CLINICAL STUDY PROTOCOL

Study Number	V87_30
Protocol Version	Version 5, Final, 24-JUN-2020
Study Title	A Phase 2, Randomized, Observer-Blind, Multicenter Study to Evaluate the Immunogenicity and Safety of Several Doses of Antigen and MF59 Adjuvant Content in a Monovalent H5N1 Pandemic Influenza Vaccine in Healthy Pediatric Subjects 6 Months to < 9 Years of Age
Study Phase	Phase 2
Product Name	H5N1 Pandemic influenza vaccine (surface antigen, inactivated, adjuvanted)
Regulatory Agency	IND: Not applicable
Identifying Number(s)	EudraCT number: 2016-001898-32
Sponsor:	Seqirus UK Ltd.
Previous Version	Final Version 4
Date	20-DEC-2019

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PROTOCOL SYNOPSIS V87_30

Name of sponsor:	**Protocol number:**	**Generic name of study vaccine(s):**
Seqirus UK Ltd.	V87_30	H5N1 Pandemic influenza vaccine (surface antigen, inactivated, adjuvanted)

Title of Study:

A Phase II, Randomized, Observer-Blind, Multicenter Study to Evaluate the Immunogenicity and Safety of Several Doses of Antigen and MF59 Adjuvant Content in a Monovalent H5N1 Pandemic Influenza Vaccine in Healthy Pediatric Subjects 6 Months to < 9 Years of Age

Study Period:	**Clinical Phase:**
Each subject is expected to participate in the study for approximately 12 months	2

Background and Rationale:

The purpose/aim of this study is to evaluate responses to vaccination with different adjuvanted pandemic influenza vaccine formulations in pediatric subjects. The data from this study are intended to provide information for health authorities to determine the best formulation for protection of children during the pandemic phase of a pandemic of a novel pandemic influenza strain (World Health Organization (WHO) 2013). Although the criteria for formulation selection for use in children are still under discussion with health authorities such as European Medicines Agency (EMA), it is expected that the results from this study will provide enough information for individual health authorities to select the appropriate formulation in the situation of an actual pandemic.

Pandemic influenza differs from seasonal influenza by representing a novel influenza strain, to which humans are immunologically naive, and has the potential for heavily impacting a young otherwise healthy population. If sustained human-to-human transmission were to occur with a pandemic influenza strain, global spread is likely, and morbidity and mortality could be staggering if efforts to contain the spread were not implemented quickly. Vaccination is the best option by which spread of a pandemic virus could be minimized or prevented. Vaccination efforts would be further enhanced by identification of the fewest number of vaccinations and lowest antigen dose needed for protection of segments of the population. The present study design will evaluate different pandemic influenza vaccine formulations in children after 2 doses of vaccine. The formulations proposed are based on prior experience with pandemic influenza A

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strains evaluated with and without MF59C.1 (hereafter referred to as MF59) adjuvant at varying antigen doses. MF59 adjuvant has been safely combined with influenza antigens given to children in clinical trials and use during the 2009 pandemic, and offers an important option for lowering the required antigenic dose for priming of immunologically naive individuals. As dose sparing is a key attribute of pandemic influenza vaccine candidates and as MF59 has been included in other licensed pandemic influenza vaccines administered to children (Focetria and Celtura), this study will not include non-adjuvanted comparator vaccine arms. In addition, as immune responses to MF59 adjuvanted influenza vaccine in children over 9 years of age appear to be similar to responses seen in adolescents and adults (Vesikari et al. 2010, Chotpitayasunondh et al. 2008), this trial will focus on the response seen in younger children, and will enroll children in age cohorts of 6 months to <36 months and 3 to <9 years.

The aH5N1 vaccine is an MF59-adjuvanted influenza vaccine that has been approved for active immunization against the H5N1 subtype of influenza A virus in adults and elderly (ages 18 years and older). The current study is designed to evaluate the safety and immunogenicity of two vaccinations of aH5N1 in healthy subjects aged 6 months to <9 years.

The study is designed to obtain safety and immunogenicity data with the formulations gauged likely to be most successful against the pandemic strain. Endpoints used in other trials of pandemic and seasonal influenza trials that examine responses in haemagglutination inhibition (HI) and microneutralization (MN) assays, respectively according to titers of 40 or greater and 4-fold or higher increases in titer, are included in the design to allow for maximum flexibility in selecting the antigen formulation for use in children.

Study Objectives:

Primary Safety Objective:

- To evaluate the safety in each study vaccine group from Day 1 through Day 387, by total population and by age cohort.

Primary Immunogenicity Objective:

- To assess by total population and by age cohort, the antibody responses to each of the study vaccines prior to (Day 1) and at 3 weeks after the first or second vaccination (Day 22 or Day 43), as measured by HI and MN assays.

Secondary Immunogenicity Objectives:

- To evaluate in each study vaccine group, by total population and by age cohort, the persistence of antibody responses to the H5N1 vaccine strain 6 months after the second vaccination (Day 202) as measured by HI and MN assays.

Exploratory Objectives:

- To further evaluate the antibody responses to seasonal and/or homologous and/or heterologous pandemic influenza strain(s), as measured by the HI, MN or SRH assays (depending on availability of adequate sera and on assay availability).

Study Design:

This randomized, observer blind, multi-center clinical trial evaluates the immunogenicity in healthy children 6 months to < 9 years of age utilizing 6 different aH5N1 vaccine formulations, in order to describe the possible impact of decreasing the quantities of antigen and/or adjuvant dosage on the antibody responses. In addition, levels of antibody persistence (at Day 202) and the safety profile of each vaccine regimen will be assessed.

Eligible subjects will be stratified by age at the time of enrollment into one of 2 age cohorts and within each age cohort will be randomly assigned (equally) to 1 of 6 study vaccine groups. Subjects in each study vaccine group will be scheduled to receive 2 injections of aH5N1 vaccine 3 weeks apart.

The vaccine regimens are:

A. Lowest-dose, less-adjuvanted vaccine = 1.875 µg H5N1 antigen + 0.125 mL MF59 adjuvant, with 2 consecutive administrations: dose 1 at Day 1 and dose 2 at Day 22

B. Low-dose, less-adjuvanted vaccine = 3.75 µg H5N1antigen + 0.125 mL MF59 adjuvant, with 2 consecutive administrations: dose 1 at Day 1 and dose 2 at Day 22

C. Mid-dose, less-adjuvanted vaccine = 7.5 µg H5N1 antigen + 0.125 mL MF59 adjuvant, with 2 consecutive administrations: dose 1 at Day 1 and dose 2 at Day 22

D. Lowest-dose, adjuvanted vaccine = 1.875 µg H5N1 antigen + 0.25 mL MF59 adjuvant, with 2 consecutive administrations: dose 1 at Day 1 and dose 2 at Day 22

E. Low-dose, adjuvanted vaccine = 3.75 µg H5N1 antigen + 0.25 mL MF59 adjuvant, with 2 consecutive administrations: dose 1 at Day 1 and dose 2 at Day 22

F. Mid-dose, adjuvanted vaccine = 7.5 µg H5N1 antigen + 0.25 mL MF59 adjuvant, with 2 consecutive administrations: dose 1 at Day 1 and dose 2 at Day 22

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

For all subjects, study participation includes a total of 4 clinic visits, 2 reminder calls, and 3 safety calls through the treatment and follow-up periods (a total study duration of approximately 12 months).

Treatment period (Day 1 through Day 43): 3 clinic visits and 2 diary completion reminder calls.

Follow-up period (Day 44 through Day 387): 1 clinic visit and 3 safety calls.

Vaccine administration will be performed intramuscularly (IM), anterolateral thigh for children ages < 2 years; deltoid for children ages ≥ 2 years, unless insufficient deltoid mass. Each vaccine administration will be performed in an observer-blind manner (ie, efforts should be taken to shield the subject/parent/legally acceptable representative and blinded study team members from the view of the vaccine administration). To maintain the observer-blind design of the study, the roles and responsibilities of “blinded” and “unblinded” team members will be defined and maintained in a site-specific blinding

plan. Safety assessments and study-related procedures and monitoring thereof must be performed by "blinded" team members.

After each vaccination, all subjects will remain under medical supervision at the study site for at least 30 minutes to be monitored and evaluated for adverse events (AEs).

Subject Diary Cards will be provided to subjects for recording of local and systemic reactions for 7 consecutive days after each vaccination.

The Subject Diary Cards will collect solicited AEs, and associated medications from Day 1 to Day 7 (inclusive) and from Day 22 to Day 28 (inclusive). Solicited AEs that continue beyond Day 7 and 28 respectively, and medications given to treat them, will be collected in the Subject Diary Card until the time of return to the clinic on Day 22 and 43, respectively, must be recorded as unsolicited AEs. In addition, during the treatment period (Day 1 through Day 43), all AEs, serious adverse events (SAEs), all adverse events of special interest (AESI), new onset of chronic disease (NOCD), AEs leading to vaccine/study withdrawal, associated concomitant medications for any of these events, and all vaccinations will be collected. These data will be captured by interview of the parent(s)/legally acceptable representative (s)(LARs), and if available by review of medical records.

During the follow-up period (Day 44 through Day 387), only a subset of unsolicited AEs and the medications/vaccinations used to treat these will be collected and included in the subjects eCRFs: all SAEs, NOCDs, AEs leading to vaccine and/or study withdrawal and/or delay, and AESIs (as described in section 7.1 of the current protocol). These data will be captured by interviewing the parent(s)/ LAR(s) and/or by reviewing the available medical records.

Number of Subjects planned:

A total of 420 subjects between 6 months and less than 9 years of age, are planned to be enrolled. Allocation to each of 6 vaccine regimens will be randomized in an equal ratio (1:1:1:1:1:1) stratified by age 6 months through < 36 months and 3 years through < 9 years of age. Approximately 35 subjects will be randomized per vaccine group in each age cohort.

Study Population and Subject Characteristics:

This study will enroll pediatric subjects 6 months <9 years of age in good health as determined by medical history, physical assessments, and clinical judgment of the investigator, if the parent(s) or LAR(s) have given consent, are able to follow all the required study procedures for the whole period of the study, and a baseline blood sample has been collected.

Subjects will be excluded when suffering from progressive, unstable or uncontrolled clinical conditions; hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study; clinical conditions representing a contraindication to intramuscular vaccination or blood draws; experienced a body temperature ≥ 38.0°C within 3 days before intended study vaccination; clinical suspicion of pandemic influenza illness within the past six months; abnormal function of the immune system resulting from clinical conditions or systemic administration of corticosteroids (per os [PO]/intravenously [IV]/IM) for more than 14 consecutive days or administration of antineoplastic and immunomodulation agents or radiotherapy, prior to each study vaccination.

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

Study Procedures:

Written informed consent (and assent if applicable) must be obtained prior to the conduct of any study-related procedures. The informed consent process may be conducted up to 10 days before day of vaccination (Day 1) or may be conducted on the day of vaccination (Day 1). Pre-vaccination study procedures will include: baseline physical examination, height and weight; review of medical history and concomitant medications; body temperature measurement; determination of eligibility; baseline blood draw and randomization. Prior to the second study vaccine administration (Day 22), review of eligibility, the Subject Diary Card, concomitant medication and body temperature measurement will be repeated, as well as blood sampling as described below.

Blood samples for serology (approximately 6 mL for HI and MN antibody responses) will be drawn after temperature measurement, ie, confirmation subject does not have fever (body temperature ≥ 38.0°C) on Day 1 (before randomization), Day 22 (before study vaccine administration), Day 43, and on Day 202.

Post-vaccination study procedures will include a 30 min safety assessment (vaccination visits only), safety data collection via the 7-day Subject Diary Card, periodic safety telephone calls, and interviews at clinic visits, to obtain safety data as described in the endpoints section. Each clinic visit will include a symptom-directed physical exam. As much safety data as possible should be collected at early termination visits, such as collection of the Subject Diary Card (if applicable) and interview, and blood sampling for serology, if applicable.

Study Vaccines:

Six different formulations including per dose either 1.875, 3.75, or 7.5 µg hemagglutinin antigen (HA) of pandemic H5N1 influenza strain combined with either 0.125 mL or 0.25 mL MF59, in two IM injections. Note that 7.5 µg HA of H5N1 influenza strain combined with 0.25 mL MF59 in a total injection volume of 0.5 mL is the currently licensed adult formulation for aH5N1 and seasonal influenza vaccines contain 15 µg HA per influenza strain. Vaccination schedule of the study vaccine for the 6 vaccine group assignments is shown in Table 1.

