Title Page

Protocol Title:

Controlled Study of Immunogenicity and Safety of the Investigational vYF Candidate Vaccine in Comparison to YF-VAX in Adults

Study Code: VYF02

Amendment Number: Amendment 2

Compound: Yellow fever (YF) vaccine vYF

Study Phase: Phase II

Short Title:

Study on an Investigational Yellow Fever Vaccine Compared with YF-VAX in Adults in the USA

Sponsor Name and Legal Registered Address:

Sanofi Pasteur SA
14 Espace Henry Vallée, 69 007 Lyon, France

Manufacturer: Same as Sponsor

Regulatory Agency Identifier Number(s):

BB-IND: IND #: 019167

WHO UTN: U1111-1261-5612

Protocol Version Number: 4.0

Approval Date: 16 February 2022

Medical Monitor Name and Contact Information are provided in the Operating Guidelines.

The study centers, the Investigators at each center, and the Coordinating Investigator(s) are listed in a separate document.

Document History

Previous Version(s)	Date	Comments
1.0	02 February 2021	Version not submitted, internal version only.
2.0	09 March 2021	Version submitted to IRB and CBER
3.0	26 May 2021	Version submitted to IRB and CBER

Overall Rationale for the Amendment 1:

In answer to CBER's comments dated 14 May 2021, the assessment of safety will be completed with the assessment of biosafety (hematology and biochemistry, local laboratory) on D01 and D11 in the subset of the 90 participants randomized for the evaluation of the early immune response on D11 (no additional timepoint or visit for these participants); in addition more information will be added in the methods of contraception (Appendix 10.4) and in the collection of MAAEs (Appendix 10.3.1).

Overall Rationale for the Amendment 2:

Investigators alerted the Sponsor of barriers to enrolment:

- due to the wording of the Exclusion criterion #E01 restricting the participation in another clinical study during the first 2 years of the follow-up; the wording is revised in order to authorize study participants to participate to another study from Year 1 onwards.
- due to the difficulties for Investigational Sites to recruit study participants as planned, and more particularly in the context of the SARS-CoV-2 crisis with emergence of new stains/variants, leading to i) Investigational Sites to re-orient their activities on COVID-19 researches; ii) potential participants to favor joining a COVID-19 vaccine trial; iii) potential participants to be immunized against COVID-19 via the immunization programs implemented (primary vaccination and/or booster vaccination).

Taking into account that students might be proposed to participate in another study and might be relocated in another state during the 5-year follow-up period, the Sponsor proposes that the site visits during the long-term follow-up might be replaced by home visits where the participant is relocated, depending on current regulation. Alternative option would be to refund travel cost (reasonable domestic travel costs). To maximize the retention of participants in the study during the long-term follow-up, phone calls in between 2 yearly visits from Year 1 to Year 5 are added during the 5-year follow-up to remind the enrollees to not miss the yearly visits in the defined time-window.

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1 Protocol Summary

1.1 Synopsis

Protocol Title:

Controlled Study of Immunogenicity and Safety of the Investigational vYF Candidate Vaccine in Comparison to YF-VAX in Adults

Short Title:

Study on an Investigational Yellow Fever Vaccine Compared with YF-VAX in Adults in the USA

Rationale:

A first study, VYF01, conducted in the USA assessed the safety, viremia and immune responses of 3 dosages of vYF and YF-VAX as a control vaccine.

The proposed study VYF02 is a Phase II, randomized, observer-blind, active-controlled (YF-VAX) study to assess the non-inferiority of the immune response, in terms of seroconversion rates of the investigational vaccine candidate vYF to the licensed YF-VAX in adults aged 18 years up to 60 years in the USA. The study will also assess the immunogenicity profile (seroprotection rate, geometric mean titer [GMT] and GMT ratio [GMTR]) and the safety profile of vYF and YF-VAX. It is planned to enroll 570 participants in 2 groups in a 2:1 ratio: 380 participants will be administered vYF and 190 participants will be administered YF-VAX at D01.

YF-VAX, the YF vaccine, currently licensed and in use in the USA, will be the control vaccine.

An Independent Data Monitoring Committee (IDMC) will be set up in the vYF program, including VYF02 and the non-inferiority studies of vYF compared to YF-VAX or Stamaril in adult and pediatric populations.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Immunogenicity • To demonstrate the non-inferiority of the antibody response in terms of seroconversion rate 28 days after vaccine administration of one dose of vYF (administered on D01) compared to the antibody response after one dose of the YF-VAX control vaccine (administered on D01) in YF-naïve participants*.	• Seroconversion rates will be assessed 28 days post-vYF (administered on D01) and post-YF-VAX (administered on D01) in a YF microneutralization (MN) assay Seroconversion is defined as a 4-fold increase in neutralizing antibody (NAb) titers as compared to the pre-vaccination value. With a nominal value of half LLOQ, ie, 5 (1/dil), assigned to baseline YF seronegative participants, the seroconversion requires an increase to at least a titer of 20 (1/dil) on 28 day post-vaccination.
Secondary	
Immunogenicity • To describe the immune response to YF in both vaccine groups using YF MN assays before (D01) and after (D11 in a subset only†, D29, M6, and yearly from Y1 to Y5) vYF or YF-VAX administration.	Seroconversion and seroprotection rates at various timepoints, based on YF NAb assessments using the YF MN assay for each group. Seroprotection is defined as NAb titers ≥ threshold of 10 (1/dil). Data will be analyzed depending on Flavivirus (FV) immune status at baseline (YF-naïve and immune, FV-naïve and immune: dengue serotypes 1-4 naïve and immune, Zika-naïve and immune).
Safety • To describe the safety profile of vYF vaccine in comparison to the safety profile of the control YF-VAX. • To describe the biosafety profile of vYF in comparison to the biosafety profile of the control YF-VAX in a subset only†.	• Presence, nature (MedDRA preferred term), duration, intensity and relationship to vaccination of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination • Presence, time to onset, number of days of presence, and intensity of solicited injection site reactions up to 7 days after vaccination • Presence, time to onset, number of days of presence, and intensity of solicited systemic reactions up to 14 days after vaccination • Presence, nature (MedDRA preferred term), time to onset, duration, intensity, and relationship to vaccination of unsolicited AEs up to 28 days after vaccination and adverse events of special interest (AESIs‡) up to 6-months after vaccination • Presence of any serious adverse events (SAEs) up to 6-months after vaccination

