Clinical Study Protocol

Protocol Title:

A parallel-group, Phase I/II, randomized, modified double-blind, 3-arm, active comparator, multi-center, prevention study to evaluate the immunogenicity and safety of two adjuvanted dose levels of Panblok H7+MF59 influenza vaccine compared with an unadjuvanted dose of Panblok H7 in participants 18 years of age and older

Study Code: VAM00001

NCT number: NCT05608005

Amendment Number: not applicable

Compound: Panblok + MF59

Brief Title:
Study on Two Adjuvanted Dose Levels of Panblok H7+MF59 Compared for Immunogenicity and Safety with an Unadjuvanted Dose of Panblok H7 in Participants 18 Years of Age and Older

Study Phase: I/II

Sponsor Name and Legal Registered Address:
Sanofi Pasteur Inc.
Discovery Drive, Swiftwater, PA 18370-0187, USA

Manufacturer: Same as Sponsor

Regulatory Agency Identifier Numbers:

WHO UTN: U1111-1256-9115

US IND Number: 28567

Protocol Version Number: 2.0

Approval Date: 14 September 2022

Responsible medical officer (RMO), and designee(s), and pharmacovigilance (PV) representative names and contact information will be provided separately.

The study centers, the investigators at each center, and the Coordinating Investigator are also listed in a separate document.

Document History

Previous Version	Date	Comments
1.0	19 May 2022	Version submitted to the US Food and Drug Administration and the Institutional Review Board (Advarra)

Overall Rationale for the Protocol Update:

The main reason for updating protocol version 1.0 to protocol version 2.0 was to address feedback from the US Food and Drug Administration. The feedback included a request to add the collection of medically attended adverse events throughout the study and to clarify that the electronic diary will be used by the study participant to record safety data.

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Brief Title:

Study on Two Adjuvanted Dose Levels of Panblok H7+MF59 Compared for Immunogenicity and Safety with an Unadjuvanted Dose of Panblok H7 in Participants 18 Years of Age and Older

Rationale:

VAM00001 will be a Phase I/II, randomized, modified double-blind, multi-center, prevention study to be conducted in approximately 700 adult participants (350 adults 18 - 64 years of age and 350 adults ≥ 65 years of age). The aim of this study is to assess the immunogenicity and safety of 2 dose levels of Panblok H7+MF59 (7.5 µg and 15 µg of recombinant hemagglutinin [rHA]) compared with an unadjuvanted dose of Panblok H7 (45 µg of rHA) in order to select one dose formulation for further clinical development. An active unadjuvanted comparator was chosen to potentially assess an antigen-sparing effect of the MF59 adjuvant. Participants will be randomized in a 3:3:1 ratio and the vaccination schedule for all participants will consist of 2 doses, administered 21 days apart.

Objectives and Endpoints

Objectives	Endpoints
Primary	
Immunogenicity To assess the antibody response induced by each study dose group of Panblok H7+MF59 vaccine (7.5 µg and 15 µg) compared with unadjuvanted Panblok H7 (45 µg) by hemagglutination inhibition using horse red blood cells (HIH) and seroneutralization (SN) measurement methods at day (D) 22 and D43 (ie, 21 days after each vaccination) in participants 18 - 64 years and ≥ 65 years of age	***Immunogenicity*** The following immunogenicity endpoints will be summarized: <u>*Immunogenicity by HIH measurement method:*</u> • Hemagglutination inhibition (HAI) antibody (Ab) titers obtained on D22 and D43 for comparison with D01, D202, and D387 • Individual HAI Ab titers ratio D22/D01 and D43/D01; and D202/D01 and D387/D01 • Seroconversion defined as titer < 10 (1/dilution [1/dil]) on D01 and post-injection titer ≥ 40 (1/dil) on D22 or D43; or defined as titer ≥ 10 (1/dil) on D01 and a ≥ 4-fold increase in titer (1/dil) on D22 or D43

	• Individual HAI Ab titers ≥ 40 (1/dil) on D22 and D43; and D01, D202, and D387 • Detectable HAI Ab titer, ie, with a titer ≥ 10 (1/dil) on D01, D22, D43, D202, and D387 *Immunogenicity by SN measurement method:* • Neutralization (NT) Ab titer obtained on D22 and D43 for comparison with D01, D202, and D387 • Individual NT Ab titers ratio D22/D01, D43/D01, D202/D01, and D387/D01 • NT Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) on D22 and D43; compared to D01, D202, and D387 • Fold increase in NT Ab titer [post/pre] ≥ 2 and ≥ 4 on D22 and D43 • Detectable NT Ab titer, ie, with a titer ≥ 10 (1/dil) on D01, D22, D43, D202, and D387
Secondary	
Safety To assess the safety profile in each study vaccine group in participants 18 - 64 years and ≥ 65 years of age throughout the study	***Safety*** The following safety endpoints will be summarized: • Presence of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after each vaccination • Presence of solicited (prelisted in the participant's electronic diary [eDiary] and case report book [CRB]) injection site reactions and systemic reactions occurring up to 7 days after each / any vaccination • Presence of unsolicited AEs up to 21 days after each / any vaccination • Presence of medically attended adverse events (MAAEs) throughout the study • Presence of adverse events of special interest (AESIs) throughout the study • Presence of serious adverse events (SAEs) (including AESIs) throughout the study

Overall Design

Type of design	parallel, multi-center

Phase	I / II
Control method	active comparator (comparator = Panblok H7 (45 µg) unadjuvanted)
Study population	healthy adults 18 years of age and older
Countries	United States
Level and method of blinding	modified double-blind
Study intervention assignment method	randomization

Brief Summary:

The purpose of this study is to compare 2 dose levels of Panblok H7 (7.5 µg and 15 µg of rHA) with a standard 9.75 mg squalene dose of adjuvant MF59 to Panblok H7 (45 µg) unadjuvanted in approximately 700 adult participants in order to select one dose formulation to be used for further clinical development. The randomization ratio will be 3:3:1 for Panblok H7 (7.5 µg) + MF59, Panblok H7 (15 µg) + MF59, and Panblok H7 (45 µg) unadjuvanted, respectively. Each study group will be stratified into the age groups 18-64 years (350 participants) and ≥ 65 years of age (350 participants).

Study details include:

Treatment Duration: Eligible study participants will be randomized to receive 2 doses by intramuscular (IM) route, 21 days apart, of either Panblok H7 (7.5 µg) + MF59, Panblok H7 (15 µg) + MF59, or Panblok H7 (45 µg) unadjuvanted. A pre-vaccination (baseline) blood sample will be taken during Visit (V) 01 (D01) and post-vaccination blood samples will be taken during V02, V03, V04, and V05 (ie, D22, D43, D202, and D387) for HIH and SN testing in order to assess the immune response after Dose 1 and Dose 2 of the study intervention and to assess the persistence of the immune response at 6 and 12 months after the last vaccination.

Visit Frequency: a total of 5 visits. Visit 2 and Visit 3 will occur 22 days and 43 days, respectively, after Visit 1. There will be 2 follow-up visits, at 6 months and 12 months after the last vaccination (ie, after Visit 2).

Number of Participants:

A total of 700 participants is expected to be randomized with the aim to obtain a total of 630 evaluable participants.

	Group 1: Panblok H7 (7.5 µg) + MF59		**Group 2: Panblok H7 (15 µg) + MF59**		**Group 3: Panblok H7 (45 µg) unadjuvanted**		**Total**
	18 - 64 years	**≥ 65 years**	**18 - 64 years**	**≥ 65 years**	**18 - 64 years**	**≥ 65 years**	

Planned number of Participants	150	150	150	150	50	50	700

Intervention Groups and Duration:

In each age group (18 - 64 years of age and ≥ 65 years of age), eligible participants will be randomized in a 3:3:1 ratio to receive 2 doses, 21 days apart (ie, D01 and D22), by IM route of either Panblok H7+MF59 at 7.5 µg, Panblok H7+MF59 at 15 µg, or unadjuvanted Panblok H7 at 45 µg.

The study duration for each participant will be approximately 13 months.

Study interventions

Two of the three Investigational Medicinal Products (IMPs) include the MF59 adjuvant which is an oil-in-water emulsion composed of squalene and stabilized by the addition of 2 emulsifiers, polysorbate 80 and sorbitan trioleate, and a low ionic-strength buffer.

Each of the 3 IMPs contains thimerosal.

The composition of the 3 IMPs to be used in this study is described below:

Panblok H7 (7.5 µg) + MF59:

Monovalent Recombinant H7 influenza vaccine [A/Guangdong/17SF003/2016 (H7N9)] with MF59

- Form: Suspension
- Composition: 0.5 mL dose, 7.5 µg rHA with 9.75 mg squalene of MF59 adjuvant, and 0.01% thimerosal presented in vials
- Route: IM

Panblok H7 (15 µg) + MF59:

Monovalent Recombinant H7 influenza vaccine [A/Guangdong/17SF003/2016 (H7N9)] with MF59

- Form: Suspension
- Composition: 0.5 mL dose, 15 µg rHA with 9.75 mg squalene of MF59 adjuvant, and 0.01% thimerosal presented in vials
- Route: IM

Panblok H7 (45 µg) unadjuvanted

Monovalent Recombinant H7 influenza vaccine [A/Guangdong/17SF003/2016 (H7N9)]

- Form: Liquid

- Composition: 0.5 mL dose, 45 µg rHA, and 0.01% thimerosal presented in vials
- Route: IM

Statistical considerations:

The statistical analysis will be conducted as follows:

- The study will be unblinded after all immunogenicity and safety data are collected for the follow-up period of 3 weeks after D22 (ie, 21 days after the last vaccination).
- The final database lock will occur after the 12-month follow-up.

No adjustment for multiplicity is planned in this study.

Details will be provided in the Statistical Analysis Plan (SAP).

Primary endpoint (Immunogenicity by HIH and SN measurement methods):

The immunogenicity parameters will be calculated with their 95% confidence intervals (CIs) using the exact binomial distribution (Clopper-Pearson method) for proportions and using normal approximation of log-transformed for geometric mean titers (GMTs) and GMTs ratio. The 95% CI of proportions difference (ie, difference in seroconversion) will be calculated using Wilson Score method without continuity correction. All analyses will be conducted by dose group and by age stratum.

- GMTs of HAI Ab titers and NT Ab titers obtained on D22 and D43 for comparison with D01, D202, and D387.
- Geometric mean of individual ratios of HAI Ab titers and NT Ab titers of D22/D01 and D43/D01; and D202/D01, and D387/D01.
- Percent of participants with seroconversion defined as HAI Ab titer < 10 (1/dil) on D01 (pre-vaccination) and post-vaccination titer ≥ 40 (1/dil) on D22 or D43; or HAI Ab titer ≥ 10 (1/dil) on D01 and a ≥ 4-fold increase in titer (1/dil) on D22 or D43.
- Percent of participants with fold increase in NT Ab titer [post-vaccination/pre-vaccination] ≥ 2 and ≥ 4 on D22 and D43; and D202, and D387.
- Percent of participants with HAI Ab titers ≥ 40 (1/dil), and percent of participants with NT Ab titers ≥ 40 (1/dil) on D22 and D43; and D202 and D387.
- Reverse cumulative distribution curves (RCDCs) of pre-vaccination titer prior to the first vaccination at D01 and post-vaccination titer at D22, D43, D202, and D387 will be generated for each dose.

Secondary endpoints (Safety):

For the main safety parameters, 95% CIs of point estimates will be calculated using exact binomial method (Clopper-Pearson method) for single proportions and using the normal approximation for quantitative data.

Analysis will be conducted for each dose group, by strata of age, and by the period of 7 days and / or the period of 21 days after each vaccination, and / or by interval of visits (ie, between Visit 4 [6-month follow-up] and Visit 5 [12-month follow-up]) for safety data collected from D01 to the end of the study.

All analyses will be descriptive, and no hypotheses will be tested.

The number of participants with documented safety will be used as denominator of the frequencies.