Table 1: Vaccination schedule

Arm*	Description	Day 1	Day 22
A	1.875 µg + 50% MF59 0.25 mL	1.875 µg	1.875 µg
B	3.75 µg + 50% MF59 0.25 mL	3.75 µg	3.75 µg
C	7.5 µg + 50% MF59 0.25 mL	7.5 µg	7.5 µg
D	1.875 µg + 100% MF59 0. 5 mL	1.875 µg	1.875 µg
E	3.75 µg + 100% MF59 0.5 mL	3.75 µg	3.75 µg
F	7.5 µg + 100% MF59 0.5 mL	7.5 µg	7.5 µg

*Approximately 70 subjects will be randomized per treatment arm, ie, 35 subjects in each age cohort.

Primary Endpoints:

Safety Endpoints:

The measures for assessing safety are as follows:

- Percentages of subjects with solicited local and systemic AEs[1] that occur within 7 days following each vaccination and calculated for 4 time intervals after vaccination: 30 minutes, 1 through 3 days, 4 through 7 days, and 1 through 7 days
- Percentages of subjects with any unsolicited AEs reported within 21 days after each vaccination within each vaccine group

[1] Including the use of antipyretics/analgesics.

- Percentages of subjects reporting SAEs, NOCDs, AESIs, AEs leading to vaccine and/or study withdrawal as collected from Day 1 through Day 387

Primary Immunogenicity Endpoints:

The measures of immunogenicity, as determined by the HI and MN assay against the H5N1 antigen include the following:

- Geometric mean titers on Day 1 and Day 22 (3 weeks after the first vaccination) or Day 43 (3 weeks after the second vaccination), as determined by HI and MN assays against the homologous H5N1 pandemic influenza strain;
- Geometric mean ratios calculated as follows: Day 22/Day 1 or Day 43/Day 1 as determined by HI and MN assays against the homologous H5N1 pandemic influenza strain;
- Percentage of subjects achieving seroconversion (non-detectable to ≥1:40, or 4-fold increase from a detectable Day 1 titer) on Day 22 or 43;
- Percentage of subjects achieving seroconversion with a titer ≥ 1:40 on Days 1, 22, or 43[2].

Secondary Immunogenicity Endpoints:

- Geometric mean titers on Day 1 and Day 202 (6 months after the second vaccination) as determined by HI and MN assays;
- Geometric mean ratios calculated as follows: Day 202/Day 1 as determined by HI and MN assays;
- Percentage of subjects achieving seroconversion (non-detectable to ≥1:40, or 4-fold increase from a detectable Day 1 titer) on Day 202;
- Percentage of subjects achieving seroconversion with a titer ≥1:40 on Day 202[3];

Exploratory Immunogenicity Endpoint(s):

Exploratory endpoints of seasonal and homologous and/or heterologous strain testing will be described in the SAP.

[2] Percentage of subjects achieving a titer ≥1:40 on Days 1, 22, or 43

[3] Percentage of subjects achieving a titer ≥1:40 on Day 202

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.
Interim Analysis: No interim analysis is planned.
Independent Data Monitoring Committee: An independent data monitoring committee (IDMC) will not be utilized for this study.

Table 2: Time and Events Table

		Treatment period					Follow-up period			
	Visit Type	**clinic visit**	**Diary reminder phone call**	**clinic visit**	**Diary reminder phone call**	**clinic visit***	**safety phone call**	**safety phone call**	**clinic visit***	**safety phone call**
	Study Day[a]	**1**	**V1 + 4**	**V1 + 21**	**V2 + 4**	**V2 + 21**	**V2 + 70**	**V2 + 130**	**V2 + 180**	**V2+ 365**
	Visit Window (days)	**-10/0**	**-1/+1**	**-1 to +7**	**-1/+1**	**-1 to +7**	**-7 to +7**	**-7 to +7**	**-7 to +7**	**-7 to +7**
	Visit Number	**V1**	**n/a**	**V2**	**n/a**	**V3**	**V4**	**V5**	**V6**	**V7**
Study event	**references**									
study treatment										
vaccination	section 5.2	**X**		**X**						
screening and safety										
informed consent[b]	section 5.1.1	**X**								
demographics[c]	section 5.1.2	**X**								
review of systems[c]	section 5.1.2	**X**		**X**		**X**			**X**	
clinical signs[c]	section 5.1.2	**X**		**X[d]**						
medical history[c, e]	section 5.1.2	**X**								
physical exam[c, f]	sections 5.1.2 and 5.3.1	**X**		**X**		**X**			**X**	
exclusion/inclusion criteria[g]	section 4	**X**		**X**						
randomization[h]	section 5.1.4	**X**								

		Treatment period					Follow-up period			
	Visit Type	**clinic visit**	**Diary reminder phone call**	**clinic visit**	**Diary reminder phone call**	**clinic visit***	**safety phone call**	**safety phone call**	**clinic visit***	**safety phone call**
	Study Day[a]	**1**	**V1 + 4**	**V1 + 21**	**V2 + 4**	**V2 + 21**	**V2 + 70**	**V2 + 130**	**V2 + 180**	**V2+ 365**
	Visit Window (days)	**-10/0**	**-1/+1**	**-1 to +7**	**-1/+1**	**-1 to +7**	**-7 to +7**	**-7 to +7**	**-7 to +7**	**-7 to +7**
	Visit Number	**V1**	**n/a**	**V2**	**n/a**	**V3**	**V4**	**V5**	**V6**	**V7**
Study event	**references**									
30 minutes post injection assessment	section 5.2.1	**X**		**X**						
Subject Diary Card dispensed with training	section 5.2.1	**X**		**X**						
Subject Diary Card reminder call[i]	section 5.2.2		**X**		**X**					
Subject Diary Card reviewed and collected[j]	section 5.3.1			**X**		**X**				
assess all AEs	section 7.1	**X**		**X**		**X**				
assess SAEs	section 7.1.4	**X**		**X**		**X**	**X**	**X**	**X**	**X**
assess NOCDs, AEs leading to withdrawal, AESIs	sections 7.1.4.1 and 7.1.3	**X**		**X**		**X**	**X**	**X**	**X**	**X**
assess relevant medications[k]	sections 5.1.2 and 6.5	**X**		**X**		**X**	**X**	**X**	**X**	**X**
Immunogenicity										
serology blood draw[l]	section 3.5	**X[m]**		**X**		**X**			**X**	

		Treatment period					Follow-up period			
	Visit Type	**clinic visit**	**Diary reminder phone call**	**clinic visit**	**Diary reminder phone call**	**clinic visit***	**safety phone call**	**safety phone call**	**clinic visit***	**safety phone call**
	Study Day[a]	**1**	**V1 + 4**	**V1 + 21**	**V2 + 4**	**V2 + 21**	**V2 + 70**	**V2 + 130**	**V2 + 180**	**V2+ 365**
	Visit Window (days)	**-10/0**	**-1/+1**	**-1 to +7**	**-1/+1**	**-1 to +7**	**-7 to +7**	**-7 to +7**	**-7 to +7**	**-7 to +7**
	Visit Number	**V1**	**n/a**	**V2**	**n/a**	**V3**	**V4**	**V5**	**V6**	**V7**
Study event	**references**									
Study termination/completion										
Study completion[n]	section 5.5									**X**

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 visit 2 and 3; Visit 2 is the baseline for calculation of all following visits; [b] Confirm consent form (and if applicable assent form) signed prior to any procedures. The informed consent process may be conducted earlier, but within 10 days prior to Day 1. [c] Pre-vaccination procedures may occur within 10 days prior to or within the Day 1 visit, if procedures are performed prior to Day 1 inclusion/exclusion criteria have to be rechecked, and the subject's eligibility must be confirmed prior to the Day 1 vaccination; [d] clinical signs includes weight, height and temperature measurement before the 1st vaccination, and only temperature measurement before 2nd vaccination; [e] Including prior and concomitant medications. [f] A physical examination will be based on a review of systems, ie, a structured interview for complaints for each organ system; [g] To be checked prior to each vaccination; [h] Randomization only to be done if baseline blood sample has been collected. [i] A reminder call after each vaccination should occur between 3 to 5 days following vaccination; [j] If a clinic visit is not possible, review should be completed upon return of the Subject Diary card. [k] 24 hours prior to vaccination antipyretic medication is not allowed; [l] Blood sample for serology to be taken after temperature measurement, but prior to vaccination; [m] Subjects must provide a baseline blood sample after informed consent, but before randomization, up to 10 days prior to the 1st vaccination. [n] Subjects who terminate the study early should complete an early termination visit when possible, see section 5.5.1, Early Termination Visit.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
AESI	Adverse Events of Special Interest
aH5N1	Monovalent H5N1 Influenza Vaccine Including MF59C.1 Adjuvant
CI	Confidence Interval
CPMP	Committee of Proprietary Medicinal Products
CRF	Case Report Form
CRO	Contract Research Organization
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicine Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMR	Geometric Mean Ratio
GMT	Geometric Mean Titer
HA	Hemagglutinin Antigen
HI	Hemagglutination Inhibition
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
IDMC	Independent Data Monitoring Committee
IM	Intramuscular(ly)
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Study File
IV	Intravenous(ly)
LAR	Legally acceptable representative
LLD	Lower Limit of Detection
MedDRA	Medical Dictionary for Regulatory Activities
MCAR	Missing Completely and Random
MN	Microneutralization
NOCD	New-Onset Chronic Disease
PI	Principal Investigator
PPS	Per Protocol Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDA	Source Document Agreement

SUSAR	Suspected Unexpected Serious Adverse Reaction
WHO	World Health Organization
Follow-up period	The follow-up period for subjects starts 21 days after the second vaccination and continues for up to study completion
Legally Acceptable Representative(s)	An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial (see ICH-GCP, ICH E6 (R2))
Qualified health care Professional	Any licensed health care professional who is permitted by institutional policy to perform clinical interventions and assessments such as physical examinations, is trained on the study procedure(s) and who is identified within the site signature and delegation log.
Trained health care Professional	Any health care professional who is permitted by institutional policy, trained to perform delegated tasks, is trained on the study procedure(s) and who is identified within the site signature and delegation log.
Treatment period	Per protocol treatment period begins at the time of vaccination (Day 1) and ends 21 days after the second vaccination.

1. BACKGROUND AND RATIONALE

1.1 Background

aH5N1 is a pandemic[4] vaccine for prophylaxis of avian H5N1 influenza. aH5N1 is an inactivated, surface antigen, A/H5N1 Influenza (flu) Vaccine, with International Nonproprietary Name (INN) Pandemic Influenza Vaccine H5N1 (surface antigen, inactivated, adjuvanted), produced in embryonated hen eggs and formulated with MF59C.1 adjuvant (MF59). For clarity, the term aH5N1 will be used in the remainder of this document to refer to Pandemic Influenza Vaccine H5N1 (surface antigen, inactivated, adjuvanted).

Nonclinical studies assessed the immunogenicity (mice, rabbits, ferrets), efficacy (mice, ferrets), and toxicity (rabbits) of aH5N1 formulations. In these studies, vaccine formulations were immunogenic and protective, and there was no evidence of local or systemic toxicity. In rabbits, vaccination did not cause maternal or embryofetal toxicity, was not teratogenic, and had no effects on post-natal development. These studies support the clinical use of aH5N1.

Inactivated influenza vaccines from the applicant, including aH5N1and aH1N1, are manufactured from the same manufacturing process but differ only in terms of antigen and adjuvant content. These vaccines are based on replication, inactivation, and purification of proteins from selected influenza viruses and each is formulated with MF59 adjuvant, which allows for administration of lower antigen doses. HA and neuraminidase (NA) proteins are included in all three vaccines. The mechanism of action of inactivated influenza vaccines is based on induction of antibodies against the purified viral HA. Production of antibodies to HA is thought to prevent viral attachment to human respiratory epithelial cells. Although there is no established correlate of protection against pandemic influenza strains, HI antibody levels have been regarded as both a sign of vaccine activity and post-vaccination HI titer ≥ 1:40 has been associated with protection against seasonal influenza in adults.

