3 or 4 and that the null GMT ratio is 1 under a two-sided test with 5% level of significance, with sample sizes of 50 and 100 evaluable subjects per group and a standard deviation of 0.5 to 1 for the $\log_{10}$ HI titers:

Table 8-1: Power calculation comparing GMT ratios (GMTrs) between groups

SD	Sample Size					
	50	100	50	100	50	100
	GMTr=2		GMTr=3		GMTr=4	
0.50	84.6	98.9	99.7	100	100	100
0.60	70.0	94.2	97.6	100	98.9	100
0.70	56.7	85.7	92.1	99.8	98.9	100
0.80	46.1	75.4	83.9	98.7	96.1	100
0.90	38.1	65.3	74.7	96.2	91.2	99.7
1.0	31.9	56.3	65.6	91.9	84.6	98.9

Thus with 100 evaluable subjects (sample size=112 with 10% drop off rate), the power to detect GMT ratio differences between any two groups is at least 85.7% with SD of the $\log_{10}$ HI titer not greater than 0.7.

8.6 Interim Analysis

No interim analysis of data from this study is planned.

9 SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

In order to ensure consistency across sites, study monitoring and auditing will be standardized and performed in accordance with the Sponsor's or delegated contract research organization's (CRO) standard operating procedures and applicable regulatory requirements (e.g., FDA, European Medicines Agency (EMA), and The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines).

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

9.1 Source Documentation

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

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

9.2 Study Monitoring, Auditing and Source Data Verification

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

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

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

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

(e.g., FDA, EMA and others) and/or ECs/IRBs. The investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

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

10 DATA MANAGEMENT

10.1 Data Entry and Management

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

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

10.2 Data Clarification

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

10.3 Data Protection

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

11 RECORD RETENTION

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

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

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

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

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

12 USE OF INFORMATION AND PUBLICATION

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

Seqirus also assures that key results of this clinical study will be posted in a publicly accessible database within the required time-frame from the end of study as defined in Section 3.10, End of Study.

In accordance with standard editorial, ethical practices and current guidelines of Good Publication Practice (Battisti et al. 2015), Seqirus will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement prior to the start of the study. The coordinating investigator will also sign the clinical study report on behalf of the principal investigators (CPMP/EWP/2747/00). Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Seqirus personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Seqirus personnel.

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

13 ETHICAL CONSIDERATIONS

13.1 Regulatory and Ethical Compliance

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

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (ICH E6(R2), with applicable local regulations including European Directive 2001/20/EC and US Code of Federal Regulations Title 21, Seqirus codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations, ICH 2016).

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

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

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

13.3 Responsibilities of the Investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/EC before study start. Properly constituted IRB/EC is defined in the integrated addendum to ICH E6: ICH Guideline for Good Clinical Practice E6 (R2). A signed and dated statement that the protocol and informed consent have been approved by the IRB/EC must be given to Seqirus before study initiation. Prior to study start and at any time the protocol is amended during study conduct, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the

instructions and procedures found in this protocol and to give access to all relevant data and records to Seqirus monitors, auditors, Seqirus Clinical Quality Assurance representatives, designated agents of Seqirus, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Seqirus immediately that this request has been made.

The investigator also responsible for the following:

- Maintaining a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.
- Demonstrating the capability of recruiting the required number of suitable subjects within the recruitment period.
- Demonstrating sufficient time and staffing to properly conduct and complete the study within the agreed study period.
- Ensuring that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions
- Ensuring that appropriately trained healthcare professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any 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 Seqirus, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject safety, the amendment can be implemented prior to IRB/EC approval. Notwithstanding, the need for formal approval of a protocol amendment, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Seqirus should be notified of this action, the IRB/EC at the study site, and, if required by local regulations, the relevant health authority) should be informed within 10 working days.

14 REFERENCE LIST

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APPENDIX 1 – SPONSOR AND INVESTIGATOR SIGNATURE PAGES

SIGNATURE ON BEHALF OF SPONSOR

I have read the protocol entitled "A Phase 2, Randomized, Study to Evaluate Safety and Immunogenicity of One or Two Heterologous Booster Vaccinations With an MF59-adjuvanted, Cell Culture-derived H5N6 Influenza Vaccine in Adults Primed With MF59-adjuvanted, Cell culture-derived H5N1 Influenza Vaccine or Unprimed." and confirm that, to the best of my knowledge; the protocol accurately describes the design and conduct of the study.