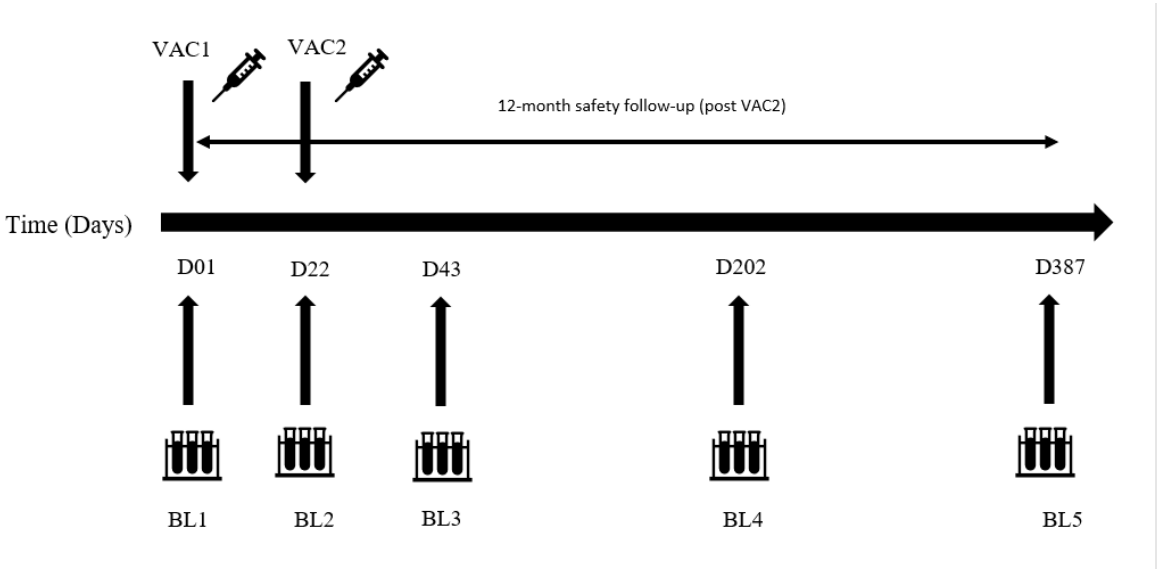
Data Monitoring/Other Committee:

No

1.1 Schema

The graphical design of VAM00001 study is presented in Figure 1

Figure 1 - Graphical study design



BL: Blood sample
VAC: vaccination

1.2 Schedule of Activities (SoA)

Table 2.1 - Schedule of activities

Phase I/II Study, 5 Visits, 2 Vaccinations, 5 Blood Samples, 13 Months' Duration Per Participant

Visit/Contact	***Collection of information in the CRF***	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Study timelines (days)		D01	21 days post V01 (D22)	21 days post V02 (D43)	6 months post V02 (D202)	12 months post V02 (D387)
Time windows (days)			[+7 D]	[+7 D]	[+14 D]	[+14 D]
Visit procedures:						
Informed consent	X	X				
Inclusion/exclusion criteria	X	X				
Collection of demographic data	X	X				
Urine pregnancy test (if applicable)		X	X			
Collection of Medical history	X Significant Medical History*	X				
Physical examination		X	X			
Temporary and definitive contraindications	X		X			
Pre-vaccination temperature		X	X			
Randomization	X	X				
Allocation of participant number	X	X				
Dose assignment by IRT		X	X			
Blood sampling (BL) [40 mL/visit]	X	BL0001 Pre-vac	BL0002 Pre-vac	BL0003	BL0004	BL0005
Vaccination (vac)	X	X	X			

Visit/Contact	*Collection of information in the CRF*	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
eDiary provided†		X				
eDiary reviewed‡			X	X	X	X
Collection of solicited injection site and systemic reactions	X	X	X	X		
Collection of unsolicited adverse events (AEs)	X	X	X	X		
Collection of concomitant medications	X Reportable concomitant medication	X	X	X		
Collection of medically attended AEs (MAAEs)	X	To be reported at any time during the study				
Collection of serious adverse events (SAEs), including AESIs	X	To be reported at any time during the study				
Collection of pregnancies	X	To be reported at any time during the study				
End of Study Intervention Phase§	X			X		
End of study**	X					X

AESI: adverse event of special interest; CRF: case report form; D: day; DC: diary card; IRT: interactive response technology; V: visit

* Significant medical history is described in Section 8.2.1 of the protocol

† Electronic diary application should be downloaded to the participant's electronic device (such as mobile phone or tablet).

‡ Electronic diary is the primary method for safety data collection. However, paper diary cards will also be available for use as a back-up solution in case of major breakdown of the app or as determined by the Sponsor's study clinical team.

§ In case of participant discontinuation at a visit, the entire visit will be completed.

** All participants will be scheduled to attend V05 for blood sampling and safety follow-up. However, if any participants discontinue the study early, they are still to be followed for safety and are to be contacted by phone to identify the occurrence of any MAAEs, SAEs, and AESIs that had not yet been reported. The site should attempt to contact them and complete the 12-month safety follow-up (and all other scheduled safety follow-ups), except if they specified that they do not want to be contacted again and it is documented in the source document.

2 Introduction

2.1 Study Rationale

VAM00001 will be a Phase I/II, randomized, modified double-blind, multi-center, prevention study to be conducted in approximately 700 adult participants (350 adults 18 – 64 years of age and 350 adults ≥ 65 years of age). The aim of this study is to assess the immunogenicity and safety of 2 dose levels of Panblok H7+MF59 (7.5 µg and 15 µg of rHA) compared with an unadjuvanted dose of Panblok H7 (45 µg of rHA) in order to select one dose formulation for further clinical development. An active unadjuvanted comparator was chosen to potentially assess an antigen-sparing effect of the MF59 adjuvant. Participants will be randomized in a 3:3:1 ratio and the vaccination schedule for all participants will consist of 2 doses, administered 21 days apart.

2.2 Background

Influenza is a contagious, acute viral respiratory disease caused by influenza type A and type B viruses. Genetic and antigenic variations are an important feature of the influenza virus with the viral hemagglutinin (HA) and neuraminidase (NA) antigens subject to continuous, sequential evolution within immune or partially immune populations. Antigenic shift occurs when completely new viral subtypes emerge, typically through gene reassortment with other circulating strains and acquisition of antigenically different gene sequences. These new influenza virus strains which arise from antigenic shift can cause influenza pandemics: global epidemics caused by an influenza virus that infects a large proportion of the human population because the new influenza virus strain has not circulated in humans previously or has not circulated for a long period of time rendering most of the human population with no immunologic memory for such a virus or limited memory in older adults who may have been exposed if the virus circulated previously. Influenza pandemics occur at irregular intervals with four influenza pandemics occurring over the past century: the Spanish flu in 1918 (H1N1), the Asian influenza in 1957 (H2N2), the Hong Kong influenza in 1968 (H3N2), and the swine flu in 2009 (H1N1pdm) (1).

Demonstrating the potential for a newly emerging pandemic strain of influenza to circulate globally within a matter of months, the most recent influenza pandemic, a novel H1N1 influenza A virus, emerged in North America in April 2009, and by June, the World Health Organization had declared a worldwide pandemic, reflecting community-level transmission of the novel H1N1 pandemic strain around the world. Estimates of influenza-related deaths worldwide during this pandemic ranged from 105,700 to 395,600 in one modeling study (2). However, the 2009 novel H1N1 disease generally did not appear to be more severe than seasonal influenza and adequate immunity was induced by a single dose of vaccine in individuals 10 years of age and older. This H1N1 strain has become a dominant circulating strain since the 2009-2010 season and has been included in subsequent seasonal influenza formulations since the 2010-2011 season.

As vaccination remains the most effective means of preventing influenza infection and complications associated with the disease (3), preparation for the next influenza strain with

pandemic potential has become a high priority for all public health authorities, with a focus on avian influenza strains such as the H5N1 and H7N9 strains.

Avian influenza is an infectious disease of birds caused by type A strains and occurs worldwide. Outbreaks of avian influenza have been caused by viruses of the H5, H6, H7, H9, and H10 subtypes of influenza A, all capable of infecting and causing disease in humans (4). Since 2013, the H7N9 avian influenza strain has been the cause of 6 annual "waves" of outbreaks among poultry handlers in China (5). Of the 1567 cases since 2013, there have been 650 deaths (42% mortality) and while there has yet to be evidence of sustained human-to-human transmission, the strain does appear to pose a credible threat as a potential pandemic strain (5). Thus, pandemic preparedness efforts have recently been directed toward the production of a vaccine for this strain. To limit the impact of such an outbreak, the availability of a sufficient number of doses of a safe and effective vaccine in a short time frame is a high priority. Since most people are immunologically naïve to an avian pandemic influenza strain, the primary difficulty is that large amounts of antigen are needed to induce antibody titers that are expected to be protective (6). Approaches such as the use of adjuvants are needed in order to both improve the immunogenicity of pandemic influenza vaccines and to allow for antigen-sparing in order to increase production capacity.

Sanofi Pasteur's Panblok H7+MF59 is a new pre-formulated, recombinant, adjuvanted (MF59), dose-sparing vaccine that is being developed to provide an efficient and effective way to prevent pandemic influenza disease and to reduce the impact of pandemic influenza A (eg, H7N9) virus.

Panblok H7 is a monovalent rHA from A/H7N9 influenza strain expressed in the baculovirus/insect cell system. The formulation will contain thimerosal and MF59 adjuvant premixed in vials for IM injection.

The MF59 adjuvant is an oil-in-water emulsion adjuvant composed of squalene and has been used for years by Novartis/Seqirus in vaccines marketed in the US, Europe, and other countries (7). With approximately 30 years of clinical experience and more than 160 million doses of adjuvanted vaccines distributed, MF59 has an established safety profile and has been shown to be well tolerated in children and adults (8) (9).

A detailed description of the chemistry, pharmacology, efficacy, and safety of Panblok H7 is provided in the Investigator's Brochure (IB).

Clinical Studies with Panblok

Since 2010, four completed clinical studies have been conducted using different formulations of Panblok (at different rHA concentrations and with or without different adjuvants). A summary of 3 clinical studies conducted by Protein Sciences Corporation (PSC) (10) (11) (12) and 1 clinical study conducted by the Biomedical Advanced Research and Development Authority (BARDA) (13) is presented below.

Study PSC22

PSC22 study was a Phase I/II randomized, prospective, modified double-blind, active-controlled, and placebo-controlled study to assess the safety and immunogenicity of 2 doses of Panblok H5 at 4 dose levels of rHA (3.8, 7.5, 15, and 45 µg) adjuvanted with Glucopyranosyl Lipid A in stable

oil-in-water emulsion (GLA/SE) compared to unadjuvanted formulations (45 and 135 µg rHA) and normal saline placebo to determine the optimal rHA dose level and to assess the added immunogenicity afforded by the addition of the GLA/SE adjuvant (10).

The rHA in Panblok H5 was derived from A/Indonesia/5/05 (H5N1) influenza virus strain. Panblok H5 was diluted in normal saline to the concentration appropriate for the assigned dose level and administered either as rHA alone (ie, unadjuvanted) or formulated at the study sites with GLA/SE adjuvant prior to administration. Two injections, 21 days apart, were administered by IM route in 392 healthy adults 18 to < 50 years of age.

Data from PSC22 study showed that adjuvanted and unadjuvanted Panblok H5 were well tolerated. Solicited injection site pain, injection site tenderness, muscle pain, and fatigue were more frequent in the adjuvanted Panblok H5 groups compared to unadjuvanted Panblok H5 and placebo groups after both doses. Unsolicited AEs from D0 to D42 were similar in frequency and relationship to vaccine across all groups. None of the SAEs reported during the study were considered to be related to study products.

The percentage of subjects with post-vaccination HAI titers ≥ 40 across all adjuvanted groups were 66% to 81.5% compared to non-adjuvanted at 16.7% to 31.5% and placebo at 0%. However, the Food and Drug Administration (FDA) criterion for licensure (lower bound of 2-sided 95% CI for percentage of subjects achieving an HAI antibody titer ≥ 1:40 should be ≥ 70%) was not met for any of the groups in the clinical study.

Study PSC25

PSC25 study was a Phase I/II randomized, observer-blind, multi-center study to assess the immunogenicity and safety of 2 doses of Panblok H5 at 3 dose levels of rHA (3.8, 7.5 and 15 µg) with a stable oil-in-water emulsion (SE) adjuvant compared to an unadjuvanted Panblok H5 (7.5 µg rHA) to select the optimal dose level of rHA to carry forward for future adjuvanted Panblok H5 vaccine development (11).