Influenza antigen doses used to immunize against seasonal influenza have been well established for inactivated influenza vaccines (15 µg HA per influenza strain per dose in individuals 3 to 18 years of age, and 7.5 µg HA per influenza strain per dose in individuals 6 to <36 months of age, for most inactivated influenza vaccines).

[4] Throughout this study protocol 'pandemic' vaccine is used for the aH5N1 vaccine, however this study is also in support of the corresponding zoonotic vaccine.

However recent experience with pandemic influenza strains has indicated that different pandemic influenza strains may require different amounts of antigen to achieve similar antibody responses. Experiences with non-adjuvanted pandemic influenza strains in adults have demonstrated that two separate doses of 90 µg HA of A/H5N1 are necessary to achieve 4-fold increases in antibodies in just over 50% of adult subjects (Treanor 2006).

During the A(H1N1)pdm09 influenza pandemic, a dose-ranging trials in adults (including elderly) and children was performed as soon as formulations were available. Ultimately, these trials established that the addition of MF59 adjuvant to A(H1N1)pdm2009 antigen allowed for administration of lower doses of antigen (7.5 µg, dose of Focetria) to achieve high seroconversion rates by HI and MN assay. Moderate seroconversion rates were also observed with even lower antigen doses (3.75 µg) when MF59 adjuvant was added (60% by HI assay). Seroconversion rates were also high in children after a single dose of 3.75 µg HA A(H1N1)pdm09 with 0.125 mL MF59 dose: 91%, 97%, 95%, and 91% in children ages 6 to 11 months, 12 to 35 months, 3 to 8 years, and 9 to 17 years, respectively.

A clinical study with still another pandemic influenza strain (A/H7N9) demonstrated that 15 µg HA antigen with 0.25 mL MF59 dose given as 2 doses was needed to achieve HI titers ≥ 1:40 in adults (Bart 2014).

These experiences illustrate that for novel influenza strains, a range of doses may need to be evaluated in order to understand how much antigen and adjuvant is needed to demonstrate desirable antibody levels, and children may not demonstrate the same responses as adults to the doses given.

1.2 Rationale

The present study is a post authorization commitment in Europe. The purpose of this study is to provide additional clinical data on aH5N1 in children in anticipation of an avian influenza pandemic, as agreed in the pediatric investigational plan with EMA/Pediatric Committee. This is a pediatric dose-ranging study for aH5N1 to dosages with decreased content of HA antigen and/or MF59 adjuvant (versus the licensed dosage for adults). The study is designed to evaluate the safety and immunogenicity of two vaccinations using three different amounts of aH5N1 and two different dosages of MF59 adjuvant, administered 3 weeks apart.

The study will be conducted according to the protocol and in compliance with Good Clinical Practice, as defined by the International Council on Harmonisation, the principles outlined in the Declaration of Helsinki and all applicable federal and local regulations.

1.3 Potential Risks and Benefits

Based upon clinical studies with the aH5N1 vaccine, the following local and systemic adverse events may occur after vaccination:

Immediate hypersensitivity type reactions including anaphylaxis.

Vaccination-related anxiety symptoms such as syncope and pre-syncope.

Local reactions: erythema, induration, and pain at the injection site.

Systemic reactions: fever, (defined as body temperature ≥38.0°C), shivering (chills), irritability, diarrhea, vomiting, sleepiness, and change in eating habits

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

The aH5N1 vaccine has a good immunogenicity and a safety profile. The benefit-risk relationship for aH5N1 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 aH5N1 vaccine may be found in the Investigators' Brochure and the participant information leaflet.

2. OBJECTIVES

The purpose of this study is to assess the safety and immunogenicity of 6 different formulations including either 1.875, 3.75, or 7.5 µg HA of pandemic H5N1 influenza strain combined with either 0.125 mL or 0.25 mL MF59, in two IM injections administered three weeks apart.

2.1 Primary Objective(s)

Primary Safety Objective:

- To evaluate the safety in each study vaccine group from Day 1 through Day 387, by total population and by age cohort.

Primary Immunogenicity Objective:

- To assess by total population and by age cohort, the antibody responses to each of the study vaccines prior to (Day 1) and at 3 weeks after the first or second vaccination (Day 22 or Day 43), as measured by HI and MN assays.

2.2 Secondary Objective(s)

Secondary Immunogenicity Objectives:

- To evaluate in each study vaccine group, by total population and by age cohort, the persistence of antibody responses to the H5N1 vaccine strain 6 months after the second vaccination (Day 202) as measured by HI and MN assays.

2.3 Exploratory Objective(s)

- To further evaluate the antibody responses to seasonal, and/or homologous and/or heterologous pandemic influenza strain(s) by vaccine group on Days 1, 22, 43, and 202, as measured by HI, MN, or SRH assays (depending on availability of adequate sera and on assay availability).

3. STUDY DESIGN

3.1 Overview of Study Design

This randomized, observer blind, multi-center clinical trial evaluates the immunogenicity in healthy children ages 6 months to <9 years of 6 vaccine regimens utilizing 6 different formulations including either 1.875, 3.75, or 7.5 µg HA of pandemic H5N1 influenza strain combined with either 0.125 mL or 0.25 mL MF59, in two IM injections administered three weeks apart, in order to describe the possible impact of decreasing the quantities of antigen and/or adjuvant dosage. Levels of antibody persistence and the safety profile of each vaccine regimen will also be assessed.

A total number of 420 subjects will be enrolled to assure at least 150 evaluable subjects per age cohort.

Eligible subjects will be stratified by age at the time of enrollment into one of 2 age cohorts and within each age cohort will be randomly assigned (equally) to 1 of 6 study vaccine groups. Randomization will be equal (1:1:1:1:1:1) for each of 6 vaccine groups, and stratified by age cohort as follows: 6 months through <36 months of age, and 3 years through <9 years of age. Approximately 35 subjects will be randomized per vaccine group in each age cohort.

Subjects in each study vaccine group will be scheduled to receive 2 injections of aH5N1 vaccine 3 weeks apart.

The study groups are described in Table 1.

Immunogenicity will be measured by HI and MN assays.

- Blood samples for serology assessments will be collected from each subject on Day 1 (before randomization), Day 22 (before vaccination), Day 43, and Day 202.
- Each subject will be followed for a period of 12 months after receipt of the second study vaccine. After informed consent is signed by the subject's parent(s) or LAR(s), and if applicable assent form is signed by the subject, eligibility is confirmed, and the Day 1 blood sample is collected, subjects will be randomized receive a single vaccination followed by a second vaccination after three weeks (Day 22). For all subjects, study participation includes a total of 4 clinic visits, 2 diary completion reminder calls, and 3 safety calls through the treatment and follow-up periods (a total duration of approximately 13 months).
- Treatment period (Day 1 through Day 43): 3 clinic visits and 2 reminder calls
- Follow-up period (Day 44 through Day 387): 1 clinic visit and 3 safety calls

Vaccine administration will be performed IM, anterolateral thigh for children ages < 2 years; deltoid for children ages ≥ 2 years, unless insufficient deltoid mass. Each vaccine administration will be performed in an observer-blind manner (ie, efforts should be taken to shield the subject/parent(s)/LAR(s) and blinded study team members from the view of the vaccine administration). To maintain the observer-blind design of the study, the roles and responsibilities of "blinded" and "unblinded" team members will be defined and maintained. Safety assessments and study-related procedures and monitoring thereof must be performed by "blinded" team members.

After each vaccination, all subjects will remain under medical supervision at the study site for at least 30 minutes to be monitored and evaluated for AEs.

Subject Diary Cards will be provided to subjects for recording of local and systemic reactions for 7 consecutive days after each vaccination.

- From Day 1 through Day 7, and from Day 22 through Day 28, all solicited AEs, all unsolicited AEs (including SAEs, NOCDs, AEs leading to vaccine and/or study withdrawal, and AESIs), and associated concomitant medications for any of these events and vaccinations given within these periods will be recorded in the subject's eCRFs.
- From Day 8 through Day 22 (before vaccination), and from Day 29 through Day 43 all unsolicited AEs (including SAEs, NOCDs, AEs leading to vaccine and/or study withdrawal, AESIs), solicited AEs that continue beyond Day 7 or Day 28 , respectively, and associated concomitant medications and all vaccinations given within these intervals will be recorded in the subject's eCRF until the time of return to the clinic on Day 22, and Day 43,respectively in the subject's eCRFs.

In the follow-up period (Day 44 through Day 387), only the following subset of unsolicited AEs and the associated concomitant medications/vaccinations will be collected and documented in the subject's eCRFs: all SAEs, NOCDs, AEs leading to vaccine and/or study withdrawal, and AESIs (as described in section 7.1 of the current protocol). These data will be captured by interviewing the subject's parent(s)/LAR(s) and/or by reviewing the available medical records.

3.2 Study Period

Each subject should expect to participate in the study for approximately 12 months, from the time of enrolment through the last study visit.

3.3 Blinding Procedures

This is a phase 2, stratified, randomized, observer-blind, multicenter study. As such it is important to ensure that the subject and parent(s)/LAR(s) are not advised of the treatment assignment in this study.

Vaccine preparation and administration should be completed by the designated unblinded team members. Any other subject related assessments should be performed by the principal investigator (PI) and/or blinded staff members as applicable.

Except in the case of medical necessity, a subject's treatment should not be unblinded without the approval of the sponsor. In such instance of medical emergency, every effort should be made to contact the sponsor prior to unblinding. If unblinding should occur (by either accidental unblinding or emergency unblinding for a serious adverse event) prior to completion of the study, the investigator must promptly contact the sponsor and document the circumstances on the appropriate forms. Instructions regarding emergency unblinding will be provided to the investigator.

3.4 Data Collection

3.4.1 Data Collected from Subjects

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

- Informed Consent
- demographic information
- physical examination[5] and clinical signs information
- adverse events
- relevant medical history
- relevant concomitant medications
- vaccination history (including influenza vaccination)
- serology results

[5] A review of systems, ie, a structured interview for complaints for each organ system, will be used to guide a physical examination.

All data collected must only be identified using the sponsor's subject ID, as described in section 5.1.4, Randomization.

3.4.2 Tools Used for Data Collection

Electronic Data Capture system and paper diary cards will be used to collect data for this study. Data will be collected in the Subject Diary Card by subject's parent(s) /LAR(s) or caregiver and recorded in electronic case report forms (eCRFs) by site staff.

Subject Diary Card

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

The Subject Diary Card will be completed by the parent(s) or LAR(s) or caregiver.

The investigator or delegated staff should monitor the Subject's Diary Card status throughout the study for compliance and any solicited local and systemic adverse events that were of concern to the subject.

1. No corrections or additions to the information recorded by the parent(s)/LAR(s)/caregiver within the Subject Diary Card will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the Subject Diary Card must be described as missing, unknown or not done in the eCRF.

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

- The site must enter all readable entries in the Subject Diary Card into the eCRF, including those values that may be biologically implausible (eg, body temperature: 400°C).
- Any illegible or implausible data should be reviewed with the parent(s)/LAR(s)/caregiver. If an underlying solicited or unsolicited adverse event is described on review with the subject's parent(s)/LAR(s)/caregiver, this should be documented in the source document and reported as an unsolicited adverse event in the adverse event eCRF (eg, if the subject's parent(s)/LAR(s)/caregiver confirms a body temperature of 40°C on the day in which body temperature:

400°C was written into his/her Subject Diary Card, this fever of 40°C should be recorded in the adverse event eCRF). No correction should be made on diary card.

– Any newly described safety information (including a solicited adverse event) must not be written into the Subject Diary Card, but must be documented in the source document as a verbally reported adverse event. Any adverse event reported in this fashion must be documented as an unsolicited adverse event and therefore entered on the adverse event eCRF.

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. Each subject's eCRF casebook will be compared with the subject's source records by a sponsor-approved study monitor (or delegate) over the duration of the study in order to ensure data collection accuracy.

3.5 Collection of Clinical Specimens

In this study the only clinical specimens required to be collected from each subject are blood samples on Day 1 (baseline)[6], Day 22, Day 43, and Day 202. Processing of each specimen should be completed by a qualified site member (or sponsor approved designee[7]) and in accordance with the study-specific clinical specimen laboratory manual. Testing of clinical specimens will be performed by the sponsor or designated laboratory. Refer to the study-specific clinical specimen laboratory manual for additional details.