Objectives	Endpoints
	• Presence of related SAEs and all deaths from D01 up to the 5 years after vaccination • Hematology and biochemistry out-of-range test results at D01 and D11 in a subset only†.
Exploratory	
To describe the serological status of FV infection (dengue and Zika) in the study population at baseline	NAb levels against FV infection (dengue and Zika) in a blood sample taken at baseline

D: day; FV: flavivirus; M: month; MedDRA: Medical Dictionary for Regulatory Activities; Y: year
* YF-naïve participants (or negative) at baseline correspond to participants with no detectable YF antibody (Ab) titers before vaccination. YF seronegative at baseline is defined as a titer < LLOQ for the assay (any participant with a baseline titer ≥ LLOQ will be eliminated from the primary analysis [Per-protocol analysis]).
LLOQ determined as 10 (1/dil), also defined the threshold of protection.

†A subset of the first 90 participants (60 participants in Group 1 and 30 participants in Group 2) enrolled at some sites will provide an additional post-vaccination blood sample on D11 to assess the immune response elicited by both vaccines in terms of NAb titers and biological safety parameters on D01 and D11.
‡The following AESIs have been defined for this clinical development program based upon the prior experience with YF vaccines:
- Serious hypersensitivity/allergic reactions
- Organ failure/serious viscerotropic events
- Serious neurologic events

Overall Design

Type of design	parallel, multi-center
Phase	II
Control method	active-controlled (control = YF-VAX) Ratio vYF: YF-VAX of 2:1
Study population	healthy adults 18-60 years of age
Country	USA
Level and method of blinding	observer-blind (modified double-blind)
Study intervention assignment method	randomization
IDMC	Yes

Disclosure Statement:

This is a parallel-group prevention study with 2 arms that is observer-blinded (participant and Investigator blinded).

Number of Participants:

A total of 570 participants are expected to be randomized.

- Group 1: vYF; N=380
- Group 2: YF-VAX; N=190

A subset, of the first 90 participants randomized in Groups 1 and 2 (60 participants in Group 1 and 30 participants in Group 2) enrolled at selected sites, will provide an additional post-vaccination blood sample on D11 to assess the immune response elicited by both vaccines in terms of NAb titers, and biological safety parameters (hematology and biochemistry) on D01 and D11.

Intervention Groups and Duration:

In each group, eligible participants (18-60 years of age) will be randomized in a 2:1 ratio to receive a single subcutaneous (SC) injection of either the vYF vaccine (380 participants) or YF-VAX (190 participants) on D01.

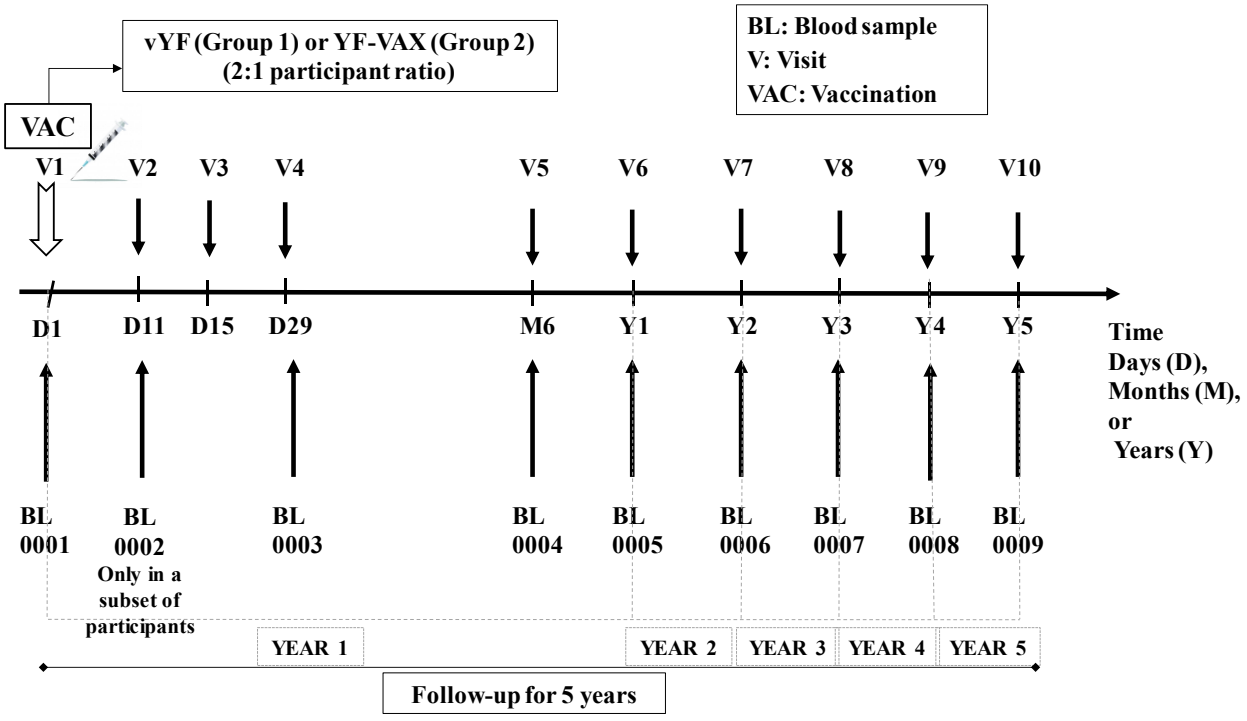
The duration of each participant's participation will be approximately 5 years.