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

Name and qualifications: ……

Role: ……

SIGNATURE OF INVESTIGATOR

I have read the protocol entitled "A Phase 2, Randomized, Study to Evaluate Safety and Immunogenicity of One or Two Heterologous Booster Vaccinations With an MF59-adjuvanted, Cell Culture-derived H5N6 Influenza Vaccine in Adults Primed With MF59-adjuvanted, Cell culture-derived H5N1 Influenza Vaccine or Unprimed.", I agree to conduct the clinical study, after approval by an Institutional Review Board or Independent Ethics Committee (as appropriate), in accordance with the protocol, the principles of the Declaration of Helsinki, the standards of Good Clinical Practice (as defined by the International Conference on Harmonisation) and applicable regulatory requirements.

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

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

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

Affiliation and qualifications: ……

Address of Investigator: ……

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

Electronic Signatures

User	Date	Justification
[redacted]	25-Jul-2022 16:23:41	Manager Approval

STUDY PROTOCOL V89_18E1

Amendment Number 1

Amendment Date: 15 JUL 22

A Phase 2, Randomized, Study to Evaluate Safety and Immunogenicity of One or Two Heterologous Booster Vaccinations With an MF59-adjuvanted, Cell Culture-derived H5N6 Influenza Vaccine in Adults Primed With MF59-adjuvanted, Cell Culture-derived H5N1 Influenza Vaccine or Unprimed

The present amendment introduces changes to the study protocol since the version 1, dated 17 DEC 21 of the protocol. These changes are reflected into the revised protocol associated to this amendment.

RATIONALE AND DESCRIPTION OF CHANGE(S)

This protocol revision includes two topics: firstly, it extends the collection and summation of medically-attended adverse events (MAAEs) from the treatment period to also occur through the entire 6 months post-vaccination of the follow-up period, and secondly it corrects the description of the statistical analyses of the immunogenicity data to accommodate the age-specific criteria for adult <65 years of age, and those older than that.

Rationale for major changes:

1. FDA provided feedback on the V89_18 protocol version 1, dated 17 Dec 2021 and recommended to improve the safety monitoring plan, in addition to collecting all unsolicited adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs), also collect and report all medically-attended adverse events (MAAEs) through six months after final vaccination.

Changes:

Section(s)	Previous text:	Amended text:
Synopsis	• All unsolicited AEs for 3 weeks following each vaccination (Day 1 through Day 43); • Serious AEs (SAEs), AEs leading to withdrawal, AEs of special interest (AESIs), as collected from Day 1 through Day 202. Furthermore, during the treatment period (Day 1 through Day 43), all unsolicited AEs, SAEs, all AESIs, AEs leading to study withdrawal, associated concomitant medications for any of these events, and all vaccinations will be collected. During the follow-up period (Day 44 through Day 202), only a subset of unsolicited AEs and associated medications used to	• All unsolicited AEs (including Medically Attended AEs (MAAEs)) for 3 weeks following each vaccination (Day 1 through Day 43); • Serious AEs (SAEs), AEs leading to withdrawal, AEs of special interest (AESIs), MAAEs as collected from Day 1 through Day 202. Furthermore, during the treatment period (Day 1 through Day 43), all unsolicited AEs (including MAAEs), SAEs, all AESIs, AEs leading to study withdrawal, associated concomitant medications for any of these events, and all vaccinations will be collected. During the follow-up period (Day 44 through Day 202), only a subset of unsolicited AEs and associated medications used to