Blood Specimens

Approximately 6 mL of blood will be drawn from all subjects at visit 1 (Day 1) before randomization, and at visit 2 (Day 22) before vaccination, visit 3 (Day 43), and visit 6 (Day 202). The blood volume must be approximately 6 mL at each time point in order to provide the necessary serum volume (approximately half of the blood draw volume) for the serology assays.

[6] Note: the baseline blood sample must be collected prior to randomization of the subject. If a baseline blood sample is not obtained, the subject is not eligible for the study.

[7] In the exceptional case that a clinic visit is not possible, and a home visit is conducted due to COVID19 restrictions.

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

The total maximum amount of blood collected over the study period per subject will be 24 mL.

3.6 Stopping/Pausing Guidelines

There are no predetermined stopping rules in this study. Subjects may be withdrawn from the study according to investigator discretion as described in Section 3.8 Premature Withdrawal from Study.

The Sponsor can halt the study at any time. If the study is halted, the Sponsor will promptly notify the health authorities and investigators, who will promptly inform the parent(s)/LAR of study subjects and Institutional Review Board(s) (IRBs)/Ethics Committee(s) (ECs) as per local regulations. Further enrollment will only occur after written authorization is provided by the Sponsor in consultation with the health authorities and IRB(s)/EC(s), as appropriate.

3.7 Independent Data Monitoring Committee

An IDMC will not be utilized for the study.

3.8 Premature Withdrawal from Study

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

The circumstances above are referred to as premature withdrawal from the study, and the reason for premature withdrawal should be clearly documented and detailed in the source documentation. The investigator should make every attempt to evaluate the subject's safety, including resolution of ongoing AEs, at the time of premature withdrawal. If a subject's parent(s)/LAR(s) wants to withdraw from the study before all doses are administered or prior to the last planned study visit, the subject's parent(s)/LAR will be asked if his/her/their child can be followed for safety for the duration of the study. When a subject withdraws, or is withdrawn, from the study, the procedures described in section 5.5.1, Early Termination Visit should be completed if possible.

The reasons for premature withdrawal from the study include: adverse event, death, withdrawal of consent, lost to follow-up, study terminated by sponsor, protocol deviation, and other. These reasons are described in greater detail below.

Adverse Event

For any subject withdrawn from study participation prior to the planned study termination visit, it is important to determine if an AE was associated with the reason for discontinuing the study. This AE must be identified on the AE 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.

Subjects who develop a serious adverse event (SAE) judged to be possibly or probably related to the study vaccine (first dose), including fever (>40 °C), febrile convulsion and hypersensitivity type reactions, should not receive subsequent vaccination (second dose).

Death

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

Withdrawal of consent

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

Lost to Follow-Up

For parent(s)/LAR (s) who fail to show up with his/her/their child for final visits (clinic or telephone calls), study staff are must make at least three documented attempts to contact the parent(s)/LAR (s) by telephone and at least one documented written attempt to contact the parent(s)/LAR(s) to encourage the completion of study termination procedures. These

efforts to contact the parent(s)/LAR (s) should be recorded in the source document. The termination date for the subject to be captured on the study termination eCRF page is the date of the last successful contact (clinic visit or telephone) with the subject's parent(s)/LAR.

Study Terminated by Sponsor

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

Protocol Deviation

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

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

Other

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

3.9 End of Study

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

Evaluation of the primary and/or secondary immunogenicity/efficacy objectives requires the testing of biological samples from the study subjects, which can only be completed

after all samples are collected. The last samples for the analysis of the primary and/or secondary objectives will be taken at visit 6. For the purpose of this protocol, end of study is defined as the completion of the Last Subject Last Visit (LSLV), i.e., the last subject's Day 387 safety assessment call, or completion of testing of biological samples, to be achieved no later than 8 months after LSLV, whichever is longer.

Evaluation of the exploratory objectives also requires the testing of biological samples, which can only be completed after all samples are collected. If this testing will take longer than the time frame indicated above, these results may be reported in a clinical study report addendum.

4. SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

Pediatric subjects in good health as determined by medical history, physical assessments, and clinical judgment of the investigator will be enrolled if the parent(s) or LAR(s) have given consent and are able to follow all the required study procedures for the whole period of the study.

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

1. Healthy male and female subjects of 6 months through <9 years of age on the day of informed consent/assent.
2. Documented consent provided by the subject's parent(s)/LAR(s) have voluntarily given written informed consent/assent after the nature of the study has been explained according to local regulatory requirements, prior to study entry.
3. Subject's parent(s)/LAR(s) able to comprehend and comply with all study procedures, and available for all clinic visits and telephone contacts scheduled in the study.
4. Subjects must provide a baseline blood sample within 10 days prior to the Day 1 vaccination.

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

4.2 Exclusion Criteria

Each subject must not have:

1. Progressive, unstable or uncontrolled clinical conditions.
2. Hypersensitivity, including allergy, to any component of vaccines, medicinal products or medical equipment whose use is foreseen in this study.
3. Clinical conditions representing a contraindication to intramuscular vaccination and blood draws, ie,
    a. Subjects who have had a fever (body temperature measurement ≥ 38°C) within three days prior to vaccination. The subject may return for vaccination after they have been free of fever for three days.
    b. History of epilepsy or convulsions (excluding febrile convulsions).

c. A subject who has any medical condition meeting the definition of AESI defined for the purposes of this trial (see appendix A).

d. Subjects who have received antipyretic medication within the past 24 hours prior to vaccination. The subject may return for vaccination after a period of 24 hours has passed since the administration of an antipyretic.

4. Abnormal function of the immune system resulting from:

   a. Clinical conditions.

   b. Systemic administration of corticosteroids (PO/IV/IM) for more than 14 consecutive days within 90 days prior to informed consent/assent. 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 from within 90 days prior to informed consent/assent.

5. Suspicion of pandemic influenza illness within past six months or have ever received previous pandemic H5N1 flu vaccination.

6. Received immunoglobulins or any blood products within 180 days prior to informed consent/assent.

7. Received an investigational or non-registered medicinal within 30 days prior to informed consent/assent.

8. Children of study site staff (this includes research or clinic staff) or children who are otherwise related to study site staff or have household members who are study site staff. Study site staff are employees with direct or indirect contact with study subjects and/or have access to any study documents containing subject information. This would include receptionists, persons scheduling appointments or making screening calls, regulatory specialists, laboratory technicians, medical assistants, document scanners, etc. study personnel as an immediate family or household member.

9. 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.

10. Individuals who received any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrolment in this study or who are planning to receive any vaccine prior to day 43. Following day 43 other vaccines may be administered, including seasonal flu.

Prior to receipt of the second vaccination, subjects must be re-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 the second vaccination. These subjects will be requested to fulfill all the scheduled clinic visits and calls for safety follow-up. No further blood samples will have to be taken. This review of eligibility should be documented in the source document and the reason for not administrating a scheduled study vaccine should be documented in the eCRF.

4.3 Criteria for Delay of Vaccination

After enrollment, subjects may encounter clinical circumstances that warrant a delay in subsequent study 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 within 3 days of intended study vaccination.
- Fever is defined as body temperature ≥38.0°C (100.4°F) within 3 days of intended study vaccination.
- Administration of any vaccine not foreseen by the study protocol within 7 days prior to intended study vaccination.

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

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

4.4 Criteria for Repeat Vaccination in the Study

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 criteria listed below, they should not receive additional vaccinations.

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

- Has experienced any serious adverse event 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.

Subjects who meet any of these criteria must not receive further study vaccinations. However, the subject's parent(s)/LAR(s) should be encouraged to continue study participation of the subject.

5. STUDY PROCEDURES

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

Table 5: Study Procedures

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

5.1 Pre-vaccination Clinic Visit(s)

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

5.1.1 Informed Consent/Assent

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

"Assent" is a term used to express willingness to participate in research by persons who are by definition too young to give informed consent but who are old enough to understand the proposed research in general, its expected risks and possible benefits, and the activities expected of them as subjects. Assent by itself is not sufficient, however. If assent is given, informed consent must still be obtained from the subject's parent(s) or LAR(s).

Informed consent of the parent(s)/LAR(s) and assent of subject following local IRB/EC guidance **must** be obtained before conducting any study-specific procedures (ie, all of the procedures described in the protocol). The process of obtaining informed consent and assent should be documented in the subject source document in addition to maintaining a copy of the signed and dated informed consent and assent. Additional specifics regarding the informed consent and assent processes are located in section 13.2, Informed Consent Procedures.

If a subject and/or parent(s)/LAR(s) is unable to read, an impartial witness should be present during the entire informed consent and assent 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 and assent process if the subject or the subject's parent(s)/LAR(s) cannot read, and who reads the informed consent form (ICF), assent and any other written information supplied to the subject. After the written ICF/assent and any other written information to be provided to subjects, is read and explained to the subject and/or parent(s)/LAR(s) and after the subject and/or parent*(s)*/LAR(s) has verbally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF/assent, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject and/or parent(s)/LAR (s) and that informed consent was freely given by the subject and/or parent(s)/LAR (s).

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

5.1.2 Screening

After an individual has consented to participate in the study and informed consent/assent is signed, that individual will be given a unique screening number manually created by the investigator. The subject's unique screening number will be documented in the screening and enrolment log. The eligibility of the subject will be determined based on the inclusion and exclusion criteria listed in section 4, Selection of Study Population and evaluated during this screening procedure.

Screening procedures will include the following:

1. Demographic data will be collected from the subject, including: age and/or Date of Birth, sex, race, ethnicity).

2. Relevant 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 adverse event that occurs during study participation, if it represents an exacerbation of an underlying disease/pre-existing problem.

3. Review of systems is a structured interview that queries the subject and/or parent(s)/LAR(s) as to any complaints the subject has experienced across each organ system. This will be performed before enrolment and used to guide 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.

4. If applicable, prior and concomitant medications or vaccinations taken prior to start of study, including influenza vaccinations in the past 2 years, should be collected (refer to section 6.5, Prior and Concomitant Medications and Vaccines for further details).

5. Collection of clinical signs is to be performed: weight, height and body temperature. If body temperature is ≥38.0°C (≥100.4°F) at the time of screening, blood draw and/or vaccination must be postponed until 3 days after the fever has resolved (see section 4.3, Criteria for Delay of Vaccination).

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

7. Collection of a baseline blood sample (approximately 6 mL) must be performed prior to randomization, and can be done after obtaining informed consent, within

10 days prior to the first vaccination. Note: if a baseline blood sample is not obtained, the subject is not eligible for the study.

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 adverse events form.

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, eg, baseline blood sample not obtained. If the individual is determined to be eligible for the study, he/she will be enrolled into the study.

5.1.3 Enrolment

After signing the informed consent/assent form, if an individual is determined to be eligible for study participation, the investigator or delegate will enroll the subject and enter the subject information and stratification information into the Electronic Data Capture system (EDC). The EDC system is integrated with interactive response technology (IRT) system for randomization.

5.1.4 Randomization

Enrolled subjects will be assigned a unique Subject ID manually entered in EDC. Subject information and stratification information (ie, age) are automatically transferred to the IRT system for randomization in a 1:1:1:1:1:1 ratio into 6 treatment groups and automatically assigned a unique pack 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. After randomization, the screening number ceases to be used and remains in the screening and enrolment log only. The list of randomization assignments is produced by the IRT service provider and approved by the sponsor or delegate prior to study start.

Randomization will be stratified by age (cohorts of 6 months through <36 months, and 3 years through <9 years) and by site. The age cohorts will be of equal size. Once an age cohort attains its planned size (ie, half of the planned study sample size) the randomization in this age cohort will be blocked.

If for any reason, after signing the ICF/assent, the subject who is eligible and enrolled fails to be randomized, this is called a randomization failure. The reason for all randomization failures should be recorded in the screening and enrolment log and in the source document as specified in the source data agreement (SDA). The information on

subjects who are randomization failures should be kept distinct from subjects who are screen failures, as described in section 5.1.2, Screening.