Data Monitoring Committee: Yes

1.2 Schema

The graphical design of VYF02 study is presented in Figure 1.1.

Figure 1.1: Graphical study design



1.3 Schedule of Activities (SoA)

Visits procedures are detailed in the Operating Guidelines.

Table 1.1: Schedule of activities

Phase II Study, 9 or 10 Visits, 1 Vaccination, 8 or 9* Blood Samples, 5-year Duration Per Participant**

Visit/Contact	***Collection of information in the CRF***	**Visit 1**	**Visit 2†**	**Visit 3‡**	**Visit 4**	**Visit 5**	**Visit 6††**	**Visit 7††**	**Visit 8††**	**Visit 9††**	**Visit 10††**
Study timelines (days/months/ years)	N/A	**D01**	**D11**	**D15**	**D29**	**6 M post visit 1**	**1 Y post visit 1**	**2 Y post visit 1**	**3 Y post visit 1**	**4 Y post visit 1**	**5 Y post visit 1**
Time windows (days)	N/A	N/A	+2 days	+2 day	+3 days	±15 days	±15 days	±15 days	±30 days	±30 days	±30 days
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Visit/Contact	***Collection of information in the CRF***	**Visit 1**	**Visit 2†**	**Visit 3‡**	**Visit 4**	**Visit 5**	**Visit 6††**	**Visit 7††**	**Visit 8††**	**Visit 9††**	**Visit 10††**
Study timelines (days/months/ years)	N/A	**D01**	**D11**	**D15**	**D29**	**6 M post visit 1**	**1 Y post visit 1**	**2 Y post visit 1**	**3 Y post visit 1**	**4 Y post visit 1**	**5 Y post visit 1**
Time windows (days)	N/A	N/A	+2 days	+2 day	+3 days	±15 days	±15 days	±15 days	±30 days	±30 days	±30 days
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Visit/Contact	***Collection of information in the CRF***	**Visit 1**	**Visit 2†**	**Visit 3‡**	**Visit 4**	**Visit 5**	**Visit 6††**	**Visit 7††**	**Visit 8††**	**Visit 9††**	**Visit 10††**
Study timelines (days/months/ years)	N/A	**D01**	**D11**	**D15**	**D29**	**6 M post visit 1**	**1 Y post visit 1**	**2 Y post visit 1**	**3 Y post visit 1**	**4 Y post visit 1**	**5 Y post visit 1**
Time windows (days)	N/A	N/A	+2 days	+2 day	+3 days	±15 days	±15 days	±15 days	±30 days	±30 days	±30 days
[redacted]											

AE: adverse event; AESI: adverse events of special interest, BL: blood sampling; CRF: case report form; D: day; M: month; min: minutes; mL: milliliter; N/A: not applicable; Pre-vac: pre-vaccination; SAE: serious adverse event Vac: vaccination

[redacted]

† Visit 2 to be performed only for the subset of participants submitted to an additional immunogenicity test at D11 and to biological safety parameters assessment on D01 and D11

‡ Visit 3 can be replaced by a phone call only in case the visit cannot be performed at Investigational site (in this case, the physical examination will not be performed)

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

‡‡Only for pregnancies with estimated conception date within the 28 days before or after study vaccination

** Phone call in between 2 yearly visits from Visit 6 (Year 1) to Visit 10 (Year 5) could be performed to enable the participant to attend the yearly visit.

††Yearly visit can be replaced by a home visit according to local regulation in case the participant is relocated in another state.

Table 1.2: Blood samples collection per visit and participant

	mL	Tests
HIV test	3.0	HIV*
Immunogenicity	10.0	NAb titers
Sero status	10.0	Pre-existing FV NAb titers
Biochemistry and hematology†	10.0	ALT, AST, CPK, alkaline phosphatase, bilirubin, creatinine, CRP RBC count, hemoglobin, hematocrit, MCV, platelets count, WBC count, quantitative differential counts

HIV: human immunodeficiency virus; FV: flavivirus; mL: milliliter; NAb: neutralizing antibody.

* At Visit 1, HIV test if no evidence of seronegativity in the 90 days preceding vaccination.

2 Introduction

Yellow fever (YF) is a mosquito-borne hemorrhagic disease caused by a single-stranded positive ribonucleic acid (RNA) virus belonging to the genus flavivirus (FV). The virus causes a hemorrhagic fever, systemic illness characterized by high viremia, and a wide spectrum of clinical signs, ranging from mild symptoms to severe illness (including hepatic, renal and myocardial injury, and hemorrhage) with high lethality. YF is widespread in sub-Saharan Africa and tropical South America and continues to be a significant health problem to residents of endemic countries and non-vaccinated domestic and international travelers entering endemic areas.

Approximately 200 000 YF-associated cases and 60 000 YF-associated deaths have been estimated to occur worldwide each year (1). The case-fatality ratio of severe YF varies widely in different studies but is typically 20% or higher (2). Jaundice or other gross evidence of severe liver disease is associated with higher mortality rates (3). The incidence rate of YF cases has not decreased over the last decade and resurgence continues with geographical expansion. For a two-week stay, the estimated risks for illness and death due to YF for an unvaccinated traveler to West Africa is 50 cases per 100 000 and 10 cases per 100 000, respectively, and to South America is 5 cases per 100 000 and 1 case per 100 000, respectively. From 1970 through 2013, a total of 11 cases of YF were reported in unvaccinated travelers from the USA and EU who traveled to West Africa (6 cases) or South America (5 cases); 8 (73%) of these 11 travelers died (4).