	treat these events, and all vaccinations will be collected in the electronic Case Report Form (eCRF): all SAEs, AESIs, AEs leading to study withdrawal. During this visit the Subject Diary will be reviewed, all unsolicited AEs and concomitant medication use (occurring after the first vaccination between Day 1 and Day 8) will be documented in the subject's source records and captured in the eCRF. A scripted safety telephone call will be made on Day 92 (window: -/+ 7 days) and Day 142 (window: -/+ 7 days) to collect only those AEs that are: SAEs, AEs leading to study withdrawal, AESIs, and concomitant medications associated with these events. Subjects will return to the clinic on Day 202 (window: +/- 14 days) for a symptom-directed physical examination, and to provide a serum sample for serologic testing. During this visit the subject will be interviewed to obtain information regarding SAEs, AEs leading to study withdrawal, and AESIs; concomitant medications associated with these events will be documented in the subject's source records and captured in the eCRF.	treat these events, and all vaccinations will be collected in the electronic Case Report Form (eCRF): all SAEs, AESIs, AEs leading to study withdrawal, and MAAEs. During this visit the Subject Diary will be reviewed, all unsolicited AEs (including MAAEs) and concomitant medication use (occurring after the first vaccination between Day 1 and Day 8) will be documented in the subject's source records and captured in the eCRF. A scripted safety telephone call will be made on Day 92 (window: -/+ 7 days) and Day 142 (window: -/+ 7 days) to collect only those AEs that are: SAEs, AEs leading to study withdrawal, AESIs, MAAEs and concomitant medications associated with these events. Subjects will return to the clinic on Day 202 (window: +/- 14 days) for a symptom-directed physical examination, and to provide a serum sample for serologic testing. During this visit the subject will be interviewed to obtain information regarding SAEs, AEs leading to study withdrawal, AESIs and MAAEs; concomitant medications associated with these events will be documented in the subject's source records and captured in the eCRF.
Table 0-1	Assess AEs leading to withdrawal,	Assess AEs leading to withdrawal,

	and AESIs	AESIs, and MAAEs
Section 3.1	Furthermore, during the treatment period (Day 1 through Day 43), all unsolicited AEs, Serious AEs (SAEs), all AEs of special interest (AESIs), AEs leading to study withdrawal, associated concomitant medications for any of these events, and all vaccinations will be collected. During the follow-up period (Day 44 through Day 202), only a subset of unsolicited AEs and associated medications used to treat these events, and all vaccinations will be collected in the electronic Case Report Form (eCRF): all SAEs, AESIs, AEs leading to study withdrawal.	Furthermore, during the treatment period (Day 1 through Day 43), all unsolicited AEs, Serious AEs (SAEs), all AEs of special interest (AESIs), AEs leading to study withdrawal, medically attended AEs (MAAEs), associated concomitant medications for any of these events, and all vaccinations will be collected. During the follow-up period (Day 44 through Day 202), only a subset of unsolicited AEs and associated medications used to treat these events, and all vaccinations will be collected in the electronic Case Report Form (eCRF): all SAEs, AESIs, AEs leading to study withdrawal, MAAEs.
Section 3.6.1	• Unsolicited AEs for 21 days following each vaccination (Day 1 through Day 43). • SAEs, AEs leading to withdrawal from the study, and AESIs, as collected from Day 1 to Day 202.	• Unsolicited AEs (including MAAEs) for 21 days following each vaccination (Day 1 through Day 43). • SAEs, AEs leading to withdrawal from the study, AESIs, and MAAEs as collected from Day 1 to Day 202.
Section 5.4.1	The subject will be interviewed to determine if any unsolicited AEs occurred and if any concomitant medications or vaccines were taken/received in the time since the last clinic visit.	The subject will be interviewed to determine if any unsolicited AEs (including MAAEs) occurred and if any concomitant medications or vaccines were taken/received in the time since the last clinic visit.
Section 5.4.2	The subject will be interviewed according to the script, and information relating to the	The subject will be interviewed according to the script, and information relating to the