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

5.1.5 Blood draw

The baseline blood draw must be performed after obtaining informed consent, but prior to randomization. Note: if a baseline blood sample is not obtained, the subject is not eligible for the study. The following volumes of blood will be withdrawn: approximately 6 mL per blood draw for subjects. Details regarding the volume of blood and testing to be performed are in section 3.5, Collection of Clinical Specimens. These data will be written in the source document (see Section 9.1, Source Documentation) and must be documented in the eCRF.

A topical analgesic/anesthetic/icepack may be used for the blood draw. However, the topical analgesic/anesthetic/icepack used for the blood draw should not be applied to the area of vaccination.

In the exceptional situation in which a clinic visit is not possible, such as in the case when a site is not able to see study subjects at the clinic due to local regulations related to the coronavirus pandemic, a home visit (only at Day 43 or 202) may be considered. The site must get approval from the sponsor to conduct home visits. The site must also have sponsored approved Standard Operating Procedures/Instructions for conducting home visits and the collection of blood samples in the home setting, prior to the home visit occuring. These procedures may also need to be approved by the site's IRB/EC depending on local and country regulations.

5.2 Vaccination Clinic Visit(s)

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 3.3, Blinding Procedures.

Prior to administration of the second vaccination at Day 22 confirm that the subject is eligible for additional study vaccinations and does not meet any criteria for delaying additional or stopping study vaccinations as described in section 4, Selection of Study Population.

5.2.1 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 unsolicited adverse events, solicited adverse events, and body temperature measurement. Record all safety data collected during this time in the subject's source document and eCRF.

A Subject Diary Card will be used in this study to document solicited adverse events. The Subject Diary Card is the only source for collection of these data; therefore, it is critical that the parent(s)/LAR(s) completes the Subject Diary Card correctly. The parent(s)/LAR(s) should be trained on how and when to complete each field of the Subject Diary Card.

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

The parent(s)/LAR(s) 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 parent(s)/LAR(s) should check body temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the Subject Diary Card.

Subject Diary Card training should be directed at the individual(s) who will perform the measurements of adverse events and who will enter the information into the Subject Diary Card. This individual may not be the parent(s)/LAR(s), but if a person other than the parent(s)/LAR(s) enters information into the Subject Diary Card, this person's identity must be documented in the Subject Diary Card and subject's source record. Any individual that makes entries into the Subject Diary Card must receive training on completion of the Subject Diary Card prior to entering data at visit 1 (Day 1) and visit 2 (Day 22). This training must be documented in the subject's source record.

The same individual (preferably) should complete the Subject Diary Card throughout the course of the study.

The site should schedule the next study activity with the subject's parent(s)/LAR(s). It is recommended for the site to already schedule in advance the remaining upcoming study activities.

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

5.2.2 Post-vaccination Reminders

Reminder calls or alerts are not intended to be an interview for collection of safety data. If the subject's parent(s)/LAR (s) wishes to describe safety information, this information should only be collected by a trained health care 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 Card reminder calls will be performed on Day 5, and on Day 26. The purpose of this call is to remind the subject's parent(s)/LAR(s) about completion of the Subject Diary Card. The call follows the Subject Diary Card reminder telephone call script provided to the site. The subject's parent(s)/LAR(s) should be reminded to contact the site via the telephone number provided in the informed consent to discuss medical questions.

5.3 Post-vaccination Visit(s)

Post-vaccination clinic visits will be performed on Day 22, Day 43, and Day 202.

5.3.1 Follow-up Clinic Visit(s)

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

During the follow-up clinic visit 2 and 5 (Days 22 and 43), the Subject Diary Card[8] will be reviewed. No changes to the information recorded within the Subject Diary Card are permissible. For details on the Subject Diary Card see sections 3.4.2, Tools Used for Data Collection and 5.2.1, Post-vaccination Procedures. The parent(s)/LAR (s) will be interviewed to determine if any unsolicited adverse events occurred and if any associated

[8] In case a clinic visit is not possible, subjects should be instructed on how to return the Subject's Diary Card.

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 health care professional reviewing these data will discuss the symptoms (if any) reported by the subject's parent(s)/LAR(s) and will determine if any additional diagnoses and/or adverse events are present. All adverse events reported by the parent(s)/LAR(s) at the follow-up clinic visits on Day 22 and Day 43 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. During the Day 202 safety follow-up clinic visit, only the following subset of unsolicited AEs and the associated concomitant medications/vaccinations will be documented in the subject's eCRFs: all SAEs, NOCDs, AEs leading to vaccine and/or study withdrawal, and AESIs.

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. 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: safety call with the subject's parent(s)/LAR(s). The subject's parent(s)/LAR(s) will receive a written reminder of the next planned study activity. The subject's parent(s)/LAR(s) 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.

5.3.2 Safety Follow-up Calls

Safety follow-up calls will be performed on Days 92, 152 and 387.

Safety follow-up calls are calls made to the subject by a qualified health care professional designated on the site's roles and responsibilities log. These calls will follow a script which will facilitate the collection of relevant safety information. The subject's parent(s)/LAR (s) will be interviewed according to the script, and information relating to the following unsolicited adverse events: SAEs, AESIs, AEs leading to withdrawal, and/or NOCD and associated concomitant medications or vaccinations. 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: clinic visit or safety call with the subject's parent(s)/LAR(s).

The parent(s)/LAR(s) 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.

5.4 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.

5.5 Study Termination Visit

The study termination visit (ie, safety phone call) will occur on Day 387. 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 termination eCRF page. For visit procedures to be performed for a subject whose planned study participation ends prematurely, please see section 5.5.1, Early Termination Visit.

During the telephone call, the following procedures will be performed if applicable: review of Subject Diary Card, collection of Subject Diary Card, review of systems, interview of the subject's parent(s)/LAR (s) to collect unsolicited AEs, AEs leading to withdrawal, SAEs, AESIs, and NOCD, interview of subject and/or parent(s)/LAR (s) to collect associated concomitant medications/ vaccinations, symptom-directed physical assessment, and blood sampling for immunogenicity.

The site will review with the subject's parent(s)/LAR(s) the plan of when information relating to the subject's participation in the study may be available (eg, 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 health care provider, if the subject's parent(s)/LAR(s) chooses to share this information.

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

5.5.1 Early Termination Visit

When a subject is withdrawn from treatment or withdraws from the study, the investigator will notify the sponsor or delegate and, when possible, will perform the procedures listed below. The reason(s) for the early termination will be included in the subject's source

documentation. If the early termination visit is a telephone call, collect as much information as possible. Early termination visits include subjects who were randomized but not treated.

At the clinic visit or during the telephone call, the following procedures will be performed as during the study termination visit, see section 5.5 Study Termination Visit, if possible.

In addition, the following procedures will be performed:

- Collect and review Subject Diary Card, if applicable.[9]
- Review the subject's safety data (if collection of these was in progress at the time of study completion).

The site will review with the subject's parent(s)/LAR (s) the plan of when information relating to the subject's participation in the study may be available (eg, 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 health care provider, if the subject's parent(s)/LAR(s) chooses to share this information.

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

[9] In case a clinic visit is not possible, subjects should be instructed on how to return the Subject's Diary Card.

6. TREATMENT OF SUBJECTS

All vaccines associated with this study are to be stored separately from other vaccines and medications in a secure location under appropriate storage conditions with temperature monitoring. **All vaccines associated with this study must be checked for expiration date prior to use. Expired vaccines must not be administered to subjects.**

6.1 Study Vaccine(s)

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

Investigational vaccine: aH5N1

Six different formulations of the aH5N1 vaccine in 6 different HA/MF59 combinations will be tested in this study, see Table 6.1. The full composition of the active vaccine components of the currently licensed adult formulation for aH5N1 (7.5 µg HA of H5N1 influenza strain combined with 0.25 mL MF59) is reported in Table 6.2.

Table 6.1: H5N1 HA and MF59 content of the 6 vaccine formulations.

Arm*	H5N1 HA content	MF59 content**	Injection volume
A	1.875 µg	50% MF59	0.25 mL
B	3.75 µg	50% MF59	0.25 mL
C	7.5 µg	50% MF59	0.25 mL
D	1.875 µg	100% MF59	0.5 mL
E	3.75 µg	100% MF59	0.5 mL
F	7.5 µg	100% MF59	0.5 mL

*Approximately 70 subjects will be randomized per treatment arm, ie, 35 subjects in each age cohort.
**50% MF59 refers to half the standard MF59 content of the licensed adult formulation for H5N1.

Table 6.2: Full composition of the active vaccine components.

Composition of the active vaccine components	
Component	7.5 µg + 100% MF59 per 0.5 mL
Influenza virus surface antigens (HA and NA) A/turkey/Turkey/1/2005 (H5N1)-like (NIBRG-23)	~7.5-µg HA
% MF59 content relative to commercial vaccine	100%
Squalene	9.75 mg
Polysorbate 80	1.175 mg
Sorbitan trioleate	1.175 mg
Sodium citrate dihydrate	0.66 mg
Citric acid monohydrate	0.04 mg
Sodium chloride	[redacted]
Potassium chloride	[redacted]
Potassium dihydrogen phosphate	[redacted]
Disodium phosphate dihydrate	[redacted]
Magnesium chloride hexahydrate	[redacted]
Calcium chloride dihydrate	[redacted]
Water for injection	Up to 0.5 mL
Vaccine Presentation	Prefilled syringe
Volume of Component	~0.5 mL

Subjects will be randomized to receive 2 doses of study vaccine, 3 weeks apart, according to the vaccine group assignments shown in Table 1.

6.2 Non-Study Vaccines

The term ‘non-study vaccine’ refers to those vaccines which will be intentionally given to study subjects but not formally included in the analysis of study objectives. No “non-study vaccines” will be given as part of this study.

Subjects are not prohibited from receiving other vaccinations during the course of the trial as long as these are not an influenza vaccination administered prior to visit 3 (Day 43). Please see section 6.5 for further details. Following Day 43 other vaccines may be administered, including seasonal flu.

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. The study vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.

The study vaccines will be supplied in kits (per subjects/per visit) containing the required materials to administer the specific formulation at the site. The kits may contain the following components, depending on the dose regimen:

- PFS, adjuvanted (50% MF59) H5N1 A/turkey/Turkey/1/2005 1.9 µg/0.25 mL
- PFS, adjuvanted (100% MF59) H5N1 A/turkey/Turkey/1/2005 1.9 µg/0.5 mL
- PFS, adjuvanted H5N1 (50% MF59) A/turkey/Turkey/1/2005 3.75 µg/0.25 mL
- PFS, adjuvanted (100% MF59) H5N1 A/turkey/Turkey/1/2005 3.75 µg/0.5 mL
- PFS, adjuvanted H5N1 (50% MF59) A/turkey/Turkey/1/2005 7.5 µg/0.25 mL
- PFS, adjuvanted (100%) H5N1 A/turkey/Turkey/1/2005 7.5 µg/0.5 mL

All formulations will be supplied as PFSs, depending on the treatment allocation 0.25 mL or 0.5 mL will be administered.

For detailed vaccine preparation and administration instructions unblinded personnel should refer to the IMP handling instructions.

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.

Eligibility for non-study vaccines should be determined by the investigator, pending the review of the package insert of the relevant vaccine and the guidelines described in section 6.2, Non-Study Vaccines.

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

Vaccine administration will be performed intramuscularly, anterolateral thigh for children ages <2 years; deltoid for children ages ≥2 years, unless insufficient deltoid mass.

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 (eg, 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 aH5N1 vaccine.

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

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

6.5 Prior and Concomitant Medications and Vaccines

All medications, vaccines, including influenza vaccines (within the last 2 years), and blood products taken or received by the subject within 3 months prior to the start of the study are to be recorded on the prior and concomitant medications eCRF. See the exclusion criteria in section 4.2, Exclusion Criteria for details on medication that is not allowed prior and during the study.

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

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

Concomitant medications include all medications (including vaccines) taken by/administered to the subject at and after enrolment and must be documented on the concomitant medications eCRF. From Day 1 to Day 43 all concomitant medications should be recorded in the eCRF. In the follow-up period (Day 44 through Day 387), only concomitant medications associated with SAEs, NOCDs, AEs leading to vaccine and/or study withdrawal, and AESIs should be recorded in the eCRF.