There is no specific treatment for YF; however, medicines can be used to relieve the symptoms and may improve the outcome for seriously ill patients.

Outbreaks occur regularly, and the disease progresses quickly, as one infected individual can lead to infection of 7 other individuals.

Recent outbreaks in Africa were reported in Angola and Democratic Republic of Congo (DRC) in 2016. The outbreak in Angola started in December 2015, peaked in February 2016, and continued until June 2016 (largest outbreak since 1971), with 4 347 suspected cases and 377 deaths. Multiple vaccination campaigns required 20 million doses, leading to a problem of vaccine supply and demand. Moreover, there were outbreaks in other countries due to movement of virus-infected travelers, and imported cases were reported in DRC, Mauritania, Kenya, and China (infected Chinese workers returning from Angola) (5); it was estimated that there should be 2 800 suspected cases, requiring a further 9.4 million doses.

A recent outbreak in Brazil was composed of 2 waves of transmission, one during the 2016-2017 seasonal period, with 778 human cases, including 262 deaths, and another during the 2017-2018 seasonal period, with 1 376 human cases, including 483 deaths (6).

Human cases reported during the 2018-2019 seasonal period in 4 municipalities in Sao Paulo State, as well as the confirmation of epizootics in the state of Parana, mark the beginning of what could be a third cycle and a progression of the outbreak towards the Southeast and South regions of the country. The government of Brazil, with the support of the Pan American Health Organization/World Health Organization (WHO) is working to ensure the protection of its population and to prevent further spread of the YF virus. Brazil is carrying out vaccination campaigns for YF in several states, while strengthening surveillance and case management throughout the country. The number of areas with recommended vaccination has increased from 3 526 municipalities in 2010 to 4 469 municipalities in 2018, and the entire country starting in 2019. In line with the WHO guidelines, Brazil has adopted a single dose vaccination scheme for YF since April 2017 (6). From 2020, a booster dose at 4 years of age was implemented in the National Immunization Calendar of Brazil for infants who received their first dose at 9 months old (7).

The number of cases reported during 2017-2018 in the region of the Americas exceeded the number reported in several decades. In South America, besides Brazil, 6 other countries reported confirmed cases of YF: Bolivia, Colombia, Ecuador, French Guiana, Surinam and Peru (8). In Peru, between epidemiological week 1 and 52 of 2018, there were 20 cases of YF reported, including 6 deaths. Among the 20 cases, 12 were laboratory-confirmed. This figure is higher than the one reported during the same period in 2017, when 10 cases of YF were confirmed (6).

YF cases were for the first time reported in China in April 2016: 11 laboratory-confirmed cases had been imported into China (including 6 in Fujian Province, the area where dengue transmission has occurred); 6 of the cases were fatal (9). The YF cases reported in China suggest that not all travelers were effectively vaccinated despite Chinese public health regulations. With a large expatriate Chinese community (approximately 20 000) in Angola, additional undetected cases may likely have been imported.

No drug has demonstrated specific benefit to treat YF disease; therefore, the management of the disease is supportive and based on symptoms and the organ systems affected. However, YF is a vaccine-preventable disease, and the occurrence of outbreaks shows that maintaining regular vaccine stockpiles is necessary to fight the disease. Each year, 6 million doses of YF vaccine are maintained by WHO and partners in a global stockpile that can be used for outbreak response at the request of countries with inadequate vaccine supply; in contrast, the recent outbreaks in

Angola and DRC used approximately 30 million doses and depleted the stockpile multiple times during 2016 (10).

Worldwide, there are several YF vaccines currently in use, all based on live-attenuated strains derived from the 17D attenuated strain and produced in embryonated eggs. Two of them, YF-VAX (Sanofi Pasteur Inc., Swiftwater, Pennsylvania) and Stamaril® (Sanofi Pasteur, France) are produced by Sanofi Pasteur and indicated for individuals from 9 months of age for active immunization against YF disease. Moreover, Stamaril is WHO prequalified, as are some of the other licensed YF vaccines.

Both YF-VAX and Stamaril are live-attenuated vaccines derived from strain 17D-204, a higher passage of the 17D strain. YF-VAX is the only YF vaccine licensed in the USA by the USA Food and Drug Administration (FDA), and is used for military and civilian travelers. [redacted] (11).

For most healthy individuals, a single dose of a live-attenuated YF vaccine provides long-lasting protection. In May 2014, the WHO World Health Assembly adopted an amendment which stipulated that the period of protection by YF vaccination and the term of validity of the certificate will change from 10 years to the duration of a person's life. This amendment became effective in June 2016. On 26 February 2015, the Advisory Committee on Immunization Practices voted that a single primary dose of YF vaccine provides long-lasting protection and is adequate for most travelers. To comply with WHO International Health Regulations (IHRs) and to be officially recognized, YF vaccines must be administered by Health Care Providers (HCPs) certified to administer YF vaccine and validate the International Certificate of Vaccination or Prophylaxis (ICVP) for YF vaccination. In the USA, HCPs are authorized to administer the vaccine by state health departments. The validity period of the ICVP is established according to IHR recommendations and starts 10 days after primary vaccination and immediately after re-vaccination.

Despite the advances in immunization activities, challenges remain in controlling epidemics due to the management of global vaccine supply, including an emergency stockpile and the control of outbreaks. The low yields of manufacturing processes are responsible for this situation and make YF vaccines still an unmet public health need in case of large outbreaks.

YF is also a viral hemorrhagic fever that perpetually threatens US military forces, Department of Defense (DoD) civilians and military dependents traveling or deploying to endemic regions such as Sub-Saharan Africa, South America, and the Caribbean. Additionally, large parts of Southeast Asia, the Middle East, North Africa and even North America to include the southern United States are at risk for YF outbreaks given the widespread prevalence of the *Aedes* mosquito vector for the YF virus. 600 million people live in endemic areas and more than 2 billion are at potential risk for an emergent outbreak of the disease. Thus, deployed military forces, dependents and civilians are at risk in any area of responsibility.