The rHA in Panblok H5 was derived from A/Indonesia/5/05 (H5N1) influenza virus strain. Panblok H5 was diluted in normal saline to the concentration appropriate for the assigned dose level and administered either as rHA alone (ie, unadjuvanted) or formulated at the study sites with SE adjuvant prior to administration. Two doses, 21 days apart, were administered by IM route in 341 healthy adults 18 to < 50 years of age.

Data from PSC25 study showed that adjuvanted and unadjuvanted Panblok H5 had an acceptable safety profile. Solicited local injection site pain and tenderness were more frequent in the adjuvanted Panblok H5 groups compared to unadjuvanted Panblok H5 group after both doses. Unsolicited AEs from D0 to D42 were similar in frequency and relationship to vaccine across all groups. The incidence of SAEs was < 1% overall, and none were considered to be related to study vaccines.

All dose levels of SE-adjuvanted Panblok H5 met FDA regulatory guidance for licensure criterion for seroconversion (ie, lower bound of the two-sided 95% CI should be ≥ 40%) after 2 doses at D42. However, FDA criterion for post-immunization titer ≥ 1:40 (ie, lower bound of the two-sided 95% CI should be ≥ 70%) was met by the adjuvanted 15 µg dose group only. No vaccine groups met any criteria for licensure after a single dose of vaccine.

Study PSC26

PSC26 study was a Phase I/II, randomized, observer-blind, two-stage, adaptive, multi-center study to evaluate the immunogenicity and safety of 2 doses of Panblok H7 at 3 dose levels of rHA (7.5 µg, 15 µg, and 30 µg) with the SE adjuvant compared to an unadjuvanted formulation (30 µg rHA) to determine in Stage 1 the optimal rHA dose level to be used in Stage 2 of the study and to demonstrate in Stage 2 that the immunogenicity of the selected dose of adjuvanted Panblok H7 meet the FDA criteria for licensure of a pandemic influenza vaccine (12).

The rHA in Panblok H7 was derived from A/Anhui/1/2013 (H7N9) influenza virus strain. Panblok H7 was formulated in multidose vials containing 0.01% thimerosal as a preservative. Two doses, 21 days apart, were administered by IM route in Stage I of the study in 407 healthy adults 18 years of age and older.

Data from Stage 1 of PSC26 study showed that the adjuvanted and unadjuvanted Panblok H7 had an acceptable safety profile. The incidences of reported solicited injection site reactions after the first dose were somewhat higher in the adjuvanted vaccine groups, compared to the unadjuvanted vaccine group with solicited injection site pain and tenderness remaining consistently higher across all adjuvanted Panblok H7 groups compared to unadjuvanted Panblok H7 after Dose 2. Unsolicited AEs were low and similar in all groups, with no clinically concerning or unexpected events during the six weeks of follow-up after initial vaccination. There were no related deaths, SAEs, or other significant AEs among vaccine recipients. No AESIs were reported in this study.

The HAI immune responses to Panblok H7, either adjuvanted or unadjuvanted, were insufficient to support further enrollment into Stage 2 of the study.

Study BARDA BP-I-17-002

BARDA BP-I-17-002 study was a Phase II, randomized, double-blind study to evaluate the safety and immunogenicity of 2 doses of Panblok H7 at 3 dose levels (3.75, 7.5, and 15 µg) adjuvanted with either AS03 or MF59 to assess the safety of AS03-adjuvanted and MF59-adjuvanted Panblok H7 and to evaluate the HAI immune response of the 3 dose levels of adjuvanted Panblok H7 (13).

The rHA in Panblok H7 was derived from A/Guangdong/17SF003/2016 (H7N9) influenza virus strain. Two doses, 28 days apart, were administered by IM route in 366 healthy adults 18 to < 50 years of age. The study vaccines were prepared by mixing Panblok H7 influenza vaccine antigen 1:1 with either MF59 or AS03 adjuvant prior to administration.

Data from BARDA BP-I-17-002 study showed that adjuvanted Panblok H7 was safe and well tolerated across all vaccine groups. Within each adjuvant group, there were no notable differences in the safety profile between the 3 dose levels of adjuvanted Panblok H7 or between Dose 1 and Dose 2. The reactogenicity of adjuvanted Panblok H7 was similar across all vaccine groups, without notable difference between the rHA dose levels or adjuvants. No unsolicited AEs, serious or non-serious, suggested a clinically significant safety issue with either vaccine dose or adjuvant. No deaths, potentially immune-mediated medical condition, AEs leading to early termination of vaccination, or AEs leading to study withdrawal were reported during the entire study.

AS03-adjuvanted Panblok H7 was highly immunogenic at the 3 dose levels with the lower bound of the 95% CI for the percent of subjects achieving an HAI antibody titer ≥ 1:40 being above 70% at D50 and remaining near or above 70% at D121 but decreasing substantially by D212. MF59-

adjuvanted Panblok H7 was highly immunogenic in the 7.5 µg and 15 µg dose levels with the lower bound of the 95% CI for the percent of subjects achieving an HAI antibody titer ≥ 1:40 being above 70% at D50 but decreased substantially by D121 and D212.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks, reasonably expected adverse events, the potential risks, and uncertainties of Panblok H7+ MF59 may be found in the IB.

2.3.1 Risks from Study Participation

The potential risks of clinical significance and risk management are summarized in Table 2.1.

Table 2.1 - Identified and Potential risks of clinical significance and risk management

Identified and Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Investigated Vaccines: Panblok H7 (7.5 µg) + MF59; Panblok H7 (15 µg) + MF59 Comparator Vaccine: Panblok H7 (45 µg) unadjuvanted		
Anaphylactic reactions	Monitor non- important identified risk. All vaccines have the potential to cause allergic reactions or anaphylaxis in individuals who may be sensitized to components of the vaccine. Refer to IB Section 4.3 for more information regarding the components of the vaccine.	Observation period of 30 minutes after vaccination for early detection and treatment. Addressed in IB (administration precautions, potential adverse events), defined AESI in the study.
Guillain-Barré syndrome	Important potential risk. Influenza vaccines have the potential to cause Guillain-Barré syndrome	Exclusion criterion E14 for those with personal or family history of Guillain-Barré syndrome. Participants enrolling in the study will be informed of the potential AEs in the informed consent form (ICF) and will be advised to contact the study center to if a serious health problem occurs. Listed as AESIs in the study.

Identified and Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Injection site reactions and systemic reactions	Monitor non-important identified risks. Injection site reactions such as redness, swelling, pain, bruising, and induration around the area where the vaccine was injected were observed. Systemic reactions such as headache, myalgia, arthralgia, fever, malaise, shivering, and fatigue were also observed. Most reactions resolved within 1 or 2 days without treatment. Additional information on adverse reactions can be found in Section 7.1 of the IB.	Participants enrolling in the study will be informed of the potential adverse reactions in the ICF and will be advised to contact the study center if a serious health problem occurs.
Study Procedures		
Vasovagal reactions (syncope), or psychogenic reactions to needle (vaccine injection or blood sampling)	Anxiety-related reactions can occur following, or even before, any vaccination as a psychogenic response to the needle injection or blood draw and may be accompanied by several neurological signs such as transient visual disturbance, paresthesia or seizure-like activity.	Observation period of 30 minutes after vaccination or until resolution of related symptoms and normalization of all vital signs.

Identified and Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Other		
Theoretical risk that participant can be exposed to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected individuals	SARS-CoV-2 virus is contagious. SARS-CoV-2 spreads through respiratory secretion or droplets. Transmission may also be possible via contaminated surfaces. Exposure can theoretically occur as a result of study procedures, including visits to the investigational sites and physical interactions with study staff.	Study site should minimize interactions between individuals when visiting the study site. The site should establish routine cleaning procedures of commonly used areas to prevent the transmission of virus on contaminated surfaces. Personal protective equipment (eg, masks for participants and site staff, clothing, goggles) to be used at sites. Home visit option for completion of study procedures in the setting of containment measures to minimize exposure. Participants will also be advised to adhere to local regulations and guidance (eg, self-isolation, social distancing) to minimize risk of exposure to SARS-CoV-2 infected individuals.

Coronavirus Disease 2019 (COVID-19) Risk Assessment

Panblok H7+MF59 is a vaccine against pandemic influenza. Panblok would not cause immune suppression. Therefore, the risk that a participant in this study will contract COVID-19 solely due to the administration of the study intervention will be similar to the risk that a person not participating in this study will contract COVID-19. However, the risk of exposure to infected people cannot be completely excluded as the participants may need to be exposed to public areas (eg, commute to/from the site and at the site).

- Risk mitigation:
  - Not start the study until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic are lifted by the local Authorities.
  - Continued risk assessment by the investigator and Sponsor before deciding to start the study.
  - Reduce the public exposure while ambulatory when possible.

2.3.2 Benefits from Study Participation

There may be no direct benefit from receiving Panblok H7+MF59. However, based on the data from previous studies (10) (11) (12) (13):

- Evaluation of the immunogenicity profile showed that many participants developed immune responses after 2 vaccine injections
- Safety evaluation indicated that this vaccine was well tolerated and no safety issues have been detected
- Participants may benefit from potential protection against a future infection by the same, or very similar, A/H7N9 virus of avian origin

As with any vaccine, Panblok H7+MF59 may not protect 100% of individuals against the disease it is designed to prevent.

2.3.3 Overall Benefit-Risk Conclusion

Considering the measures taken to minimize risk to participants enrolled in this study, the potential risks that may result from study participation are balanced by the anticipated benefits that may be afforded to participants.

3 Objectives and Endpoints

The study objectives and the corresponding endpoints are described in Table 3.1.

Table 3.1 - Objectives and endpoints

Objectives	Endpoints
Primary	
Immunogenicity To assess the antibody response induced by each study dose group of Panblok H7+MF59 vaccine (7.5 µg and 15 µg) compared with unadjuvanted Panblok H7 (45 µg) by HIH and SN measurement methods at D22 and D43 (ie, 21 days after each vaccination) in participants 18 – 64 years and ≥ 65 years of age	***Immunogenicity*** The following immunogenicity endpoints will be described: *Immunogenicity by HIH measurement method:* • HAI Ab titers obtained on D22 and D43 for comparison with D01, D202, and D387 • Individual HAI Ab titers ratio D22/D01 and D43/D01; and D202/D01 and D387/D01 • Seroconversion defined as titer < 10 (1/dil) on D01 and post-injection titer ≥ 40 (1/dil) on D22 or D43; or defined as titer ≥ 10 (1/dil) on D01 and a ≥ 4-fold increase in titer (1/dil) on D22 or D43 • Individual HAI Ab titers ≥ 40 (1/dil) on D22 and D43; and D01, D202, and D387 • Detectable HAI Ab titer, ie, with a titer ≥ 10 (1/dil) on D01, D22, D43, D202, and D387 *Immunogenicity by SN measurement method:* • NT Ab titer obtained on D22 and D43 for comparison with D01, D202, and D387 • Individual NT Ab titers ratio D22/D01, D43/D01, D202/D01, and D387/D01 • NT Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) on D22 and D43; compared to D01, D202, and D387 • Fold increase in NT Ab titer [post/pre] ≥ 2 and ≥ 4 on D22 and D43 • Detectable NT Ab titer, ie, with a titer ≥ 10 (1/dil) on D01, D22, D43, D202, and D387

Secondary	
Safety To assess the safety profile in each study vaccine group in participants 18 - 64 years and ≥ 65 years of age throughout the study	***Safety*** The following safety endpoints will be described: • Presence of any unsolicited systemic AEs reported in the 30 minutes after each vaccination • Presence of solicited (prelisted in the participant's eDiary and CRB) injection site reactions and systemic reactions occurring up to 7 days after each / any vaccination • Presence of unsolicited AEs up to 21 days after each / any vaccination • Presence of MAAEs throughout the study • Presence of AESIs throughout the study • Presence of SAEs (including AESIs) throughout the study

4 Study Design

4.1 Overall Design

The design of the study is summarized in Table 4.1.