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

6.6 Vaccine Supply, Labeling, Storage and Tracking

The sponsor will ensure the following:

- Supply of the study vaccine(s).
- Appropriate labeling of all study vaccines provided that these comply with the legal requirements of each country where the study is to be performed.

The investigator must ensure the following:

- Acknowledge receipt of the study vaccines by a designated staff member at the site, including:
  - Confirmation that the vaccines were received in good condition
  - Confirmation to the sponsor or delegate of the temperature range during shipment from the sponsor to the investigator's designated storage location
  - In case of temperature excursions during shipment: Confirmation by the sponsor or delegate that the vaccines are authorized for use.
- Proper storage of the study vaccines, including:
  - Storage in a secure, locked, temperature-controlled location.

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

- Appropriate use of the study vaccines, including:
  - Use only in accordance with the approved protocol.
  - Proper handling, including confirmation that the vaccine has not expired prior to administration.
  - Appropriate documentation of administration of vaccines to study subjects including:
    - Date, dosage, batch/lot numbers, expiration dates, unique identifying numbers assigned to subjects and study vaccines, and time of vaccine administration. This information will be maintained on the Vaccine Administration 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 and the volume 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 upon approval from the sponsor.
- 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 upon approval from the sponsor.

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 are destroyed locally (upon approval from sponsor) or returned to the sponsor.

7. ASSESSMENTS

7.1 Safety Assessment

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

The period of observation for AEs extends from the time the subject signs informed consent /assent until he or she completes the specified safety follow-up period visit 7 (Day 387) or terminates the study early (whichever comes first). AEs occurring after the ICF/assent is signed but prior to receiving study vaccine/product will be documented as an adverse event in EDC and recorded within the source document. However, any AEs occurring prior to receipt of any study vaccine will be analyzed separately from "treatment emergent" AEs (AEs occurring after administration of the first study vaccine).

AEs are collected as either solicited or unsolicited adverse events. Solicited events are derived from organized data collection systems, such as subject diaries or interview.

7.1.1 Solicited Adverse Events

The term "reactogenicity" refers to solicited signs and symptoms ("solicited adverse events") occurring in the hours and days following a vaccination, to be collected by the subject's parent(s)/LAR(s)/caregiver for 7 consecutive days, using a pre-defined Subject Diary Card. In this study there will be 2 versions of the Subject Diary Card; one version for children <3 years and one version for children ages 3 years and older.

The following solicited adverse events are included in the Subject Diary Card. Each adverse event is to be assessed according to defined severity grading scales.

For children ages 6 months through <3 years, solicited local AEs will include injection-site erythema, injection-site induration, injection-site ecchymosis, and injection-site tenderness; solicited systemic AEs will include change in eating habits, shivering, sleepiness, irritability, vomiting, diarrhea, and body temperature ≥38.0°C.

For children ages 3 years and older, solicited local AEs will include injection-site erythema, injection-site induration, injection-site ecchymosis, and injection-site pain; solicited systemic AEs will include loss of appetite, nausea, fatigue, malaise, generalized myalgia, generalized arthralgia, headache, shivering/chills, vomiting, diarrhea, and body temperature ≥38.0°C.

Solicited local or systemic adverse event continuing beyond Day 7 after vaccination, must also be recorded as an unsolicited AE on the AE eCRF.

Other Indicators of Reactogenicity

The use of analgesics/antipyretics will be captured as "absent" or "present" and will also be summarized by "for treatment" or "for prophylaxis".

Instructions for Temperature Collection

Temperature should preferably be measured using the thermometer provided to the parent(s)/LAR(s) by the site staff. Ideally the subject's temperature should be taken orally, however if for some reason it cannot be taken in this way, the alternate route of administration should be recorded on the Subject Diary Card.

The parent(s)/LAR(s) should be advised to begin measuring the subject's temperature approximately 6 hours after the vaccination or prior to the subject going to bed if this is before. For the next 6 days following vaccination, the subject's temperature should be measured at least once a day, preferably in the evening and at the same time each day. If the subject feels warm or unusually cold at any time during the 7 day post vaccination reporting period, the parent(s)/LAR(s) should be advised to record an additional temperature. If multiple temperatures are collected on any given day, only the highest temperature measured that day should be recorded.

If the subject's temperature is below 35.5°C the parent(s)/LAR(s) should be advised to take a repeat measurement to ensure the temperature is correct. If the subject's temperature is 38.0°C or higher at day 7, the parent(s)/LAR(s) should continue to measure the subject's temperature each day until it returns below 38.0°C. The date of the last day that the subject's temperature was above 38.0 °C should be recorded on the Subject Diary Card.

If the subject's temperature is ≥38.0°C and is accompanied by one or more of the following symptoms: cough, sore throat, nasal congestion or runny nose, the parent(s)/LAR(s) should be advised to contact the study site immediately.

Instructions for Recording Injection Site Reactions

It is important to advise the parent(s)/LAR(s) that they should record both when an injection site reaction was observed as well as when one was not by checking the

appropriate tick box on the Subject Diary Card. The parent(s)/LAR(s) should be advised to complete their assessments at approximately the same time each day, preferably in the evening.

When a measurable reaction is observed such as hardness, bruising or redness the parent(s)/LAR(s) making the assessment should use the ruler provided by the site to measure the size in mm of the affected area. This information should be recorded by the parent(s)/LAR(s) on the Subject Diary Card.

When tenderness at the reaction site is noticed the parent(s)/LAR(s) should monitor the monitor the symptoms throughout the day and enter the most severe status that was observed (ie, mild, moderate or severe). If a reaction continues past day 7 the subject's parent(s)/LAR(s) should be advised to record the last day that the reaction was observed.

Instructions for Recording General Symptoms (changes in eating habits, sleepiness, vomiting, diarrhea, irritability and shivering)

When general symptoms are observed by the subject's parent(s)/LAR(s) they should be monitored throughout the day and the most severe status observed (mild, moderate or severe) should be recorded on the Subject Diary Card. Definitions of these categories for each the general symptoms inquired about can be found in the diary. It is important to advise the parent(s)/LAR(s) that they should record both when a reaction was observed as well as when one wasn't by checking the appropriate tick box on the Subject Diary Card. If a symptom is still present at Day 7, the date of the last day the symptom was present should be recorded.

Instructions for Recording Medicines Taken for Reactions and General Symptoms on the Day of Vaccination and/or on the First 6 days after Vaccination

The subject's parent(s)/LAR(s) should be advised to report any medications that were taken to treat any of the reactions or symptoms which occurred following the vaccination administration and for the next 3 weeks. With a tick box this should be recorded on the diary for the first 6 days after vaccination.

Other Solicited Adverse Events

The study staff must review the data entered into the Subject Diary Card as described in section 3.4.2, Tools Used for Data Collection and section 5.3.1, Follow-up Clinic Visit(s).

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 adverse event on the adverse event eCRF:

- Solicited local or systemic AE that leads to a visit to a health care provider (see section 7.1.3, Evaluation of Adverse Events).

- Solicited local or systemic AE leading to the subject withdrawing from the study or the subject being withdrawn from the study by the investigator (AE leading to withdrawal, see section 7.1.3, Evaluation of Adverse Events).
- Solicited local or systemic AE that otherwise meets the definition of a 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 and/or parent(s)/LAR(s) who has signed the informed consent.

The period of observation for AEs extends from the time of informed consent until the subject either completes the specified safety follow-up period (Day 387) or at early termination. Adverse events that occur after the ICF is signed but prior to receiving study vaccine are to be documented as an AE and recorded within the source document. All AEs that start during the treatment period (Day 1 to Day 43) are to be recorded in the eCRF. During the safety follow-up period (Day 44 to Day 387), only AEs that meet any of the following criteria are to be recorded in the eCRF: SAE, AESI, NOCD, or AE leading to withdrawal. Potential unsolicited AEs may be medically attended (defined as symptoms or illnesses requiring hospitalization, or emergency room visit, or visit to/by a health care provider), or were of concern to the subject and/or parent(s)/LAR(s). In case of such events occur during the first 3 weeks after the study vaccine administration, subject's parent(s)/LAR(s) will be instructed to contact the site as soon as possible to report the event(s). The detailed information about the reported unsolicited AEs will be collected by the qualified site personnel during the interview and will be documented in the subject's records.

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

7.1.3 Evaluation of Adverse Events

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

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

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

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

1. Not Related

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

2. 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: all solicited AEs from Day 1 to Day 7 will be considered Adverse Drug Reactions (ADRs). 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:

- "New Onset of Chronic Disease": an AE that represents a new diagnosis of a chronic medical condition that was not present or suspected in a subject prior to study enrolment.
- Adverse events leading to withdrawal: AEs leading to study or vaccine withdrawal.

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

When the subject's parent(s)/LAR(s) are 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/source document.

7.1.4 Serious Adverse Events

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

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

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

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

Serious AEs will be captured on the Adverse Events eCRF. All SAEs will be evaluated by the investigator for relationship of the event to study vaccine. SAEs that are judged to be possibly or probably related to the study vaccine should be reported to the sponsor as related/suspected events.

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

1. Related/suspected

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

2. Not Related

The SAE is not related if exposure to the study vaccine has not occurred, **or** the occurrence of the SAE is not reasonably related in time, **or** the SAE is considered unlikely to be related to use of the study vaccine, ie, 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 delegate for "expectedness." An unexpected AE is one that is not listed in the current summary of product characteristics or the Investigator's Brochure or an event that is by nature more specific or more severe than a listed event.

In addition, a pre-existing event or condition that results in hospitalization should be recorded on the medical history eCRF. If the onset of an event occurred before the subject entered the study (eg, 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

The investigator will be provided with a list of AESIs prior to study start (Appendix A: Adverse Events of Special Interest).

Subjects will be assessed at each clinic visit for any new medical events or signs or symptoms that could possibly indicate an AESI. The subject's parent(s)/LAR(s) will be asked whether any new diagnosis has been given to the subject through a review of recent

medical history. The subject's parent(s)/LAR(s) will be instructed, prior to the visit, to bring any medical records/documentation of any new medical diagnosis or medical problem. The medical records/documentation will be thoroughly reviewed by the site staff and recorded into the subject's medical chart/source documents. A review of organ systems and a targeted physical examination of the subject will also take place. A qualified health care practitioner listed on the site's responsibilities and delegation logs are required to evaluate subjects. Should a qualified health care practitioner who is not the investigator suspect a potential AESI, she/he should promptly inform the investigator. A diagnosis of an AESI should be categorized as an SAE and must be documented on the AE eCRF within 24 hours of the site becoming aware of an AESI diagnosis. If the eCRF is not available, then the study site must complete the paper SAE Report Form and email the Seqirus Pharmacovigilance and Risk Management (PVRM) (or delegate) at ae.reporting@seqirus.com within 24 hours of becoming aware. Once the eCRF is available, the AESI should be documented on the AE eCRF as soon as possible.

The AESI diagnosis will also be recorded in the medical chart/source document. This is also applicable to any medication(s) used to treat the condition.

7.1.4.2 New Onset of Chronic Disease

NOCD is defined as an illness that starts during the course of the study that did not exist prior to enrollment into the study and is likely to persist throughout the lifetime of the subject. A chronic disease is one that can be treated but for which no cure exists. For example, a new onset of asthma (occurs for the first time during the study and has been evaluated longitudinally to ensure that a diagnosis of asthma is appropriate) is classified as a NOCD. This is applicable for any chronic disease affecting any organ class that arises during the study that is likely to persist throughout the subject's lifetime (even if in remission). Infectious diseases, such as Hepatitis C Virus or tuberculosis, are not considered NOCDs as there are antibiotics and antivirals that are potentially able to cure such diseases (this is a generalizable cure and not specific to the subject). In case of doubt, diagnoses of NOCD should be discussed with the study medical monitor. Of note, a NOCD may be a condition listed in AESI.

7.1.5 Methods for Recording Adverse Events and Serious Adverse Events

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

All SAEs which occur during the course of the study, whether considered to be associated with the study vaccination or not, must be documented on the AE eCRF **within 24 hours of the site becoming aware of the event**. If the eCRF is not available, then the study site

must complete the paper SAE Report Form and email the 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 AE will be recorded on the appropriate eCRF(s) in addition to the outcome of the AE.

After receipt of the initial report, Seqirus PVRM 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 applicable regulatory authorities in accordance with institutional policy/regulatory requirements and adequate documentation of this notification must be provided to the sponsor or its delegate.