YF-VAX is currently in use by the DoD and is the only FDA approved YF vaccine. However, recent epidemics coupled with manufacturing delays have caused an unprecedented global shortage of the vaccine, prompting the use of an alternative, European-licensed vaccine in the US

through investigational new drug status. Additional, expected outbreaks will only exacerbate the shortage of this vaccine. Lack of access to vaccine would not only threaten the health of DoD personnel traveling to at risk regions, but also negatively impact mission accomplishment as legal travel between multiple countries is contingent upon proof of vaccination. The current study seeks to evaluate the next-generation vaccine developed and produced in a manner that would obviate manufacturing delays and, hence, improve the reliable accessibility to YF vaccine for all DoD personnel.

A safe and efficacious YF vaccine, produced with significantly higher yields than the current ones, is therefore required, to enable the continuation of immunization programs and to provide protection to populations residing in YF endemic or epidemic regions and to travelers who will spend time in these areas. The development of a high-quality new YF vaccine, manufactured with high yields in extensively characterized Vero cells in the absence of animal serum, and purified and controlled in conformance with international Good Manufacturing Practice standards, represents an advantage over other currently available vaccines produced in embryonated eggs.

2.1 Study Rationale

A first study, VYF01, aimed to assess the safety, viremia and immune responses of 3 dosages of vYF and of YF-VAX, as a control vaccine, in the USA is completed. YF-VAX is currently licensed and in use in the USA.

The proposed study VYF02 is a Phase II, randomized, observer-blind, active-controlled (YF-VAX) study to assess the non-inferiority of the immune response, in terms of seroconversion rates, of the investigational vaccine candidate vYF to the licensed YF-VAX in adults aged 18 years up to 60 years in the USA. The study will also assess the immunogenicity profiles (seroprotection rates, GMTs and GMTR) and the safety profiles of vYF and YF-VAX. It is planned to enroll 570 participants in 2 groups in a 2:1 ratio: 380 participants will be administered vYF and 190 participants will be administered YF-VAX on D01. The persistence of the immune response over time, up to 5 years post-vaccination, will be assessed yearly.

VYF02 assessment will be based on immunogenicity and safety profiles of the vYF vaccine in comparison to YF-VAX, which is the current YF vaccine licensed in the US in travelers and military personal.

The YF neutralizing antibody titers will be determined in a microneutralization assay that was developed by Sanofi Pasteur and used in VYF01. The final analysis on the 73 participants randomized (72 participants of them vaccinated with either vYF 4 Log $CCID_{50}$/dose, 5 Log $CCID_{50}$/dose, 6 Log $CCID_{50}$/dose or YF-VAX) shows that in all vaccines group GMT well above the threshold of protection were observed on D28 post vaccine administration (Per-Protocol analysis in YF-naïve population[a]) and that 100% of YF-naïve participants seroconverted[b] and

[a] YF-naïve population, or YF negative population, corresponds to participants with no pre-existing (ie, no detectable as below LLOQ equal to 10 (1/dil) which also defines the threshold for protection) Ab titers. Those participants are given a value equal to half LLOQ, ie, 5 (1/dil).

[b] In VYF01, seroconversion is achieved for a 4-fold increase as compared to pre-vaccination value; and in YF-naïve participants seroconversion is achieved for a value equal or greater than 40 (1/dil).

were seroprotected on D28. The satisfactory safety profile of all vYF dosage groups and the measurement of quantified viremia over time from D01 to D15 completed the interim analysis. Therefore, the dosage of 5 Log $CCID_{50}$/dose is deemed appropriate for the next phases of the clinical development of vYF, starting with VYF02, which is the first non-inferiority study in adults.

VYF02 is designed to assess the immune response and the maintenance of the antibody titers over time up to 5-year post vaccine administration as the existing YF vaccines are well known for inducing a long-lasting immunity. In addition, a subset of participants will be assessed on D11 to describe the early immune response induced in the 2 vaccine groups, and biological safety parameters on D01 and D11.

The AESIs that are considered for the development of vYF were defined based on the knowledge of existing YF vaccines licensed by Sanofi Pasteur (YF-VAX and Stamaril):

- Serious hypersensitivity/allergic reactions
- Organ failure/serious viscerotropic events
- Serious neurologic events.

2.2 Background

As for the existing licensed YF vaccines, the new vYF vaccine is a live-attenuated vaccine derived from the wild-type Asibi strain. It is being developed as an alternative to the egg-based vaccines, as manufactured in extensively characterized Vero cells, in the absence of animal serum, hence potentially also increasing vaccine safety.

Therefore, it should facilitate the management of YF vaccine outbreaks and epidemics which is challenging due to limited amounts of YF vaccine stocks. The development of a new attenuated live vYF vaccine, manufactured in extensively characterized Vero cells represents a major progress. The safety, immunogenicity and clinical efficacy of this new vaccine is planned to be compared to the Sanofi Pasteur licensed YF vaccines and VYF02 is the first non-inferiority study in adult populations in the USA.