Table 4.1 – Overall design

Type of design	parallel, multi-center
Phase	I / II
Control method	active comparator (comparator = Panblok H7 (45 µg) unadjuvanted)
Study population	healthy adults 18 years of age and older
Level and method of blinding	modified double-blind
Study intervention assignment method	randomization
Number of participants	Total of 700 participants Group 1 (Panblok H7 (7.5 µg) + MF59): 150 participants 18 - 64 years of age 150 participants 65 years of age and older Group 2 (Panblok H7 (15 µg) + MF59): 150 participants 18 - 64 years of age 150 participants 65 years of age and older Group 3 (Panblok H7 (45 µg) unadjuvanted): 50 participants 18 - 64 years of age 50 participants 65 years of age and older
Intervention groups	Eligible participants will be randomized in a 3:3:1 ratio and stratified into two age groups (18 - 64 years of age and ≥ 65 years of age). The participants will receive 2 doses, administered 21 days apart, by IM route of either Panblok H7 (7.5 µg) + MF59, Panblok H7 (15 µg) + MF59, or Panblok H7 (45 µg) unadjuvanted.
Total duration of study participation	The study duration for each participant will be approximately 13 months.
Countries	United States
Use of an Independent Data Monitoring Committee, Dose Escalation Committee, or similar review group	No

4.2 Scientific Rationale for Study Design

This is a Phase I / II, randomized, modified double-blind study to assess the immunogenicity and safety of the investigational vaccines with the goal of dose selection for the pivotal Phase III study in adults and the pediatric Phase I/II study.

The study design will be a modified double-blind as the study will include adjuvanted study vaccines that may have a different appearance than the unadjuvanted vaccine. Therefore, designated site staff involved in preparing and administering the vaccine would be unblinded. The investigator/Sub-investigator/staff involved in the safety assessment will be blinded in order to decrease the risk of potential bias in safety assessment.

Given most participants will be naïve in the case of a novel pandemic influenza strain, a dose schedule requiring 2 vaccinations, 21 days apart, will be evaluated in the study. Immune responses after 1 or 2 vaccinations will be assessed by comparing immune responses at D43 versus D22.

Vaccine-triggered immune responses against seasonal influenza vaccines diminish with advancing age due to immunosenescence (aging of the immune system) (14). Thus, participants will be enrolled in 2 age groups (18 - 64 years of age and 65 years of age and older) to evaluate the effect of age on the immune responses and on safety of Panblok H7+MF59.

This study will not include an early safety data review as the vaccine had an acceptable safety profile when administered to adults as shown in Study BARDA BP-I-17-002 and given prior clinical studies completed with similar Panblok formulations with different influenza strains. The safety of the adjuvant MF59 has also been established through the safety database of Seqirus' adjuvanted seasonal influenza vaccine Fluad®. However, participants' safety will be continuously monitored by the Sponsor's internal safety review committee which includes safety signal detection at any time during the study. The study team will monitor the safety during the conduct of the study through periodic Safety Management Team meetings as well as clinical data review meetings.

4.3 Justification for Dose

The 7.5 µg and 15 µg doses were selected based on data from Study BARDA BP-I-17-002 in which these 2 doses showed an immunogenic response without any safety issue. The addition of adjuvant is expected to increase antibody responses, but the dose-sparing potential of the adjuvant will be assessed by using age-matched control groups of unadjuvanted vaccine (ie, Group 3).

Based on data from previous clinical studies and given that most participants will be naïve in the case of a novel pandemic influenza strain, a dose schedule requiring 2 vaccinations, 21 days apart, will be evaluated in the study.

4.4 End of Study Definition

A participant is considered to have completed the immunogenicity evaluation in the study if he/she has completed the last visit of the study intervention phase (ie, V03) planned in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study.

However, for periodic safety reports, the study is considered completed when the clinical study report is finalized.

5 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted in this study.

5.1 Inclusion Criteria

Participants are eligible for the study only if all of the following criteria are met:

Age

I01: Aged 18 years or older on the day of inclusion[a]

Type of participant and disease characteristics

I02: Participants who are healthy as determined by medical evaluation including medical history and physical examination

Sex, contraceptive/barrier method and pregnancy testing requirements

I03: A female participant is eligible to participate if she is not pregnant or breastfeeding and one of the following conditions applies:

- Is of non-childbearing potential. To be considered of non-childbearing potential, a female must be post-menopausal for at least 1 year, or surgically sterile.

OR

- Is of childbearing potential and agrees to use a highly effective contraceptive method or abstinence from at least 4 weeks prior to each study intervention administration until at least 12 weeks after the last study intervention administration.

A female participant of childbearing potential must have a negative highly sensitive pregnancy test (urine or serum as required by local regulation) within 24 hours before the first dose of study intervention

Informed Consent

I04: Informed consent form has been signed and dated

[a] "18 years" means from the day of the 18th birthday

OTHER INCLUSIONS

I05: Able to attend all scheduled visits and to comply with all study procedures

5.2 Exclusion Criteria

Participants are not eligible for the study if any of the following criteria are met:

Medical conditions

E01: Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, within the preceding 6 months; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)

E02: Known systemic hypersensitivity to any of the study intervention components, or history of a life-threatening reaction to the study interventions used in the study or to a product containing any of the same substances[b]

E03: Thrombocytopenia or bleeding disorder contraindicating intramuscular injection based on investigator's judgment

E04: Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion[c]

E05: Neoplastic disease or any hematologic malignancy (except localized skin or prostate cancer that is stable at the time of study intervention administration in the absence of therapy, and participants who have a history of neoplastic disease and who have been disease-free for ≥ 5 years)

E06: Moderate or severe acute illness/infection (according to investigator judgment) or febrile illness (temperature ≥ 100.4°F) on the day of study intervention administration. A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided

E07: Alcohol, prescription drug, or substance abuse that, in the opinion of the investigator, might interfere with the study conduct or completion

Prior/concomitant therapy

E08: Receipt of any vaccine in the 14 days preceding Visit 1 or planned receipt of any vaccine prior to Visit 3, except for seasonal flu vaccine, which may be received at least 2 weeks after Visit 2

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[b] The components of study interventions are listed in Section 6.1 of the protocol and in the Investigator's Brochure.

[c] Chronic illness may include, but is not limited to, cardiac disorders, renal disorders, auto-immune disorders, diabetes, psychiatric disorders, or chronic infection

E09: Previous vaccination against H7N9 with an investigational vaccine

E10: Receipt of immune globulins, blood or blood-derived products in the past 3 months

Prior/concurrent clinical study experience

E11: Participation at the time of study enrollment (or in the 4 weeks preceding the first study intervention administration) or planned participation during the present study period in another clinical study investigating a vaccine, drug, medical device, or medical procedure

Other exclusions

E12: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily

E13: Identified as an Investigator or employee of the Investigator or study center with direct involvement in the proposed study, or identified as an immediate family member (ie, parent, spouse, natural or adopted child) of the Investigator or employee with direct involvement in the proposed study

E14: Personal or family history of Guillain-Barré syndrome

E15: Self-reported seropositivity for Hepatitis B antigen or Hepatitis C

If the participant has a primary physician who is not the investigator, the site should contact this physician with the participant's consent to inform him / her of the participant's participation in the study. In addition, the site should ask this primary physician to verify exclusion criteria relating to previous therapies, such as receipt of blood products or previous vaccines.

5.3 Lifestyle Considerations

No other restrictions than the ones listed in the exclusion criteria or in the contraindications for subsequent vaccinations are required.

5.4 Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to study intervention. Screening information is recorded in the source documents.

Individuals who do not meet the criteria for participation in this study (screen failure) can be rescreened.

5.5 Criteria for Temporarily Delaying Enrollment, Randomization, Administration of Study Intervention, or Blood Samplings

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures proposed in

Appendix 10.5: Contingency measures for a regional or national emergency that is declared by a governmental agency should be considered for enrollment, randomization, administration of study intervention, or blood samplings.

6 Study Interventions and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Note: Vaccines or products administered outside of study protocol are not considered as study interventions and are reported in the CRF as reportable medications (see Section 6.8). Study procedures (eg, blood sampling) are also not considered as study interventions.

6.1 Study Interventions Administered

Study interventions are described in Table 6.1.

Table 6.1 - Study interventions Administered

Intervention Name	Panblok H7 (7.5 µg) + MF59	Panblok H7 (15 µg) + MF59	Panblok H7 (45 µg) unadjuvanted
Use	Experimental	Experimental	active comparator
IMP and NIMP	IMP	IMP	IMP
Type	Vaccine	Vaccine	Vaccine
Dose Form	Suspension for injection in a vial	Suspension for injection in a vial	Liquid for injection in a vial
Unit Dose Strength	7.5 µg of rHA of A/Guangdong/17SF003/2016 (H7N9) with 9.75 mg squalene of MF59 adjuvant per dose	15 µg of rHA of A/Guangdong/17SF003/2016 (H7N9) with 9.75 mg squalene of MF59 adjuvant per dose	45 µg of rHA of A/Guangdong/17SF003/2016 (H7N9) per dose
Excipients/Diluent	0.01% Thimerosal in 10 mM phosphate buffered saline with 0.005% Polysorbate 80	0.01% Thimerosal in 10 mM phosphate buffered saline with 0.005% Polysorbate 80	0.01% Thimerosal in 10 mM phosphate buffered saline with 0.005% Polysorbate 80

Dosage Level(s)	0.5 mL per dose	0.5 mL per dose	0.5 mL per dose
Number of Doses / Dosing Interval	2 doses, 21 days apart	2 doses, 21 days apart	2 doses, 21 days apart
Route of Administration	IM injection	IM injection	IM injection
Site of Administration	Deltoid muscle in the upper arm	Deltoid muscle in the upper arm	Deltoid muscle in the upper arm
Injection Site Side	Preferably the opposite arm from which blood was drawn	Preferably the opposite arm from which blood was drawn	Preferably the opposite arm from which blood was drawn
Sourcing	Provided by the Sponsor	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	Each study intervention will be provided in an individual box. Each study intervention will bear one fixed label and each box will bear one fixed label containing the treatment number. All will be labeled as required per country requirement.		
Current/Former Names or Aliases	Panblok H7 + MF59	Panblok H7 + MF59	Panblok H7 unadjuvanted
Batch Number	TBD	TBD	TBD
Storage Conditions	Study interventions will be stored in a refrigerator at a temperature ranging from +2°C to +8°C. The study interventions must not be frozen.		

IMP: Investigational Medicinal Product; NIMP: Non-Investigational Medicinal Product; TBD: to be determined

6.2 Preparation, Handling, Storage, and Accountability

The study intervention should be allowed to reach room temperature before use. It must be shaken before use. Prior to administration, the study intervention must be inspected visually for cracks, broken seals, correct label content, and extraneous particulate matter and / or discoloration, whenever solution and container permit. If any of these conditions exists, the study intervention must not be administered. Another dose is to be used, and the event is to be reported to the Sponsor.

The study intervention is to be administered intramuscularly into the deltoid muscle (preferably on the opposite arm from which blood was drawn before vaccination).

Participants must be kept under observation for 30 minutes after vaccination to ensure their safety, and any reactions during this period will be documented in the CRF.

1) The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2) Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3) The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4) Further guidance and information for the final disposition of unused study interventions will be provided to the study personnel.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization and Allocation Procedures

Randomization of participants will be performed with the blocked method, with stratification by age stratum. Each participant who meets all the inclusion criteria and none of the exclusion criteria and signs the ICF will be randomly assigned according to the participant's age group, to either Group 1, Group 2, or Group 3 via an interactive response technology (IRT) system, according to a 3:3:1 ratio.

Before vaccination, authorized qualified study staff will connect to the IRT system, enter the identification and security information, and confirm a minimal amount of data in response to IRT system prompts. The IRT system will then provide-the vaccine dose identification number. Participant numbers and vaccine dose identification numbers will be recorded in the eCRF.

The full detailed procedures for group allocation are described in the IRT User Guide. If the participant is not eligible to participate in the study, then the information will only be recorded on the participant recruitment log.

If the dose initially allocated for vaccination cannot be used (eg, because the syringe broke or particulate matter was observed), authorized qualified study staff will obtain a replacement dose. Thus, the site personnel must contact the IRT system to receive the replacement dose allocation.

Participant numbers that are assigned by the IRT will consist of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit participant identifier). For example,

Participant 840000100005 is the fifth participant enrolled in Center Number 1 in the US (840 being the US country code).

Participant numbers should not be reassigned for any reason. The randomization codes will be kept securely in the IRT and an internal system.