	following unsolicited adverse events: SAEs, AESIs, and AEs leading to withdrawal, and concomitant medications or vaccinations associated with those events.	following unsolicited adverse events: SAEs, AESIs, AEs leading to withdrawal, MAAEs, and concomitant medications or vaccinations associated with those events.
Section 5.6	During the clinic visit, the following procedures will be performed: review of systems, symptom-directed physical assessment, interview of subject to collect the following unsolicited adverse events: SAEs, AEs leading to withdrawal, and AESIs, and concomitant medications/ vaccinations associated with those events, and blood sampling for immunogenicity.	During the clinic visit, the following procedures will be performed: review of systems, symptom-directed physical assessment, interview of subject to collect the following unsolicited adverse events: SAEs, AEs leading to withdrawal, AESIs, MAAEs and concomitant medications/ vaccinations associated with those events, and blood sampling for immunogenicity.
Section 7.1.2	In this study, all unsolicited AEs will be collected during the treatment period (Day 1 through Day 43) and only specific unsolicited AEs (SAEs, AEs leading to withdrawal and AESIs) will be collected during the follow-up period (Day 44 through Day 202).	In this study, all unsolicited AEs (including MAAEs) will be collected during the treatment period (Day 1 through Day 43) and only specific unsolicited AEs (SAEs, AEs leading to withdrawal, AESIs and MAAEs) will be collected during the follow-up period (Day 44 through Day 202).
Section 7.1.3	Adverse events will also be evaluated by the investigator for the co-existence of any of the other following conditions: • AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal; • AESIs: Please see Appendix 2 for the full list of AESIs.	Adverse events will also be evaluated by the investigator for the co-existence of any of the other following conditions: • AEs leading to withdrawal: adverse events leading to study or vaccine withdrawal; • AESIs: Please see Appendix 2 for the full list of AESIs; • MAAEs: AEs that lead to an

		unscheduled visit to/by a healthcare professional.
Section 8.1.2.1	• All unsolicited AEs for 21 days following each vaccination (Day 1 through Day 43); • SAEs, AEs leading to withdrawal from the study, AESIs as collected from Day 1 through Day 202.	• All unsolicited AEs (including MAAEs) for 21 days following each vaccination (Day 1 through Day 43); • SAEs, AEs leading to withdrawal from the study, AESIs, MAAEs as collected from Day 1 through Day 202.
Section 8.4.3.1.3	Separate summaries will be produced for the following categories: • Serious adverse events. • Adverse events that are possibly or probably related to vaccine. • Adverse events of special interest. • Adverse event leading to withdrawal. During the follow-up period (Day 44 to Day 202), only AEs that meet the reporting criterion (an SAE, AESI, or AE leading to withdrawal) are to be recorded in the eCRF.	Separate summaries will be produced for the following categories: • Serious adverse events. • Adverse events that are possibly or probably related to vaccine. • Adverse events of special interest. • Adverse event leading to withdrawal. • Medically attended adverse events. During the follow-up period (Day 44 to Day 202), only AEs that meet the reporting criterion (an SAE, AESI, AE leading to withdrawal or MAAE) are to be recorded in the eCRF.

2. Addition of the CBER criteria for adults <65 years of age, reference to the correct guidance, and added guidance citation to protocol Section 14: Reference list.

Changes:

Section(s)	Previous text:	Amended text:
Section 8.4.2.3.3	In addition, SCRs and the percentages of subjects achieving HI antibody titer ≥ 1:40 results collected at Day 8, Day 22, and Day 43 will also be evaluated against the Center for Biologics Evaluation and Research (CBER) criteria, CBER Guidance Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines (United States Food and Drug Administration (FDA), 2007): • The lower bound of the two-sided 95% confidence interval for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 30%. • The lower bound of the two-sided 95% confidence interval for the percentage of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 60%.	In addition, SCRs and the percentages of subjects achieving HI antibody titer ≥ 1:40 results collected at Day 8, Day 22, and Day 43 will also be evaluated against the age appropriate Center for Biologics Evaluation and Research (CBER) criteria, CBER Guidance Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines (United States Food and Drug Administration (FDA), 2007): • The lower bound of the two-sided 95% confidence interval for the percentage of subjects achieving seroconversion for HI antibody should meet or exceed 30% for adults ≥65 years of age and 40% for adults <65 years of age • The lower bound of the two-sided 95% confidence interval for the percentage of subjects achieving an HI antibody titer ≥ 1:40 should meet or exceed 60% for adults ≥65 years of age and 70% for adults <65 years of age.
Section 14		US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (2007) Guidance for Industry: Clinical data needed to support the licensure of pandemic influenza vaccines.

Summary of minor changes:

Typographical errors and minor edits have been implemented throughout.

Electronic Signatures

User	Date	Justification
[redacted]	15-Jul-2022 18:47:21	Manager Approval