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks, reasonably expected adverse events (AEs), the potential risks, and uncertainties of vYF vaccine candidate may be found in the Investigator's Brochure (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: Potential risks of clinical significance and risk management

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
Investigated Vaccine: vYF		
The following AESIs have been defined for this clinical development program based upon the prior experience with YF vaccines:		
Serious hypersensitivity/allergic reactions (eg, anaphylaxis)	All vaccines have the potential to cause allergic reactions or anaphylaxis in individuals who may be sensitized to components of the vaccine.	Exclusion criteria E07 (Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances) 30-minute observation period after vaccination for early detection and treatment
Organ failure/serious viscerotropic events (YF vaccine-associated viscerotropic disease [YEL-AVD]) Serious neurologic events (YF vaccine-associated neurotropic disease [YEL-AND]) YEL-AVD and YEL-AND are theoretical risks for the studied vaccine, according to preclinical tests.	Serious AE related to YF vaccines are YEL-AVD and YEL-AND. They are very rare and thus unlikely to be seen in the setting of a clinical trial.	Exclusion criteria E10 (personal or family history of thymic pathology [thymoma, thymectomy, or myasthenia]) for those at increased risk. Observation period of 28 days after vaccination for early detection and treatment. Addressed in the "Operating Guidelines for Assessing Viscerotropic and Neurotropic AEs" in studies using YF vaccines (standalone guidance provided to the Investigational sites before the start of the study).
Comparator: YF-VAX		
Severe allergic reactions (eg, anaphylaxis) may occur following the use of YF-VAX, even in individuals with no prior history of hypersensitivity to the vaccine components.	Identified and potential risks observed in post-marketing surveillance.	Exclusion criteria E07 (Known systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccines used in the study or to a

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
		vaccine containing any of the same substances) YF-VAX is contraindicated in anyone with a history of acute hypersensitivity reaction to any component of the vaccine, in infants less than 9 months of age due to an increased risk of encephalitis, in individuals with severe immunosuppression Exclusion/inclusion criteria take in account contraindications, warnings and precautions as defined in product label. See Section 5 of this document. 30-minute observation period after vaccination for early detection and treatment
Organ failure/serious viscerotropic events (YEL-AVD) Serious neurologic events (YEL-AND) There is an increased risk of severe systemic adverse reactions to YF-VAX in individuals 60 years of age and older and in immunocompromised individuals.	Serious AE related to YF vaccines are YEL-AVD and YEL-AND. They are very rare and thus unlikely to be seen in the setting of a clinical trial. Refer to the IB Section 6 for more information regarding the data from previous experience	Exclusion criterion E10 (Personal or family history of thymic pathology |thymoma, thymectomy, or myasthenia]) for those at increased risk. Observation period within 28 days after vaccination for early detection and treatment. Inclusion criteria I01 state the upper limit of age up 60 years on the day of inclusion[a] Exclusion criterion E05 (Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy) Addressed in: -IB (administration precautions, potential adverse events), defined AESI in the trial. "Operating Guidelines for Assessing Viscerotropic and Neurotropic Adverse Events in studies using YF vaccines" (standalone guidance provided to the Investigational sites before the start of the study)

[a] "18 to 60 years" means from the day of the 18th birthday up to the day before the 60th birthday

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Risk Management
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	30-minute observation period after vaccination for early detection and treatment

2.3.2 Benefits from Study Participation

This study is experimental research and there is no guarantee that participants enrolled in VYF02 will get any benefit.

vYF is a next-generation live-attenuated YF vaccine produced on serum-free Vero cells without any component of animal origin. vYF has been developed to induce a life-long immunity against YF and to be at least as immunogenic as other licensed YF-17D vaccines and well-tolerated.

Participants enrolled in VYF02 will be followed up yearly up to 5 years post vaccine administration to assess the maintenance over time of the immune response.

It is expected that participants enrolled in VYF02 will be protected against YF, which means that both the new investigational vaccine as well as the current licensed YF-VAX vaccine, elicit a safe, protecting, and long-lasting immune response.

International Certificate of Vaccination or Prophylaxis for YF Vaccination

At the end of the first interim analysis and at the end of the study, the Investigators will be provided with individual listings detailing for each participant the vaccine group assignment and the neutralizing antibody titers at the successive time points. Participants are responsible for contacting the study site to find out which study group they were assigned to and which vaccine they received.

Participants enrolled in the YF-VAX group can be provided by the investigational site with the ICVP for YF vaccination, while those enrolled in a vYF group would be informed that they need to obtain a licensed YF vaccine prior to travel to endemic areas.

2.3.3 Overall Benefit-Risk Conclusion

Vaccination is the most effective preventive measure against YF infection. The important potential risks for vYF are those currently described for YF-VAX and Stamaril: anaphylaxis, YEL-AVD and YEL-AND. However, data from nonclinical studies suggest that the risk of occurrence of YEL-AVD and YEL-AND following vYF administration is theoretical. These

potential and theoretical risks will be specifically monitored during the VYF02 study and addressed through pharmacovigilance activities.
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 demonstrate the non-inferiority of the antibody response in terms of seroconversion rate 28 days after vaccine administration of one dose of vYF (administered on D01) compared to the antibody response after one dose of the YF-VAX control vaccine (administered on D01) in YF-naïve participants*.	• Seroconversion rates will be assessed 28 days post-vYF (administered on D01) and post-YF-VAX (administered on D01) in a YF MN assay in YF-naïve participants Seroconversion is defined as a 4-fold increase in NAb titers as compared to the pre-vaccination value. With a nominal value of half LLOQ, ie, 5 (1/dil), assigned to baseline YF seronegative participants, the seroconversion requires an increase to at least a titer of 20 (1/dil) on 28 day post-vaccination.
Secondary	
Immunogenicity • To describe the immune response to YF in both vaccine groups using YF MN assays before (D01) and after (D11 in a subset† only, D29, M6, and yearly from Y1 to Y5) vYF or YF-VAX administration	YF antibody assessments will be performed using YF MN assay as follows for each group: NAb titers on D01, D11 (subset only†), D29, M6, and yearly from Y1 to Y5 Derived endpoints are: • Seroconversion rates: at D11 (subset only†) and D29, M6, and yearly from Y1 to Y5 Seroconversion is defined as a 4-fold increase in NAb titers: i) as compared to the D01 titers at each time point up to M6; ii) as compared to the last planned previous time point from Y1 onwards