6.3.2 Blinding and Code-breaking Procedures

The study will be conducted in a modified double-blind fashion:

- Investigators and study staff who conduct the safety assessment, laboratory personnel who analyze the blood samples, Sponsor's personnel and study Team members, and the participant will not know which study intervention is administered
- Only the study staff who prepare and administer the study intervention and are not involved with the safety evaluation will know which study intervention is administered

The investigator responsible for safety assessment will not attend the vaccination session but will be available in case of emergency (eg, anaphylactic shock).

Dose numbers will be used to identify each vaccine vial for the purpose of randomization, vaccination, and the recording of vaccine dose administered. Dose numbers will be randomly assigned to the 3 study interventions. The IRT vendor will be responsible for providing the participant identification and dose number to be received by the enrolled participant.

The code may be broken in the event of an AE only when the identification of the study dose intervention received could influence the treatment of the participant. Code-breaking should be limited to the participant(s) experiencing the AE.

The blind can be broken by the investigator or a designee through the IRT system. Once the emergency has been addressed by the site, the investigator or a designee must notify the Sponsor's RMO if a participant's code was broken. All contact attempts with the Sponsor prior to unblinding are to be documented in the source documents, and the code-breaking CRF is to be completed.

The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must be notified of the code-breaking, in accordance with local regulations. All documentation pertaining to the event must be retained in the site's study records and in the Sponsor's files. Any intentional or unintentional code-breaking must be reported, documented, and explained, and the name of the person who requested it must be provided to the Sponsor.

A request for the code to be broken may also be made:

- by the Global Pharmacovigilance (GPV) Department through an internal system for reporting to Health Authorities in the case of an unexpected SAE considered causally related, as described in International Council for Harmonisation (ICH) E2A. In this case, the code will be broken only for the participant(s) in question. The information resulting from code-breaking (ie, the participant's study intervention or group assignment) will not be communicated to either the investigator or the immediate team working on the study, except for the GPV representative.

At the time of the interim analysis (see Section 9.5), study unblinding will take place to inform selection of the dose formulation for Phase III clinical development. The unblinding code data will be maintained with the Sponsor until the end of the study. The study team will strive not to communicate the study unblinding data to sites in order to minimize bias in collecting the follow-up safety data. The study participants and the laboratory personnel who analyze the blood samples for the study will remain blinded throughout the study.

6.4 Study Intervention Compliance

The following measures will ensure that the study intervention is administered as planned (see Table 6.1), and that any non-compliance is documented so that it can be accounted for in the data analyses:

- All study interventions will be administered by qualified and trained study personnel
- The person in charge of study intervention management at the site will maintain accountability records of study intervention delivery to the study site, study intervention inventory at the site, dose(s) given to each participant, and unused or wasted doses

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 10.5: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

6.5 Dose Modification

Not applicable.

6.6 Continued Access to Study Intervention After the End of the Study

Not applicable.

6.7 Treatment of Overdose

Since the study intervention is administered by a health care professional, it is unlikely that overdose by injection occurs.

However, in the event of an overdose, the investigator should:

1) Contact the RMO immediately.
2) Evaluate the participant to determine, in consultation with the RMO, whether study intervention should be interrupted.
3) Closely monitor the participant for any AE/SAE.
4) Document the quantity of the excess of the overdose in the source documents.

6.8 Concomitant Therapy

At the time of enrollment, ongoing medications and other therapies (eg, blood products) should be recorded in the source document as well as new medications prescribed for new medical conditions / AEs during study participation.

Documentation in the CRF of ongoing concomitant medication(s) will be limited to specific categories of medications of interest beginning on the day of first vaccination.

Reportable medications include medications that may affect the interpretation of safety data (eg, an antipyretic or analgesic that could have reduced the intensity or frequency of an adverse event) or may interfere with the development or measurement of the immune response (eg, the use of immune-suppressors, immune-modulators, or some antibiotics that can affect certain bioassays). Some medications such as steroids can affect both the evaluation of the safety and the immune response to a vaccine.

This may include medications of interest that were started prior to the day of vaccination, and even stopped prior to enrollment if there is a reasonable possibility that they may have an impact on safety and / or immune assessment during study participation.

The following reportable medications are defined:

- Medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs, systemic steroids/corticosteroids)
  Note: Topical analgesics should NOT be applied at the injection site of study intervention; however, if they are applied inadvertently, they should be recorded.
- Medications impacting or that may have an impact on the immune response (eg, other vaccines, blood products, antibiotic classes that may interfere with bioassays used by the Sponsor's laboratory or other testing laboratories, systemic steroids/corticosteroids, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors)
- Medications impacting or that may have an impact on both the safety and the immune response (eg, systemic steroids/corticosteroids)

Reportable medications will be collected in the CRF until the end of the solicited and unsolicited follow-up period.

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded (except topical analgesics applied at the injection site of study intervention). However, in case of an SAE, all medications and supplements including homeopathic medications taken for the SAE should be reported in the SAE form.

Medications given in response to an AE will be captured in the "Action Taken" section of the AE CRF only. No details will be recorded in the concomitant medication Form of the CRF unless the medication(s) received belongs to the reportable medications list. Medications will be coded using the WHODrug dictionary.

6.8.1 Rescue Medicine

Appropriate medical equipment and emergency medications, including epinephrine (1:1000), must be available at the study site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 10.1.

7.1 Discontinuation of Study Intervention

7.1.1 Temporary Contraindications

Should a participant experience one of the conditions listed below, the investigator will postpone further vaccination until the condition is resolved. Postponement must still be within the timeframe for vaccination indicated in the SoA.

If the postponement occurs out of the timeframe for vaccination, the participant will be permanently discontinued from study intervention but will continue to be followed for safety and will not have any further blood sample drawn.

TCI01: Moderate or severe acute illness/infection (according to investigator judgment) or febrile illness (temperature ≥ 100.4°F) on the day of study intervention administration. A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided

Temporary intervention discontinuation may be considered by the investigator because of suspected AEs or disruption of the clinical study due to a regional or national emergency declared by a governmental agency (Appendix 10.5: Contingency Measures for a regional or national emergency that is declared by a governmental agency). For all temporary intervention discontinuations, duration should be recorded by the investigator in the source documents.

In the event of a local or national immunization program with a SARS-CoV-2 or other vaccine, participants who receive these vaccines at any time during the study will not be withdrawn from the study.

7.1.2 Definitive Contraindications

Participants will permanently discontinue (definitive discontinuation) study intervention for the reasons listed below. These participants must not receive any additional dose of study intervention but should continue to be followed for safety and will not have any further blood sample drawn. Additional unscheduled visits may be performed for safety reasons and information will be reported in the source documents.

Should a participant experience at least one of the conditions listed below, the investigator will discontinue vaccination:

DCI01: Pregnancy, as indicated by a positive urine test (if applicable)

DCI02: An anaphylactic or other significant allergic reaction to the previous dose of vaccine

DCI03: SAE assessed as related to the study vaccine following the previous dose of vaccine, based on Investigator's judgment

DCI04: Receipt of any immune globulins, blood, or blood-derived products between V01 and V02

DCI05: Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anti-cancer chemotherapy or radiation therapy, since the preceding visit; or long-term systemic corticosteroid therapy (prednisone or equivalent for more than 2 consecutive weeks since the preceding visit)

DCI06: Thrombocytopenia or bleeding disorder, which may be a contraindication for IM vaccination, based on Investigator's judgment

DCI07: Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with study conduct or completion

DCI08: Development of any condition that in the opinion of the Investigator would pose a health risk to the subject or could interfere with the evaluation of the study intervention (including Guillain-Barré syndrome, hepatitis B, or hepatitis C)

In the event of a local or national immunization program with a SARS-CoV-2 or other vaccine, participants who receive these vaccines at any time during the study will not be withdrawn from the study.

7.1.3 Other Reasons

A participant may discontinue from study intervention at any time at his/her own request, or at the discretion of the investigator for safety, behavioral, or compliance reasons.

Participants should continue to be followed for safety and will not have any further blood sample drawn.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon.
- The reason for withdrawal should be clearly documented in the source documents and in the CRF.
- The participant will be permanently discontinued from the study intervention and from the study at that time. However, the site should attempt to contact them and complete all

scheduled safety follow-ups, except if they specified that they do not want to be contacted again and it is documented in the source document.

- If the participant withdraws consent for disclosure of future information, the Sponsor will retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws consent, he/she may request destruction of any biological samples taken (unless local law requires not to destroy them), and the investigator must document this in the site study records.
- Withdrawn participants will not be replaced.

7.3 Lost to Follow-up

In the case of participants who fail to return for a follow-up examination, documented reasonable effort (ie, documented telephone calls and certified mail) should be undertaken to locate or recall them, or at least to determine their health status while fully respecting their rights. These efforts should be documented in the CRF and in the source documents.

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the site for a required study visit or cannot be contacted as planned in the SoA:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered lost to follow-up.

8 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to

record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Safety / laboratory results that could unblind the study will not be reported to sites or other blinded personnel until the study has been unblinded.

Urine (as applicable) and blood samples will be collected as described in the SoA table (Section 1.2).

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, is not planned to exceed 240 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Guidance and information for the sample collection, preparation, storage, and shipment will be provided to the study personnel.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 10.5: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

8.1 Efficacy and Immunogenicity Assessments

Planned time points for all immunogenicity assessments are provided in the SoA.

8.1.1 Efficacy Assessments

No clinical efficacy data will be obtained in the study.

8.1.2 Immunogenicity Assessments

Assays will be performed by the Sponsor's laboratory (Swiftwater, PA, USA).

Immunogenicity will be evaluated using samples taken before each vaccination (ie, D01 and D22 [+7 days]), and at D43 (+7 days), D202 (+14 days), and D387 (+14 days) after the first vaccination using the HIH and SN assays.

Anti-Influenza Virus Antibody Titration by Inhibition of Hemagglutination using Horse Red Blood Cells (HIH)

The influenza virus HIH assay is based on the ability of specific anti-influenza antibodies to inhibit agglutination of horse red blood cells (HRBCs) induced by influenza virus HA. The sera are pre-treated to eliminate the non-specific inhibitors. Serial dilutions of sera are incubated with a fixed amount of influenza virus. Antibodies present in the serum sample will inhibit the agglutination of HRBCs when influenza virus is added. The endpoint of the assay is the highest serum dilution in which complete inhibition of hemagglutination occurs.

Influenza Virus Neutralization Test (also known as SN Assay)

The influenza virus neutralization test measures Abs directed against the viral neutralization epitopes of the influenza virus, which may be different from the hemagglutination epitopes, therefore, the NT titers may be different from the HAI titers.

Two-fold serially diluted, heat-inactivated human serum samples will be pre-incubated with a fixed amount of challenge virus prior to the addition of Madin-Darby canine kidney (MDCK) cells. After overnight incubation, the viral nucleoprotein production in infected MDCK cells is measured by enzyme-linked immunosorbent assay (ELISA), using monoclonal Ab specific to influenza A nucleoprotein. Since serum neutralizing Abs to the influenza virus inhibits the viral infection of MDCK cells, the ELISA optical density results are inversely proportional to the titers of neutralizing Ab present in the serum. The lower limit of quantitation is set at the reciprocal of the lowest dilution used in the assay, ie, 10 (1/dil). Titers below this level are reported as < 10 (1/dil). Titers > 10240 (1/dil) will be pre-diluted, retested, and end point titers will be reported.

8.2 Safety Assessments

This section presents safety assessments other than AEs which are presented in Section 8.3.

Planned timepoints for all safety assessments are provided in the SoA (Section 1.2).

8.2.1 Medical History

Prior to enrollment, participants will be assessed for pre-existing conditions and illnesses, both past and ongoing. Any such conditions will be documented in the source document. Significant (clinically relevant) medical history (reported as diagnosis) including conditions/illnesses for which the participant is or has been followed by a physician or conditions/illnesses that could resume during the course of the study or lead to an SAE or to a repetitive outpatient care will be collected in the CRF. Collected information will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

8.2.2 Physical Examinations

At Visit 1 and Visit 2, the investigator or a designee will perform a clinical or medically-driven physical examination. Information will be recorded in the source document and in the CRF.

8.2.3 Vital Signs

Oral pre-vaccination temperature will be systematically collected by the investigator on the source document. Tympanic, skin, and temporal artery thermometers must not be used.

8.2.4 Clinical Safety Laboratory Tests

Not applicable.