Seqirus or delegate must also comply with the applicable regulatory requirement(s) related to the reporting of suspected unexpected serious adverse vaccine reactions (also known as SUSARs) to the regulatory authority(ies) and the IRB/EC. If a SUSAR or other safety signal relating to use of one of the study vaccines is reported to the sponsor 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.

7.1.5.1 Post-Study Events

For this study no post-study follow-up will be defined. A 12 months' follow-up period after the vaccinations is already included in the study design.

7.1.6 Pregnancies

Not applicable.

7.1.7 Safety Laboratory Measurements

Not applicable.

7.2 Efficacy Assessment

Not applicable.

7.3 Immunogenicity Assessment

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

The measures of immunogenicity used in this study have been described/adopted in guidance/based on scientific consensus/other and have been deemed appropriate to describe the immune response against A/H5N1 in this study.

Immunological responses to the different doses of antigens and adjuvant contained in the vaccine (A/H5N1) will be evaluated using HI and MN assays (and SRH assay if sufficient serum if available). Blood samples will be obtained prior to the first vaccination on Day 1, on Day 22, 3 weeks after the first vaccination, on Day 43, 3 weeks after the second vaccination, and on Day 202, 6 months after the second vaccination.

Measuring HI and MN antibody titers on Days 22 and 43, approximately 21 days after first and second study vaccination, is the typical timing to evaluate the antibody response of subjects. These titers will be compared against baseline antibody titers (Day 1, prior to vaccination) and will be used to evaluate immunogenicity.

Testing will be conducted by the sponsor designated laboratory (ies) in a blinded manner to the treatment arm and the visit. Please see the laboratory manual for name(s) and other details.

8. STATISTICAL CONSIDERATIONS

A complete description of the statistical analyses and methods will be available in the Statistical Analysis Plan, which will be finalized before the database is locked.

This study will evaluate the safety and immunogenicity endpoints related to different formulations of the vaccine. The statistical analysis will be mainly descriptive in nature without any pre-specified inferential analyses.

8.1 Endpoints

8.1.1 Primary Endpoint(s)

8.1.1.1 Primary Safety Endpoint(s)

The measures for assessing safety and reactogenicity are as follows:

- Percentages of subjects with solicited local and systemic AEs[10] that occur within 7 days following each vaccination and calculated for 4 time intervals after vaccination: 30 minutes, 1 through 3 days, 4 through 7 days, and 1 through 7 days.
- Percentages of subjects with any unsolicited AEs reported within 21 days after each vaccination within each vaccine group.
- Percentages of subjects reporting SAEs, NOCDs, AESIs, and AEs leading to vaccine and/or study withdrawal , as collected from Day 1 through Day 387.

8.1.1.2 Primary Efficacy Endpoint(s)

This study does not have primary efficacy endpoint(s).

8.1.1.3 Primary Immunogenicity Endpoint(s)

The measures of immunogenicity, as determined by the HI and MN assay against the H5N1 pandemic influenza homologous strain include the following:

- Geometric mean titers (GMTs) on Day 1 and Day 22 (3 weeks after the first vaccination) or Day 43 (3 weeks after the second vaccination) as determined by HI and MN assays against the homologous H5N1 pandemic influenza strain;

[10] Including the use of antipyretics/analgesics

- Geometric mean ratios (GMRs) calculated as follows: Day 22/Day 1 or Day 43/Day 1 as determined by HI and MN assays against the homologous H5N1 pandemic influenza strain;
- Percentage of subjects achieving seroconversion (non-detectable to ≥ 1:40 , or 4-fold increase from a detectable Day 1 titer) on Day 22 or 43;
- Percentage of subjects achieving seroconversion with a titer ≥ 1:40 on Days 1, 22 or 43[11].

All primary immunogenicity endpoints will be described by treatment group, overall and by age cohort.

In addition, reverse cumulative distribution functions for HI and MN titers will be computed on Days 1, 22, 43, and 202 (as applicable) and presented graphically and/or in tabulated form.

8.1.2 Secondary Endpoint(s)

8.1.2.1 Secondary Safety Endpoint(s)

This study does not have secondary safety endpoint(s).

8.1.2.2 Secondary Efficacy Endpoint(s)

This study does not have secondary efficacy endpoint(s).

8.1.2.3 Secondary Immunogenicity Endpoint(s)

All secondary immunogenicity endpoints will be described by treatment group and by age cohort.

The measures of persistence of antibody responses on Day 202 to study vaccine after primary vaccinations, as determined by the HI and MN assays against the H5N1 pandemic influenza homologous strain:

- Geometric mean titers on Day 1 and Day 202 (6 months after the second vaccination) as determined by HI and MN assays;
- Geometric mean ratios calculated as follows: Day 202/Day 1 as determined by HI and MN assays;

[11] Percentage of subjects achieving a titer ≥1:40 on Days 1, 22, or 43

- Percentage of subjects achieving seroconversion (non-detectable to ≥1:40, or 4-fold increase from a detectable Day 1 titer) on Day 202;
- Percentage of subjects achieving seroconversion with a titer of ≥1:40 on Day 202[12]

8.1.3 Exploratory Endpoint(s)

8.1.3.1 Exploratory Safety Endpoint(s)

This study does not have exploratory safety endpoint(s).

8.1.3.2 Exploratory Efficacy Endpoint(s)

This study does not have exploratory efficacy endpoint(s).

8.1.3.3 Exploratory Immunogenicity Endpoint(s)

If adequate sera will be available and depending on assay availability, antibody responses and their persistence to seasonal and/or homologous and/or heterologous pandemic influenza strains as measured by HI, MN and SRH assays may be described at Days 1, 22, 43, and 202 in the same manner as for primary and secondary immunogenicity endpoints.

Other exploratory immunogenicity analyses may be described in the SAP or in an addendum to such a plan.

8.2 Success Criteria

There is no pre-defined success criterion in this study.

8.2.1 Success Criteria for Primary Objective(s)

There is no pre-defined success criterion for primary objectives.

8.2.1.1 Success Criteria for Primary Safety Objective(s)

There is no pre-defined success criterion for safety objectives.

8.2.1.2 Success Criteria for Primary Efficacy Objective(s)

Not applicable to this study.

[12] Percentage of subjects achieving a titer ≥1:40 on Day 202

8.2.1.3 Success Criteria for Primary Immunogenicity Objective(s)

There is no pre-defined success criterion for immunogenicity objectives.

8.2.2 Success Criteria for Secondary Objective(s)

8.2.2.1 Success Criteria for Secondary Safety Objective(s)

Not applicable to this study.

8.2.2.2 Success Criteria for Secondary Efficacy Objective(s)

Not applicable to this study.

8.2.2.3 Success Criteria for Secondary Immunogenicity Objective(s)

There is no pre-defined success criterion for secondary immunogenicity objectives.

8.3 Analysis Sets

8.3.1 All Enrolled Set

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

8.3.2 All Exposed Set

All subjects in the enrolled set who receive at least one or a partial dose of study vaccination.

8.3.3 Safety Set

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

All subjects in the exposed set with any solicited adverse event data and/or indicators of solicited adverse events.

Subjects with a confirmation of no indicators of solicited adverse event (for example vomiting is none or injection site-induration is 0 mm [none]) will be included in this population as well.

Unsolicited Safety Set (unsolicited adverse events)

All subjects in the exposed set with unsolicited adverse event data.

Subjects with a confirmation of no unsolicited adverse event will be included in this population as well.

Overall Safety Set

All subjects who are in the solicited safety set and/or unsolicited safety set.

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

Subjects randomized in the wrong age stratum will be reassigned to the correct age stratum and will be analyzed using corrected stratum for all safety sets (ie, solicited safety set, unsolicited safety set and overall safety set). If a subject is unblinded during the study, he/she will be included in all the safety sets.

8.3.4 Full Analysis Set (FAS) Efficacy/Immunogenicity Set

Full Analysis Set Efficacy

Not applicable to this study.

Full Analysis Set Immunogenicity

All subjects in the all enrolled set who are randomized, receive at least one study vaccination and provide immunogenicity data at any time point.

In case of vaccination error, subjects in the FAS sets will be analyzed "as randomized" (ie, 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 Set (PPS) Efficacy/Immunogenicity Set

Per Protocol Set Efficacy

Not applicable to this study.

Per Protocol Set Immunogenicity

All subjects in the FAS immunogenicity who:

- Correctly receive the vaccine (ie, receive the vaccine to which the subject is randomized and at the scheduled time points).

- Provide at least the baseline and one post-baseline blood sample, with evaluable immunogenicity data.
- Have no protocol deviations leading to exclusion (see section 8.3.8, Protocol Deviations) as defined prior to unblinding / analysis.
- Are not excluded due to other reasons defined prior to unblinding or analysis (see section 8.3.8, Protocol Deviations). Examples for subjects excluded due to other reasons than protocol deviations are subjects who withdrew informed consent/assent.

Note that missing immunogenicity data at some time points following vaccination will not be considered a reason to exclude the subject from PPS Immunogenicity.

8.3.6 Other Analysis Sets

Not applicable to this study.

8.3.7 Subgroups

Age cohort (6 months to <36 months and 3 to <9 years based on the actual age) will be used as a subgroup for all study primary and secondary endpoints.

8.3.8 Protocol Deviations

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

8.4 Statistical Analysis Plan

A complete description of the statistical analyses and methods will be available in the Statistical Analysis Plan (SAP), which will be finalized prior to unblinding.

8.4.1 Analysis of Demographic and Baseline Characteristics

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

Distributions of subjects by sex, race, ethnicity, country and previous influenza vaccination status will be summarized overall, by vaccine group and age cohort.

8.4.1.1 Subject Disposition

The number of subjects enrolled into the study and completed the study, will be presented in summary tables by treatment group, overall and by age cohort. The number in the Enrolled population will be used as the denominator. The primary reason for withdrawal from the study vaccination or from the study will summarized overall, by vaccine group, and age cohort. All data will be listed by subject.

8.4.1.2 Concomitant Medications

Use of concomitant medication will be presented by treatment, age cohort, therapeutic area, and preferred drug name.

Concomitant medications are all medications taken during the study period, including those started before but ongoing at vaccination.

If a start date for a medication is partially or fully missing, and it is unclear as to whether the medication is prior or concomitant, it will be assumed that it is concomitant.

Medications will be coded using the WHO Drug dictionary.

8.4.2 Analysis of Primary Objective(s)

8.4.2.1 Analysis of Primary Safety Objective(s)

8.4.2.1.1 Analysis of Extent of Exposure

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

8.4.2.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

Frequencies and percentages of subjects experiencing each AE occurring after first study vaccination, will be presented for each symptom overall and by maximum severity. Summary tables showing the occurrence of any local or systemic AE overall and at each time point will also be presented.

Post-vaccination solicited AEs reported from Day 1 to Day 7 will be summarized for the intervals Day 1-3, Day 4-7, Day 1-7 by maximal severity and by vaccine group, excluding the 30 minute measurement, which will be summarized separately.

The severity of solicited local AEs including injection-site erythema, injection-site induration, injection-site ecchymosis, and either injection-site tenderness (for children

ages 6 months through <3 year) or injection-site pain (for children 3 years and older). Injection-site erythema, induration and ecchymosis will be summarized according to categories: 1 to 10 mm, 11 to 25 mm, 26 to 50 mm, >50 mm. Injection site pain/tenderness and systemic AEs (except fever) occurring up to 7 days after each vaccination will be summarized according to "mild", "moderate" or "severe".

Body temperature will be summarized by 0.5 °C and 1.0 °C increments from 36.0°C up to ≥ 40°C and will be broken down according by route of measurement. Fever, ie, body temperature ≥38°C will also be categorized as mild (38.0-38.4°C), moderate (38.5-38.9°C), severe (39.0-40.0°C), and potentially life threatening (≥40.0°C).

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

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

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

8.4.2.1.3 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. This analysis will include solicited AEs continuing beyond Day 7, which will be considered as possibly related AEs. AE starting prior to the first vaccination will only be listed. The original verbatim terms used by investigators to identify AEs in the eCRFs will be mapped to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. The AEs will then be grouped by MedDRA preferred terms into frequency tables according to system organ class.