Objectives	Endpoints
	• Seroprotection rates: participants with antibody titer ≥ 10 (1/dil) at baseline (D01), at D11 (subset only†), D29, M6, and yearly from Y1 to Y5 • Geometric means of the individual titer ratios (GMTRs) for D11/D01 (subset only†), D29/D01, M6/D01 and yearly ratios. The corresponding parameters are seroconversion rate, seroprotection rate, GMT, and GMTR. Seroprotection is defined as NAb titers ≥ threshold of 10 (1/dil). Data will be analyzed depending on FV immune status at baseline (YF-naïve and immune, FV-naïve and immune: dengue serotypes 1-4 naïve and immune, Zika-naïve and immune).
Safety • To describe the safety profile of vYF vaccine in comparison to the safety profile of the control YF-VAX • To describe the safety of vaccination in all participants up to 28 days after vaccination • To describe all serious adverse events (SAEs) up to 6-month follow-up • To describe related SAEs and all deaths from D01 to 5 years after vaccination • To describe all AESIs up to 6-month after vaccination‡ • To describe the biosafety profile of vYF in comparison to the biosafety profile of the control YF-VAX in a subset only	• Presence, nature (Medical Dictionary for Regulatory Activities [MedDRA] preferred term), duration, intensity and relationship to vaccination of any unsolicited systemic adverse events (AEs) reported in the 30 minutes after vaccination • Presence, time to onset, number of days of presence, and intensity of solicited (pre-listed in the participant's diary and electronic case report form [eCRF]) injection site reactions up to 7 days after vaccination • Presence, time to onset, number of days of presence, and intensity of solicited systemic reactions up to 14 days after vaccination • Presence, nature (MedDRA preferred term), time to onset, duration, intensity, and relationship to vaccination (for systemic AEs only) of unsolicited (spontaneously reported) AEs, including AESIs, up to 28 days after vaccination • Presence of any serious adverse events (SAEs) including serious AESIs, up to 6-month after vaccination • Presence of related SAEs and all deaths from D01 to 5 years after vaccination

Objectives	Endpoints
	• Hematology and biochemistry out-of-range test results at D01 and D11 in a subset only†.
Exploratory	
To describe the serological status of FV infection (dengue and Zika) in the study population at baseline	• NAb levels against FV infection (dengue and Zika) in a blood sample taken at baseline

AESI: adverse event of special interest; D: day; eCRF: electronic case report form; FV: flavivirus; GMT: geometric means titer; GMTR: geometric means of titer ratio; M: month; MN: microneutralization; NAb: neutralizing antibody; Y: year; YF: yellow fever.
* YF-naïve participants (or negative) at baseline correspond to participants with no detectable YF antibody (Ab) titers before vaccination. YF seronegative at baseline is defined as a titer < LLOQ for the assay (any participant with a baseline titer ≥ LLOQ will be eliminated from the primary analysis [Per-protocol analysis]).
LLOQ determined as 10 (1/dil), also defined the threshold of protection.
‡ The following AESIs have been defined for this clinical development program based upon the prior experience with YF vaccines:
• Serious hypersensitivity/allergic reactions
• Organ failure/serious viscerotropic events
• Serious neurologic events
†A subset of the first 90 participants (60 participants in Group 1 and 30 participants in Group 2) enrolled at some sites will provide an additional post-vaccination blood sample on D11 to assess the immune response elicited by both vaccines in terms of NAb titers, and biological safety parameters on D01 and D11.

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	II
Control method	active-controlled (control = YF-VAX) ratio 2:1
Study population	healthy adults aged 18 to 60 years*
Level and method of blinding	observer-blind (modified double-blind)
Study intervention assignment method	randomization
Number of participants	570 participants
Intervention groups	In each group, randomization to receive either the vYF vaccine candidate or the YF-VAX vaccine, in a 2:1 ratio

Total duration of study participation	approximately 5 years
Countries	USA
Use of an Independent Data Monitoring Committee	YES (IDMC), see Section 9.6

*"18 to 60 years" means from the day of the 18th birthday up to the day before the 60th birthday

4.2 Scientific Rationale for Study Design

The proposed study VYF02 is a Phase II, randomized, observer-blind, active-controlled (YF-VAX) study to assess the non-inferiority of the immune response, in terms of seroconversion rates, of the investigational vaccine candidate vYF at the selected dose of 5 Log $CCID_{50}$/dose to the licensed YF-VAX in adults aged 18 years up to 60 years in the USA. The study will also assess the immunogenicity profiles (seroprotection rates, GMTs and GMTRs) and the safety profiles of vYF and YF-VAX. It is planned to enroll 570 participants distributed in 2 groups with a 2:1 ratio: 380 participants will be administered with vYF and 190 participants will be administered with YF-VAX on D01. A subset of 90 participants out of the 570 participants (60 participants from vYF Group and 30 participants from YF-VAX Group) will be assessed for the early immune response on D11 and for biosafety profile on D01 and D11.

YF-VAX, will be used in the control arm, being the YF vaccine licensed in the USA.

The study design is aligned with the WHO Technical Report Series (WHO TRS) recommendations (12) stated that the demonstration of an immune response to YF vaccination should be based on the measurement of neutralizing antibody titers both pre- and post-vaccination. The WHO TRS states in section C.2.1 that '*Geometric mean titers (GMTs), seroconversion rates and reverse cumulative distributions (RCDs) should be provided. Seroconversion may be defined as either a fourfold increase in neutralizing antibody or the induction of measurable neutralizing antibody in a previously seronegative individual'*. Therefore, the choice of the seroconversion rates for assessing the non-inferiority in studies carried out in adults and in pediatric populations is appropriate.

Only adults aged 18 to 60 years will be enrolled, as those over 60 years of age are at a higher risk of developing YEL-AVD or YEL-AND.