8.2.5 Pregnancy Testing

Urine pregnancy testing will be performed in women of childbearing potential before each vaccination. See Appendix 10.2 and the SoA (Section 1.2) for the timing and frequency.

8.3 Adverse Events (AEs), Serious Adverse Events, and Other Safety Reporting

The definitions of an AE, SAE, and the different categories of AEs can be found in Appendix 10.3.

AEs will be reported by the participants to the investigator, then by the investigator to the Sponsor.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention and / or study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Immediate Post-vaccination Observation Period

Participants will be kept under observation for 30 minutes after each vaccination to ensure their safety. The post-vaccination observation should be documented in the source document.

Reactogenicity

Solicited injection site reactions will be collected from the day of vaccination (DX) until 7 days after each vaccination (DX + 7 days).

Solicited systemic reactions will be collected from the day of vaccination (DX) until 7 days after each vaccination (DX + 7 days).

The solicited injection site reactions and systemic reactions that are pre-listed in the eDiary and CRF, together with the intensity scales, are presented in Appendix 10.3.5.1.1.

Unsolicited Non-serious Adverse Events

Unsolicited non-serious adverse events will be collected from the day of vaccination (DX) until 21 days after each vaccination (DX + 21 days).

The intensity grading scale for unsolicited non-serious adverse events is presented in Appendix 10.3.5.1.2.

Medically Attended Adverse Events (MAAEs)

MAAEs will be collected throughout the study.

Adverse Events of Special Interest (AESIs)

AESIs will be collected throughout the study.

See Section 8.3.6 for the list of AESIs.

SAEs

Information on SAEs will be collected and assessed throughout the study, from the first study intervention administration until 12 months after the last vaccination. However, before the first study intervention administration, only SAEs related to study procedures are to be collected in the CRF (eg, SAEs related to blood sampling).

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 10.3. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting AEs and SAEs

Individual eDiary, specifically designed for this study by the Sponsor and provided to the study sites, will be available to study participants for the recording of daily safety information. The eDiary is the primary method for safety data collection. However, paper diary cards will also be available for use as a back-up solution in case of major breakdown of the app or as determined by the Sponsor's study clinical team. The eDiary will include pre-listed terms and intensity scales as well as areas for free text to capture additional safety information or other relevant details. Participants will also be provided with rulers for measuring the size of injection site reactions, and with standard digital thermometers for measuring daily temperatures. To ensure consistency of reporting, the study sites will instruct participants on how to correctly use these tools.

At specified intervals, the investigator or a designee will interview the participants to confirm the information recorded in the eDiary, and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically using a web-based CRF. Any information that was not documented in the eDiary will first be captured in the source document and then reported electronically.

The 12-month follow-up should be done at least 365 days after the last vaccination for all participants having received at least one dose of the study intervention, by interviewing participants during Visit 5 (or over the telephone if the visit cannot be performed in-person) using a questionnaire to capture MAAEs, SAEs, and AESIs, if applicable.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts, unless a participant refuses further contact. All AEs that are

considered by the investigator as serious, or related to the study intervention administered, or that led to study or vaccination discontinuation, or AESIs (as defined in Section 8.3.6), will be followed during the conduct of the study until resolution, stabilization, or the participant is lost to follow-up (as defined in Section 7.3). For related SAEs ongoing at last study visit, such follow-up may need to continue after the end of the study.

Further information on follow-up procedures is provided in Appendix 10.3.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.3.5 Pregnancy

Pregnant women are not eligible to participate in the study and women of childbearing potential agree to use an effective contraceptive method, as defined in the inclusion criteria. However, a participant could potentially become pregnant during her participation.

- Details of all pregnancies in female participants will be collected in the GPV database after the start of study intervention and until delivery in the GPV database.
- If a pregnancy is reported, the investigator should promptly inform the Sponsor and will record pregnancy information together with the contraceptive method on the appropriate form and submit it to the Sponsor within 1 month of learning of the pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will be required for at least 6 months to 1 year beyond the estimated delivery date, but will be in accordance with local regulations.

Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention until delivery or until delivery and end of lactation. However, the participant will be followed for safety assessment (and may be followed for immunogenicity assessment, if applicable).

8.3.6 Adverse Events of Special Interest

AESIs will be captured as SAEs and will be collected throughout the study. These include anaphylactic reactions, Guillain-Barré syndrome, encephalitis / myelitis (including transverse myelitis), Bell's palsy, thrombocytopenia, optic neuritis, brachial neuritis, and vasculitis (15) (16) (17).

8.3.7 Medically Attended Adverse Events

MAAEs will be collected using the same process as other AEs. See Appendix 10.3.1 for definition of MAAEs.

8.4 Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.5 Genetics

Genetics are not evaluated in this study.

8.6 Biomarkers

No other biomarkers than those described in the immunogenicity assessments section (Section 8.1.2) are evaluated in this study.

8.7 Immunogenicity Assessments

See Section 8.1.2.

8.8 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8.9 Leftover Biological Samples and Use of Data

Any unused part of the biological samples (ie, serum samples) collected for this study are being retained in long-term storage to support answers to regulatory questions related to the product's licensure and the potential revalidation of the study results.

In addition, participants will be asked to indicate in the ICF whether they will permit the future use of any unused stored biological samples for other tests and the corresponding data, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of any unused biological samples will not be included in the site-specific ICF). If they refuse permission, the biological samples will not be used for any testing other than that directly related to this study. If they agree to this future use, they will not be paid for giving permission. Data and samples will be used in compliance with the information provided to participants in the ICF Part 2 (future research). The aim of any possible future research is unknown today and may not be related to this particular study. It may be to improve the knowledge of vaccines and their mechanism of action, the knowledge of infectious diseases, or to improve existing tests or develop new tests to assess vaccines, or to help identify new vaccine targets or biomarkers that predict participant response to the vaccine. Such research may also include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, a specific individual consent will be obtained.

All study participant data and biological samples will be coded such that no direct identifiers will be linked to participants. Coded data and biological samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

The biological samples will be securely stored at the Sanofi Pasteur laboratory or contract Research Laboratory up to 25 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and sample related coded data will be anonymized unless otherwise required by applicable laws.

Study participant coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymized unless otherwise required by applicable laws (the same will apply to the data of a study participant who has requested the destruction of his/her samples).

Participant's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

Note: The other biological samples collected to qualify the participant for inclusion in the study are dedicated for immediate use. If any of these biological samples are not completely used up, they will be destroyed at the latest at the end of the study or after the time requested by local law.

9 Statistical Considerations

All statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics Platform using the SAS® software, Version 9.4 or above.

The SAP core body will be written and peer-reviewed before the initiation of the study. In accordance with the protocol, the SAP core body will describe all analyses to be performed by the Sponsor.

For descriptive purposes, the following statistics will be presented:

Table 9.1 - Descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number and percentage of participants
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum
Safety results	**Categorical data**	Solicited and biological safety: Number and percentage (95% CIs) of participants Unsolicited: Number and percentage (95% CIs) of participants, and number of events
	Continuous data	At least mean, standard deviation, minimum, and maximum
Immunogenicity results	**Categorical data (such as seroconversion)**	Number and percentage (95% CIs) of participants
	Continuous data **(titer / data)**	Log_{10}: Mean and standard deviation Anti-Log_{10} (work on Log_{10} distribution, and anti-Log_{10} applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum Graphical representation by RCDC

9.1 Statistical Hypotheses

No hypotheses will be tested in this study.

9.2 Sample Size Determination Based on HAI Data

Assuming a dropout rate of approximately 10%, a total of approximately 630 participants evaluable for immunogenicity is anticipated.

Table 9.2 shows the expected number of evaluable participants in each study group and each age stratum, and the probability that the lower bound of the 95% CI exceeding the threshold defined by Center for Biologics Evaluation and Research (CBER) requirement for seroconversion and percentage of subjects achieving an HAI antibody titer ≥ 1:40 (18).

Table 9.2 - Probability calculation

Age in Years	Evaluable Number of Participants (Study Group)	Expected Proportion	CBER: Lower Bound of 2-Sided 95% CI Greater Than	Probability (%)
Percent of participants with HAI antibody titer ≥ 1:40				
≥ 18	270 (Groups 1 or 2)	0.80	70%	96%
18 to < 65	135 (Groups 1 or 2)	0.82	70%	88%
≥ 65	135 (Groups 1 or 2)	0.72	60%	82%
≥ 18	90 (Group 3)	0.85	70%	93%
18 to < 65	45 (Group 3)	0.85	70%	< 80%
≥ 65	45 (Group 3)	0.80	60%	83%
Percent of participants with seroconversion for antibody				
≥ 18	270 (Groups 1 or 2)	0.50	40%	90%
18 to < 65	135 (Groups 1 or 2)	0.52	40%	<80%
≥ 65	135 (Groups 1 or 2)	0.42	30%	82%
≥ 18	90 (Group 3)	0.55	40%	80%
18 to < 65	45 (Group 3)	0.70	40%	97%
≥ 65	45 (Group 3)	0.50	30%	<80%

9.3 Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Randomized	All participants randomized by study IRT to one of the 3 study doses (one of three study groups).
Safety Analysis Set (SafAS)	Participants who have received at least one study intervention. All participants will have their safety analyzed after each dose according to the intervention actually received, and after any dose according to the intervention received at the 1st dose. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Full analysis set (FAS)	Subset of randomized participants who received at least 1 dose of the study vaccine and had a post-vaccination blood sample for D22 or D43.

	Participants will be analyzed according to the study dose group to which they were randomized.
Per-protocol analysis set (PPAS)	To be able to compare and present the results of immunogenicity in the same table, only one PPAS will be derived in this study. Subset of the FAS participants who have provided D22 and D43 blood samples. Participants presenting with at least one of the following relevant protocol conditions will be excluded from the PPAS: • Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria • Participant did not complete the vaccination schedule • Participant received a vaccine other than the one that he / she was randomized to receive • Preparation and / or administration of vaccine was not done as per-protocol • Participant did not receive vaccine in the proper time window • Participant did not provide a post-dose serology sample at D22 (+7 days) and D43 (+7 days) in the proper time window or a post-dose serology sample was not drawn • Participant received a medication impacting or that may have an impact on the immune response as described in Section 6.8 • Re-randomized participants Any other deviation identified during the study conduct and judged by the clinical team during data review as having a potential impact on the assessment of immunogenicity will be used to exclude a participant from the PPAS. Participants with missing SN data or participants with no valid test results of SN will be included in PPAS if they meet all the other requirements to be included in PPAS for HIH. In the event of a local or national immunization program with a SARS-CoV-2 or other vaccine, participants who receive 1 or more doses of the vaccine listed above at any time during the study will not be withdrawn from the study.

9.4 Statistical Analyses

The SAP core body will be finalized before the initiation of the study and may be amended, if necessary, prior to database lock. It will include a more technical and detailed description of the statistical analysis outlined in this section.

9.4.1 General Considerations

The statistical analysis will be conducted as follows:

- The study will be unblinded after all immunogenicity and safety data are collected for the follow-up period of 3 weeks after D22 (ie, 21 days after the last vaccination) (see Section 6.3.2 and Section 9.5).
- The final database lock will occur after the 12-month follow-up.

No adjustment for multiplicity regarding multiple comparisons between study doses is planned in this study. Details will be provided in the SAP.

9.4.2 Primary Endpoints

Primary Immunogenicity Objective:
The immunogenicity parameters will be calculated with their 95% CIs using the exact binomial distribution (Clopper-Pearson method) for proportions and using normal approximation of log-transformed for GMTs and GMTs ratio. The 95% CI of proportions difference (ie, difference between vaccine groups in seroconversion) will be calculated using Wilson Score method without continuity correction (19). All analyses will be conducted by study group and also by age stratum.

The time windows used for collecting blood samples are: D01, D22 [+7], D43 [+7], D202 [+14], and D387 [+14]. To avoid redundancy and typing errors, these time windows will not be reported in all sections of this document.