All reported AEs, as well as AEs judged by the investigator as at least possibly related to study vaccine, will be summarized according to system organ class and preferred term within system organ class. These summaries will be presented by vaccination group. When an adverse event 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:

- SAEs
- AEs that are possibly or probably related to vaccine

- AEs of special interest
- New onset of chronic disease
- AEs leading to withdrawal from the study or the second vaccination

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

8.4.2.1.4 Analysis of Safety Laboratory Values

Not applicable for this study.

8.4.2.2 Analysis of Primary Efficacy Objective(s)

Not applicable for this study.

8.4.2.2.1 Statistical Hypotheses

This study does not have statistical hypotheses.

8.4.2.2.2 Analysis Sets

All immunogenicity analyses (primary, secondary, and exploratory) will be performed on the PPS Immunogenicity. The primary immunogenicity analyses will be also performed based on the FAS Immunogenicity if the percentage of subjects excluded from the PPS immunogenicity is greater than 5%. All solicited safety analyses will be performed in solicited safety set. All unsolicited safety analyses will be performed ontheunsolicited safety set. Further details are given in section 8.3, Analysis Sets.

8.4.2.2.3 Statistical Methods

8.4.2.3 Analysis of Primary Immunogenicity Objective(s)

The antibody titers below lower limit of detection (LLD) will be coded as half of LLD (for example, 5 if LLD is 10). Missing immunogenicity data will be excluded from analysis of immunogenicity endpoints. Imputation methods will therefore not be applied. Sensitivity analyses may be considered to assess the impact of missing data in case of substantial missing data.

For analysis requiring quantitative summarization of antibody titers (such as GMT or GMR) all antibody titers will be $\log_{10}$-transformed. Geometric mean ratios with 95% CIs will be calculated by estimating arithmetic means and 95% CIs for a normal variate on

log_{10}-transformed scale, then back-transformation of these statistics using exponentiation at the base of 10.
For analysis of binary data (ie, percentage of subjects with seroconversion and percentage of subjects with titer ≥1:40), the counts and percentages will be determined, the CIs will be calculated using Clopper-Pearson method.

Seroconversion will be defined as either of the two conditions: subjects with a baseline titer <1:10 by either HI or MN assay with a post-vaccination titer ≥1:40 OR subjects with baseline titer ≥1:10 by either HI or MN assay with a 4-fold or higher increase in post-vaccination titer.

No formal statistical hypothesis will be tested.

8.4.2.3.1 Statistical Hypotheses

This study does not have statistical hypotheses.

8.4.2.3.2 Analysis Sets

See section 8.4.2.2.2, Analysis Sets

8.4.2.3.3 Statistical Methods

See section 8.4.2.2.3, Statistical Methods.

8.4.3 Analysis of Secondary Objective(s)

All secondary immunogenicity endpoints will be analyzed in the same manner as primary immunogenicity endpoints.

8.4.3.1 Analysis of Secondary Safety Objective(s)

8.4.3.1.1 Analysis of Extent of Exposure

Not applicable to this study as all safety objectives are considered primary.

8.4.3.1.2 Analysis of Solicited Local, Systemic and Other Adverse Events

Not applicable to this study as all safety objectives are considered primary.

8.4.3.1.3 Analysis of Unsolicited Adverse Events

Not applicable to this study as all safety objectives are considered primary.

8.4.3.1.4 Statistical Hypotheses

Not applicable to this study as all safety objectives are considered primary.

8.4.3.1.5 Analysis Sets

Not applicable to this study as all safety objectives are considered primary.

8.4.3.1.6 Statistical Methods

Not applicable to this study as all safety objectives are considered primary.

8.4.3.2 Analysis of Secondary Efficacy Objective(s)

Not applicable to this study.

8.4.3.2.1 Statistical Hypotheses

Not applicable to this study.

8.4.3.2.2 Analysis Sets

Not applicable to this study.

8.4.3.2.3 Statistical Methods

Not applicable to this study.

8.4.3.3 Analysis of Secondary Immunogenicity Objective(s)

Secondary immunogenicity endpoints will be analyzed in the same manner as primary immunogenicity endpoints.

8.4.3.3.1 Statistical Hypotheses

Not applicable to this study.

8.4.3.3.2 Analysis Sets

See section 8.4.3.2.2, Analysis Sets.

8.4.3.3.3 Statistical Methods

See section 8.4.2.2.3, Statistical Methods.

8.4.4 Analysis of Exploratory Objectives

8.4.4.1 Analysis of Exploratory Safety Objective(s)

Not applicable to this study.

8.4.4.2 Analysis of Exploratory Efficacy Objective(s)

Not applicable to this study.

8.4.4.3 Analysis of Exploratory Immunogenicity Objective(s)

Exploratory immunogenicity endpoints related to evaluation antibody responses to seasonal and/or homologous and/or heterologous pandemic influenza strain(s) will be analyzed in the same manner as primary and secondary immunogenicity endpoints.

As an additional exploratory analysis, an analysis of co-variance will be conducted on log transformed (base ten) Day 22 or Day 43 HI (or MN) titers as the outcome variables and terms for covariates: age cohort, dose of MF59 adjuvant, amount of antigen and – where applicable – the Day 1 prevaccination HI (or MN) titer. Potential covariate interaction effects will also be examined in this model.

The SAP may specify additional exploratory analyses of immunogenicity data.

8.5 Sample Size and Power Considerations of Primary Objective

This is a dose-ranging study without inferential hypothesis testing. The total sample size to be randomized is 420 subjects equally divided for two age cohorts. This number of subjects should provide sufficiently accurate estimates of the GMT to evaluate the pediatric dose. Assuming an exclusion rate of up to 14% of subjects from the analysis, around 180 subjects per age cohort will be included in the analysis. With equal allocation to one of six vaccine groups, we expect at least 60 subjects per vaccine group and at least 30 per vaccine group and age cohort to be evaluable for the statistical analysis. No formal power calculations have been done. However, the accuracy of the estimates of the GMT's can be illustrated by the length of the 95% confidence intervals. Assuming a SD of $\log_{10}$-transformed HI titers as 0.7 (based on studies V87_25 and V87_26 in healthy elderly):

- With n=30 per dose group per age cohort; the 95% CI will be from 0.56 to 1.78 times the GMT estimate

- With n=60 per dose group; the 95% CI will be from 0.67 to 1.50 times from the GMT estimate.

In pairwise dose-group comparisons with n=60 per dose group it would be feasible to detect a difference of 2.5 in the GMT ratio with statistical power of 80% with the two sample T-test at significance level of 0.05.

8.6 Interim Analysis

No interim analysis is planned for this study.

9. SOURCE DOCUMENTATION, STUDY MONITORING AND AUDITING

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

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

9.1 Source Documentation

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

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

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

All safety data reported by subject's parent(s)/ LAR(s) must be written down in source documents prior to entry of the data into eCRFs. If there are multiple sources of information (eg, Subject Diary Card, verbal report of the subject, telephone contact details, medical chart) supporting the diagnosis of an adverse event, these sources must be identified in the source documents, discrepancies between sources clarified, the ultimate diagnosis must be justified and written in the source documents, and this diagnosis must be captured in the adverse event eCRF (AE eCRF). The AE eCRF must also capture

which source(s) of information were used to determine the adverse event (eg, subject recall, medical chart, Subject Diary Card).

9.2 Study Monitoring, Auditing and Source Data Verification

Prior to enrolment of the first study subject, the sponsor or delegate (eg, a CRO) will develop a Clinical Monitoring Plan to specify how centralized and/or on-site monitoring, including clinical specimens reconciliation, will be performed for the study. Study progress will be monitored by the sponsor or delegate 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 sponsor 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.

The investigator and/or site staff must make source documents of subjects enrolled in this study available for inspection by the sponsor or delegate 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 (eg, FDA, EMA and others) and/or ECs/IRBs. The investigator and study site staff must comply with applicable privacy, data protection and medical confidentiality laws for use and disclosure of information related to the study and enrolled subjects.

10. DATA MANAGEMENT

10.1 Data Entry and Management

In this study, all clinical data (including, but not limited to, AE/SAEs, concomitant medications, medical history, and physical assessments) and safety data, data will be entered onto eCRFs in a timely fashion by the investigator and/or the investigator's dedicated site staff. Data entered onto eCRFs are stored on a secure server. 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 or delegate prior to activation for data entry by sites. The investigator or designated delegate must review data entered and electronically sign the eCRFs to verify their accuracy.

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

10.2 Data Clarification

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

10.3 Data Protection

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

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

11. RECORD RETENTION

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

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

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

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

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

12. USE OF INFORMATION AND PUBLICATION

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

The sponsor also assures that key results of this clinical study will be posted in a publicly accessible database within the required time-frame from the end of study as defined in section 3.9, End of Study.

In accordance with standard editorial, ethical practices and current guidelines of Good Publication Practice (Graf 2009), the sponsor will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement prior to the start of the study. The coordinating investigator will also sign the clinical study report on behalf of the principal investigators (Committee of Proprietary Medicinal Products (CPMP)/Efficacy Working Party (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 sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate sponsor personnel.

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

13. ETHICAL CONSIDERATIONS

13.1 Regulatory and Ethical Compliance

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

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations: including, including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, ICH E6 (R2), and Japanese Ministry of Health, Labor, and Welfare, the sponsor codes on protection of human rights, and with the ethical principles laid down in the Declaration of Helsinki (European Council 2001, US Code of Federal Regulations, ICH 1997).

13.2 Informed Consent Procedures

Eligible subjects may only be included in the study after providing written informed consent or assent, as described in section 5.1.1, Informed Consent/Assent. Before the start of the study, the investigator will have the informed consent/assent 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's parent(s)/LAR(s) of all pertinent aspects of the study. A copy of the written informed consent/assent will be given to the subject's parent(s)/LAR(s). The subject's parent(s)/LAR(s) must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject's parent(s)/LAR(s) **must** sign the consent form indicating their agreement to participate in the study before any study-related procedures are conducted. The informed consent/assent process may be conducted up to 10 days prior to vaccination on Day 1. If the subject's parent(s)/LAR(s) is unable to read and write, a witness must be present during the informed consent/assent discussion and at the time of informed consent/assent signature.

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

Before the start of the study, the investigator will have the informed assent, the informed consent, and any other materials that will be provided to the subject's parent(s)/LAR(s) 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's parent(s)/LAR(s) of all pertinent aspects of the study. A copy of the written informed consent and informed assent will be given to the subject's parent(s)/LAR(s).

In addition, the investigator or designee should explain pertinent aspects of the study in an age appropriate manner to pediatric subjects who are eligible for informed assent in accordance with local policies. The subject's parent(s)/LAR(s) must be allowed ample time to ask about the details of the study and to make a decision as to whether or not to participate in the study. The subject/parent(s)/LAR(s) must sign the consent/assent forms indicating their agreement to participate in the study before any study-related procedures are conducted. If the subject's parent(s)/LAR(s) are unable to read and write, a witness must be present during the informed consent/assent discussion and at the time of informed consent/assent signature.

13.3 Responsibilities of the Investigator and IRB/EC

The protocol and the proposed ICF/assent 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/assent have been approved by the IRB/EC must be given to the sponsor or delegate 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 sponsor monitors, auditors, the sponsor clinical quality assurance representatives, designated agents of the sponsor, IRBs/ECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the sponsor or delegate immediately that this request has been made.

The investigator is 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 or qualified health care professionals are responsible for all study-related medical decisions and for ensuring appropriate medical care of subjects experiencing any adverse event related to the study.
- If permission to do so is given by the subject's parent(s)/LAR(s), ensuring that the subject's primary health care 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 (eg, 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 (non-substantial amendment) 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 (eg, change of telephone number(s), logistical changes). Protocol amendments must be approved by the sponsor, health authorities where required, and the IRB/EC. In cases when the amendment is required in order to protect the subject 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, the sponsor should be notified of this action, the IRB/EC at the study site, and, if required by local regulations, the relevant health authority) should be informed within 10 working days.

14. REFERENCE LIST

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

Appendix A: Adverse Events of Special Interest

AEs of special interest (AESI) will include those listed in below. The AESIs will be defined according to the following MedDRA preferred terms.

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: eg, non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis, Cranial nerve disorders, including paralyses/paresis (eg, 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

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.