- Immunogenicity by HIH measurement method
  - GMTs of HAI Ab titers obtained on D22, and on D43 for comparison with D01, D202, and D387.
  - Geometric mean of individual ratios of HAI Ab titers D22/D01 and D43/D01; and D202/D01 and D387/D01.
  - Percent of participants with seroconversion defined as HAI Ab titer < 10 (1/dilution [1/dil]) on D01 and post-injection titer ≥ 40 (1/dil) on D22 or D43; or defined as HAI Ab titer ≥ 10 (1/dil) on D01 and a ≥ 4-fold increase in titer (1/dil) on D22 or D43.
    The interpretation of the results will account for seroconversion thresholds reported in FDA guideline (18) for participants 18 – 64 years and ≥ 65 years of age.
  - Percent of participants with HAI Ab titers ≥ 40 (1/dil) on D22, and percent of participants with HAI Ab titers ≥ 40 (1/dil) on D43. The same statistic will be calculated for D01, D202, and D387.
    The interpretation of the results will account for seroconversion thresholds reported in FDA guideline (18) for participants 18 – 64 years and ≥ 65 years of age.
  - Percent of participants with detectable HAI Ab titer with a titer ≥ 10 (1/dil) on D01, D22, D43, D202, and D387.
  - Difference and its 95% CI in seroconversion between the 3 study doses (Group 1 - Group 3; Group 2 - Group 3, and Group 2 - Group 1) at D22 and D43.
  - Ratio of GMTs and its 95% CI for: Group1/Group3, Group2/Group3, and Group2/Group1 at D22, and at D43.

- The RCDCs of pre-vaccination titer prior to the first vaccination (D01), and post-vaccination titer at D22, D43, D202, and D387 will be generated for each study dose. The RCDCs will include the plots of the 3 doses on the same figure.

- Immunogenicity by SN measurement method
  - GMTs of NT Ab titer obtained on D22, and on D43 for comparison with D01, D202, and D387.
  - Geometric mean of individual ratios of NT Ab titer for D22/D01, D43/D01, D202/D01, and D387/D01.
  - Percentage of participants with NT Ab titers ≥ 20 (1/dil), ≥ 40 (1/dil), ≥ 80 (1/dil) on D22, and on D43; compared to D01, D202, and D387.
  - Percent of participants with fold increase in NT Ab titer [post-vaccination/ pre-vaccination] ≥ 2 and ≥ 4 on D22 and D43.
  - Percent of participants with detectable NT Ab titer ≥ 10 (1/dil) on D01, D22, D43, D202, and D387.
  - Difference and its 95% CI in percent of participants with fold increase between the 3 study doses (Group 1 - Group 3, Group 2 - Group 3, and Group 2 - Group 1) on D22, and on D43.
  - Ratio of GMs and its 95% CI for: Group1/Group3, Group2/Group3, and Group2/Group1 on D22, and on D43.
  - The RCDCs of pre-vaccination titer prior to the first vaccination (D01) and post-vaccination titer at D22, D43, D202, and D387 will be generated for each study dose. The RCDCs will include the plots of the three doses on the same figure.

For each immunogenicity measurement method, the analysis will be conducted for each immunogenicity variable on the PPAS and on FAS.

9.4.3 Secondary Endpoints

Safety Objective:

For the main safety parameters, 95% CIs of point estimates will be calculated using exact binomial method (Clopper-Pearson method) for single proportions and using the normal approximation for quantitative data.

All analyses will be descriptive; no hypotheses will be tested.

The number of participants with documented safety will be used as denominator of the frequencies.

- For solicited reactions, the denominator will be the total number of participants who have non-missing data for the endpoint considered
- For unsolicited AEs, the denominator will be the total number of participants who were vaccinated with the dose analyzed

Solicited reactions

Solicited reactions will be presented according to their nature (Medical Dictionary for Regulatory Activities [MedDRA, the latest version at database lock] preferred term [PT]), intensity (Grade 1, 2, or 3), time to onset, and number of days of occurrence.

Unsolicited AEs

Unsolicited AEs included in the analysis will be summarized in the safety overview and analyzed according to their nature (MedDRA [the latest version at database lock] system organ class [SOC] and PT classification) and relationship to the vaccination.

Injection Site Reactions

For each dose, the number and percentage of participants experiencing any injection site reaction after injection will be calculated.

The description of injection site reactions will be presented according to:

- Solicited injection site reactions

  All solicited injection site reactions that occur each day within 7 days after injection will be summarized and presented.

- Unsolicited injection site reactions

  All unsolicited injection site reactions after vaccination, reported within 21 days after each vaccination will be described according to the type of events.

Systemic Events and Reactions

For each dose, the number and percentage of participants experiencing any unsolicited immediate systemic event in the 30 minutes after injection will be calculated.

In addition, the description of systemic events will be structured according to:

- Solicited systemic reactions

  All solicited systemic reactions that occur each day within 7 days after injection will be analyzed

- Unsolicited systemic events

  All unsolicited systemic events reported after vaccination within 21 days after each vaccination will be described according to the type of events.

Medically Attended Adverse Events

MAAE safety summaries will be reported for within 21 days after each vaccination, from D01 to D42, from D43 to D202, from D203 to D387, and overall study.

Adverse Events of Special Interest

The number and percentage of participants with AESIs reported after vaccination, within 21 days after each vaccination, and throughout the study will be calculated by outcome and seriousness.

Serious Adverse Events

The number and percentage of participants with SAEs reported after vaccination, within 21 days after each vaccination, will be calculated by outcome, seriousness, and relationship to the dose administered.

The SafAS will be used for the safety analysis.

9.4.4 Other Analysis

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on immunogenicity (eg, missing data due to the emergency) and safety will be detailed in the SAP.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 10.5: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

9.5 Interim Analyses

The blind will be broken at the participant level after collecting all immunogenicity and safety data up to 21 days after last vaccination, data are cleaned, and database is locked. The study participants and the laboratory personnel who analyze the blood samples will remain blinded throughout the study. The study team will strive not to communicate the study unblinded data to the sites in order to minimize the bias in collecting the follow-up safety data.

The main analysis of immunogenicity (HIH and SN measurement methods) data and safety will include all data up to 21 days after the last vaccination. The results of this analysis will help in selecting the dose formulation for further clinical development. The results of this main analysis may be reported in an interim clinical study report (CSR).

A final database lock will occur after all data, including up to the 12-month follow-up period, are collected. A final CSR would include the analysis of the safety and immunogenicity data at 6- and 12-month after the last vaccination to assess the persistence of the antibody levels.

No statistical adjustment is necessary because no hypothesis will be tested. Unblinded early looks at the safety data may take place to assess safety.

10 Supporting Documentation and Operational Considerations

10.1 Appendix: Regulatory, Ethical, and Study Oversight Considerations

Note: The term "participant" is used throughout this protocol. However, the term "subject" will be used in the CRF in order to comply with the Clinical Data Interchange Standards Consortium (CDISC) requirements.

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation [GDPR])
- The protocol, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator or the Sponsor (according to local regulations) and reviewed and approved by the IRB/IEC before the study is initiated
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants
- The investigator or the Sponsor (according to local regulations) will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:

- The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
- The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.
- The participant in a clinical study has the right to opt out of being notified by the investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie*,* changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial Disclosure

Information related to financial disclosure is described in the investigator's contract.

10.1.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participants and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements including those of the General Data Protection Regulation (GDPR) and of the French law, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- The actual ICF used at each center may differ, depending on local regulations and IEC / IRB requirements. However, all versions must contain the standard information found in the sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IEC / IRB prior to the form being used.
- If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, this will be communicated to him / her in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.
- Participants must be re-consented to the most current version of the ICF during their participation in the study. Where participants are not in the study anymore, the Sponsor must define if those participants must or not re-consent or be informed of the revision (eg, if the processing of personal data is modified, if the Sponsor changes).
- A copy of the ICF must be provided to the participant.

The ICF will contain a specific section that addresses the use of remaining mandatory samples for optional exploratory research, unless prohibited by local laws or IRBs/IECs. The investigator or designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

Recruitment Procedures

Before the start of the study, the investigator or designee will contact an appropriate pool of potential participants and invite them to participate in the study. The site will ensure that any advertisements used to recruit participants (eg, letters, pamphlets, posters) are submitted to Sanofi Pasteur prior to submission to the IEC / IRB for approval.

For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg. study visit delays/treatment extension).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 10.5: Contingency Measures for a regional or national emergency that is declared by a governmental agency.

10.1.4 Data Protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant personal data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

- Participants' race and ethnicity will be collected in this study because these data are required by regulatory agencies (20).
- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "product development program", ie, for this study as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agency's disqualification list.
- Personal data can be communicated to the following recipients:

  - Personnel within Sanofi or partners or service providers involved in the study
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the Transcelerate Investigator Registry project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the Transcelerate project. This sharing allows investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the Transcelerate project.
- Professionals have the right to object to the processing, to request for access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees Structure

Participant safety will be continuously monitored by the Sponsor's internal safety review committee which includes safety signal detection at any time during the study. The Sponsor's internal safety review committee, led by the PV representative and the RMO and designee(s), will be responsible for the blinded review, assessment, and evaluation of safety data generated from this study up to the D43 data unblinding for the main analysis. This committee is empowered to recommend a pause in recruitment and/or further vaccination while it investigates any potential signal or concern.

This study will not include an early safety data review.

10.1.6 Dissemination of Clinical Study Data

Study participants

At the end of the clinical study, the Sponsor may publish the study results in scientific journal(s). As part of the review for publication, independent scientists may need to use "coded" data of all the study participants to independently verify the study's results.

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in patients are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organizations".

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRFs unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the CRF Completion Instructions.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact patient safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.
- The protocol will be signed by the RMO, and a Protocol Investigator Agreement Form (PIAF) will be signed by all investigators. The clinical study report will be signed by the RMO and the coordinating investigator. In case no coordinating investigator has been designated, it will be the responsibility of the RMO or designee(s) to identify the signatory investigator.

10.1.8 Source Documents

"Source data" are the data contained in source documents. Source documents are original documents or certified copies, and include, but are not limited to, DCs, medical and hospital records, screening logs, informed consent forms, telephone contact logs, and worksheets.

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and Site Start and Closure

Study personnel will be informed of which clinical supplies will be provided by the Sponsor or the site.

The study start date is considered the date of the first visit planned in the SoA of the first participant.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been either destroyed or returned to the Sponsor, all samples are shipped to the appropriate laboratories, the center study-site has all the documents necessary for archiving and a study-site closure visit has been performed along with a site close out form submitted to the IRB, as required.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development
- Information on the study intervention leads to doubt as to the benefit/risk ratio

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication Policy

Information related to publication policy is described in the investigator's contract.

10.2 Appendix: Clinical Laboratory Tests

- The tests detailed in Table 10.1 will be performed at the study site.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10.1 - Protocol-required safety laboratory tests

Laboratory Tests	Time period for assessment	Parameters
Pregnancy testing	before each vaccination	• Highly sensitive [serum or urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)*
* Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.		

Investigators must document their review of each laboratory safety report.

10.3 Appendix: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Other Definitions

Adverse Reaction:

An adverse reaction (AR) is any noxious and unintended response to a study intervention related to any dose.

Immediate Event/Reaction:

Immediate events are recorded to capture medically relevant unsolicited systemic AEs which occur within the first 30 minutes after vaccination.

Reactogenicity / Solicited Reactions:

The **reactogenicity** of a vaccine refers to the property of such vaccine to be able to produce common "expected" adverse reactions (either systemic or at the injection site) and its associated signs and symptoms.

A solicited reaction is an “expected” adverse reaction (sign or symptom) observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF (eg, injection site pain or headache occurring between the day of vaccination and the next 7 days).

By definition, solicited reactions are considered as being related to the corresponding IMP administered.

For injectable vaccines, solicited reactions can either be solicited injection/administration site reactions or solicited systemic reactions

Injection / Administration Site Reactions:

An injection/administration site reaction is an AR at and around the injection/administration site of the IMP. Injection/administration site reactions are commonly inflammatory reactions.

Solicited injection / administration site reactions are reactions at and around the injection / administration site of the IMP observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF. It is considered by default as being related to the IMP administered at that site.

Note: “Administration site reaction” term is only to be used for vaccines that are not intended to be administered by injection.

Systemic AR:

Systemic ARs are all ARs that are not injection or administration site reactions. They therefore include systemic manifestations such as headache, fever, as well as localized or topical manifestations that are not associated with the injection or administration site (eg, erythema that is localized but that is not occurring at the injection site).

Solicited systemic reactions are systemic AEs observed and reported under the conditions (nature and onset) pre-listed in the protocol and CRF. Solicited systemic reactions occurring during the specified collection period are always considered related to the IMP even if there is evidence of alternative etiology.

Unsolicited AE/AR:

An unsolicited AE is an observed AE that does not fulfill the conditions of solicited reactions, ie, pre-listed in the CRF in terms of diagnosis and onset window post-vaccination. For example, varicella or a solicited term such as headache starting after the solicited observation period (eg, headache starting on Day 10 post-vaccination in the case where headache occurring between the day of vaccination and the next 7 days is pre-listed in the protocol and CRF as a solicited reaction).

An unsolicited AR is an unsolicited AE that is considered related to an IMP.

Unsolicited AEs includes both serious (SAEs) and non-serious unsolicited AEs.

All unsolicited AEs occurring at and around the IMP injection/administration site are to be considered by default as related to the IMP administered at that site and are therefore referred as unsolicited injection/administration site ARs.

All unsolicited AEs which are not at and around the IMP injection/administration site, are referred as systemic unsolicited AE. For each unsolicited systemic AE, the investigator assesses the relationship to the IMP. Systemic AEs assessed as related to IMP are referred as systemic ARs.

Adverse Event of Special Interest (AESI):

An AESI (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's study intervention or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the study Sponsor to other parties (eg, regulators) might also be warranted.

Medically Attended AE (MAAE):

An MAAE is a new onset or a worsening of a condition that prompts the participant to seek unplanned medical advice at a physician's office or Emergency Department. Physician contact made over the phone or by e-mail will be considered a physician office visit for the purpose of MAAE collection. This includes medical advice seeking during the study visit or routine medical care. This definition excludes follow-up visits of chronic conditions with an onset prior to entry in the study, and solicited reactions.

10.3.2 Definition of SAE

An SAE is defined as any adverse event that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is other medically important event

- The term "Other medically important events" refers to events which do not meet any of the above seriousness criteria, but which are considered as serious based on investigator medical judgment.
- Medical or scientific judgment should be exercised by the investigator in deciding whether expedited reporting is appropriate in other situations such as significant medical events that may jeopardize the health of the participant or may require intervention to prevent one of the other outcomes listed in the above definition. These important medical events should also usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse, new-onset diabetes or autoimmune disease, or suspected transmission of any infectious agent via an authorized medicinal product.

Note: *Serious* and *severe* are not synonymous. The term *severe* is often used to describe the intensity of a specific event as corresponding to Grade 3. This is not the same as *serious,* which is based on participant / event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the CRF pages.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Causal Relationship

By convention, all AEs reported at the injection site (either solicited or unsolicited) and all solicited systemic AEs are considered to be related to the IMP (see definition in Section 6) and therefore are referred to as reactions and do not require the investigator's opinion on relatedness.

- Causal relationship of unsolicited systemic AEs and SAEs will be recorded as follows:
  - For non-serious unsolicited systemic AEs (except for non-serious AESIs), relationship to study intervention will usually be assessed by the investigator only.
  - For SAEs and non-serious AESIs, relationship to study intervention will be assessed by both the investigator and the Sponsor (except for injection site reactions which will be related by default). Sponsor assessment is entered in the GPV database only.
  - For SAEs only, the causal relationship to study procedures (related/not related to study procedures) will be assessed by both the investigator and the Sponsor. Sponsor assessment is entered in the GPV database only.
- The investigator will assess the ***causal relationship*** between each unsolicited systemic AE and the study intervention administered as either ***not related*** or ***related***, based on the following definitions:

- Not related – The AE is clearly / most probably caused by other etiologies such as participants' underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the first vaccination (screening phase, if applicable)
- Related – There is a "reasonable possibility" that the AE was caused by the study intervention administered, meaning that there are facts (evidence) or arguments to suggest a causal relationship

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causal relationship.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always makes an assessment of causal relationship for every event before the initial transmission of the SAE data to the Sponsor.
- The investigator may change his/her opinion of causal relationship in light of follow-up information and send an SAE follow-up report with the updated causal relationship assessment.
- The causal relationship assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causal relationship of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, when available the investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

- Serious adverse events likely to be related to the study intervention, that persist at the end of the study will be followed up by the investigator until their complete disappearance or the stabilization of the participant's condition. The investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

10.3.4 Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).

SAE Reporting to the Sponsor via Paper CRF

- The SAE paper CRF can be sent to the Sponsor by one of the following means:
  - By fax, to the following number: 1-570-957-2782
  - In PDF format to the following e-mail address, using a method of transmission that includes password protection:
    PV.outsourcing@sanofi.com or USPVmailbox@sanofi.com
  - By express mail, to the following address:
    Sanofi GPV mail room
    55 Corporate Drive
    Bridgewater, New Jersey 08807

Safety Emergency Call

If, as per the investigator's judgment, a participant experiences a medical emergency, the investigator may contact the Sponsor's RMO for advice on how to address any study-related medical question or problem. If the RMO is not available, then the investigator may contact the Call Center—available 24 hours a day, 7 days a week—that will forward all safety emergency calls to the appropriate primary or back-up Sanofi Pasteur contact, as needed. The toll-free contact information for the Call Center will be provided separately.

This process does not replace the need to report an SAE. The investigator is still required to follow the protocol-defined process for reporting SAEs to the GPV Department.

In case of emergency code-breaking, the investigator is required to follow the code-breaking procedures described in Section 6.3.2.

10.3.5 Assessment of Intensity

The investigator will make an assessment of intensity for each AE reported during the study. An intensity grade will be assigned to each AE. The intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007".

10.3.5.1 Tables for Clinical Abnormalities

10.3.5.1.1 Solicited AR Intensity Grading Scale

Table 10.2 - Solicited injection site reactions: terminology, definitions, and intensity scales – Adults 18 years of age and older

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling	Injection site induration	Injection site ecchymosis
eDiary term	Pain	Redness	Swelling	Hardening	Bruising
Definition	Pain either present spontaneously or when the injection site is touched or injected limb is mobilized	Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling	Hardening at or near the injection site. Hardening is caused by a slow diffusion of the product in the tissue leading to a thick or hard area to touch at or near the injection site and thus can be best described by looking at the size of the hardening.	Bruising is the result of the diffusion of blood in the skin from ruptured blood vessels that forms a purple or black and blue spot on the skin. It can be best described by looking at its size.

Intensity scale*	**CRF:** Grade 1: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Grade 2: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. Grade 3: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **eDiary:** Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm	Grade 1: ≥ 25 to ≤ 50 mm Grade 2: ≥ 51 to ≤ 100 mm Grade 3: > 100 mm

* For pain, the scale will be provided in the CRF and the intensity will be registered in the eDiary. For other injection site reactions (erythema, swelling, induration, and ecchymosis), the classification as Grades 1, 2, or 3 will be applied at the time of statistical analysis; the scale is provided for information purposes only. The actual size of the reaction will be reported in the CRF.

Table 10.3 - Solicited systemic reactions: terminology, definitions, and intensity scales – Adults 18 years of age and older

CRF term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia
eDiary term	Temperature	Headache	Feeling unwell	Muscle aches and pains
Definition	Elevation of temperature to ≥°38.0°C (≥ 100.4°F)	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include ligaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as injection site pain.
Intensity scale*	Grade 1: ≥ 38.0°C to ≤ 38.4°C, **or** ≥ 100.4°F to ≤ 101.1°F	**Grade 1:** CRF: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. **eDiary**: No interference with activity		
	Grade 2: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	**Grade 2:** CRF: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant. **eDiary**: Some interference with activity		
	Grade 3: ≥ 39.0°C **or** ≥ 102.1°F	**Grade 3:** CRF: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. **eDiary**: Significant; prevents daily activity		

* For all reactions (except fever), the scale will be provided in the CRF and the intensity will be registered in the eDiary. For fever, the body temperature will be recorded, and the classification as Grade 1, 2, or 3 will be assigned at the time of the statistical analysis based on the unit used to measure the temperature and the intensity scale.

Important notes for the accurate assessment of temperature:

Participants are to measure body temperature once per day, preferably always at the same time, and using the same standard unit of the considered country (Celsius or Fahrenheit) consistently. The optimal time for measurement is the evening, when body temperature is the highest. Temperature is also to be measured at the time of any apparent fever. The observed daily temperature and the route of measurement are to be recorded in the eDiary, and the highest temperature will be recorded by the site in the CRF. The preferred route for this study is oral.

10.3.5.1.2 Serious and Non-serious Unsolicited AE Intensity Grading Scale

For measurable unsolicited AEs that are part of the list of solicited reactions, the corresponding scale for solicited reactions will be used (see Section 10.3.5.1.1).

All other unsolicited AEs, including SAEs, will be classified according to the following intensity scale:

- Grade 1
  - CRF: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
  - eDiary: No interference with activity.
- Grade 2
  - CRF: A type of adverse event that is usually alleviated with additional therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
  - eDiary: Some interference with activity.
- Grade 3
  - CRF: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
  - eDiary: Significant; prevents daily activity.

10.4 Appendix: Contraceptive and Barrier Guidance

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).
If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1) Premenarchal
2) Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3) Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception Guidance

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion/ligation
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation – oral – injectable
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
• **Effective Methods[c] That Are Not Considered Highly Effective** *Failure rate of ≥ 1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Considered effective, but not highly effective - failure rate of ≥ 1% per year. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 Appendix: Contingency measures for a regional or national emergency that is declared by a governmental agency

Continuation of the study in the event of a regional or national emergency declared by a governmental agency:

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested below and in Sections 5.5, 6.4, 7.1.1, 8, 9.4.4, and 10.1.3 for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect study integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical study should be proposed, and enrollment, randomization, administration of study intervention, and blood sampling may be temporarily delayed/halted (see also Section 5.5).

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc.) may be planned for the blood collection and collection of possible safety data,
- If onsite visits are not possible visit windows may be extended for assessment of safety and/or data that cannot be obtained remotely.

Contingencies implemented due to emergency will be documented.

10.6 Appendix: Risk-based Approach

ICH E6-R2 guideline for GCP is introducing the « risk-based approach » concept which permits to focus efforts on what is critical for a study and most specifically on Critical Data and Critical Processes. Critical data and processes are defined for the study with associated risks in the Study Risk Management Plan.

10.7 Appendix: Abbreviations

1/dil	1/dilution
Ab	antibody
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BARDA	Biomedical Advanced Research and Development Authority
CBER	Center for Biologics Evaluation and Research
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulation
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CNIL	Commission Nationale de l'Informatique et des Libertés
COVID-19	Coronavirus Disease 2019
CRB	case report book
CRF	case report form
CSR	clinical study report
D	day
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
eDiary	electronic diary
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GLA/SE	Glucopyranosyl Lipid A in stable oil-in-water emulsion
GMT	geometric mean titer
GPV	Global Pharmacovigilance
HA	hemagglutinin
HAI	hemagglutination inhibition
HCG	human chorionic gonadotropin
HIH	hemagglutination inhibition using horse red blood cells
HIPAA	Health Insurance Portability and Accountability Act

HRBC	horse red blood cells
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IM	intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Boards
IRT	interactive response technology
LLT	lowest level term
MAAE	medically attended adverse event
MDCK	Madin-Darby canine kidney
MedDRA	Medical Dictionary for Regulatory Activities
NA	neuraminidase
NIMP	Non- Investigational Medicinal Product
NT	Neutralization
PPAS	Per-protocol analysis set
PSC	Protein Sciences Corporation
PT	preferred term
PV	pharmacovigilance
QTL	quality tolerance limits
RCDC	reverse cumulative distribution curve
rHA	recombinant hemagglutinin
RMO	Responsible Medical Officer
RNA	ribonucleic acid
SAE	Serious adverse events
SafAS	Safety Analysis Set
SAP	Statistical analysis plan
SARS-COV-2	severe acute respiratory syndrome coronavirus 2
SE	stable emulsion
SIP	Shared Investigator Platform
SN	seroneutralization
SoA	Schedule of Activities
SOC	system organ class

SUSAR	suspected unexpected serious adverse reactions
TBD	to be determined
V	visit
WOCBP	Woman of Childbearing Potential

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12 Sponsor Signature Page

Signature Page for VV-CLIN-0615867 v3.0
Global-Pandemic-Flu-VAM00001-protocol-v2.0

Approve & eSign	[redacted] Clinical [redacted]