The number of participants in each group was defined based on statistical considerations for immunogenicity and safety (see Section 9.2). Primary analyses will be performed in YF-naïve population (Per-Protocol Analyses Set). The objective is to demonstrate that the humoral response (in terms of seroconversion) of vYF (Group 1) is non-inferior to YF-VAX (Group 2) 28 days after a single dose in YF-naïve participants.

A subset of 90 participants (60 participants in Group 1 and 30 participants in Group 2) enrolled in a limited number of sites will provide an additional post-vaccination blood sample at D11 to assess the immune response elicited by both vaccines, and biological safety parameters on D01 and D11.

Since participants will not be screened for a history of prior FV infection or vaccination, it is likely that some participants have evidence for past FV infection or vaccination by the assessment

of FV serostatus at baseline. Given the small numbers of FV-experienced individuals expected in USA settings, the absence of any safety concern for FV-seropositive individuals receiving the investigational vaccination and the infeasibility of performing, offsite, virus neutralization titers in the course of participant recruitment, the assessment at baseline of FV serostatus will not be used as a criterion for study eligibility. FV- or YF-seropositive participants will therefore not be excluded from the study and seroconversion will be evaluated in this population as a secondary objective.

In addition, for the purpose of assessing the impact on immunogenicity, neutralizing antibody titers against a panel of epidemiologically important and immunologically relevant FVs (such as Zika virus, or dengue serotypes 1-4 viruses) will be measured on baseline sera, prior to vaccination, for the analysis of the immune response based on serostatus at baseline.

As a secondary objective for this Phase II study, safety of the new vYF vaccine candidate will be also described.

As a consequence, the total enrolled cohort is 570 participants (380 participants in Group 1 [vYF] and 190 participants in Group 2 [YF-VAX]).

4.3 Justification for Dose

The yVF dose selected for this study is of 5 Log $CCID_{50}$/dose, based on preclinical immunogenicity and toxicity study results and the safety, viremia and immunogenicity data generated in the first-in-human VYF01 study.

4.4 End of Study Definition

A participant is considered to have completed the study if he/she has completed the last visit planned in the schedule of activities (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.

All participants enrolled in this study will be followed up for 5 years after vaccine administration. They will be kept in the study (and so, will not be withdrawn) even if they fail to come to one or more of the yearly visits during the 5-years follow-up. In the event blood samples taken during home visits might be acceptable as regards to the current regulation, the yearly visits could in exceptional circumstances be replaced by home visits.

5 Study Population

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

5.1 Inclusion Criteria

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

I01: Aged 18 years to 60 years on the day of inclusion[a]

I02: 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 postmenopausal for at least 1 year, or surgically sterile.

OR

- Is of childbearing potential and agrees to use an effective contraceptive method or abstinence[b] from at least 4 weeks prior to study intervention administration until at least 4 weeks after 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) before any dose of study intervention on Day 1 and will be repeated on D29 to confirm the participant is still not pregnant within the 28 days of vaccine administration

I03: Informed consent form has been signed and dated

I04: Able to attend all scheduled visits and to comply with all study procedures

5.2 Exclusion Criteria

Potential participants will be recruited from a pool of volunteers who meet site-specific screening requirements.

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

E01: Participation at the time of study enrollment (or in the 4 weeks preceding the study vaccination) or planned participation during the first year of the 5-year follow-up in another clinical study investigating a vaccine, drug, medical device, or medical procedure. Enrollment in another study after the first year is permitted (starting the first day of Year 2, and onwards), assuming it does not exclude participation in this study.

E02: Receipt of any vaccine in the 4 weeks preceding the study vaccination or planned receipt of any vaccine in the 4 weeks following the study vaccination (prior to Visit 4), except for influenza vaccination, which may be received at least 2 weeks before study vaccines. This exception includes pandemic influenza vaccines including monovalent pandemic influenza vaccines.

E03: Previous vaccination against a FV disease at any time including YF with either the study vaccine or another vaccine.

E04: Receipt of immune globulins, blood, or blood-derived products in the past 6 months.

[a] "18 to 60 years" means from the day of the 18th birthday up to the day before the 60th birthday

[b] See Appendix 10.4

E05: 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).

E06: Known history of FV infection.

E07: Known systemic hypersensitivity to any of the vaccine components, eggs, or history of a life-threatening reaction to the vaccines used in the study or to a vaccine containing any of the same substances[a].

E08: Known history or laboratory evidence of HIV infection.

E09: Known history of hepatitis B or hepatitis C seropositivity

E10: Personal or family history of thymic pathology (thymoma, thymectomy, or myasthenia).

E11: Deprived of freedom by an administrative or court order, or in an emergency setting, or hospitalized involuntarily.

E12: Alcohol, prescription drug, or substance abuse that, in the opinion of the Investigator, might interfere with the study conduct or completion.

E13: Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion[b], including malignancy, such as leukemia, or lymphoma.

E14: Moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination or febrile illness (temperature ≥ 100.4°F). A prospective participant should not be included in the study until the condition has resolved or the febrile event has subsided.

E15: Administration of any anti-viral within 2 months preceding the vaccination and up to the 6 weeks following the vaccination.

E16: 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.

E17: Planned travel in a YF endemic country within 6 months of investigational or control vaccine administration.

If the participant has a primary physician who is not the Investigator, the site may contact this

[a] The components of the Study Interventions are listed in Table 6.1 and the components of the study intervention in the Investigator Brochure

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

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.

There is no screening period in this study. However, in case of an eligibility criterion requiring specific procedures before enrolment of the participant in the study, or moderate or severe acute illness/infection or febrile illness (temperature ≥ 100.4°F) on the day of vaccination, the enrolment can be postponed until the additional information is available or the condition is resolved.

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

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. Screening information is recorded in the source documents.

6 Study Intervention

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: routine vaccines administered outside of study protocol are not considered as study interventions.

6.1 Study Interventions Administered

Study interventions are described in Table 6.1.

Table 6.1: Identity of study interventions

Intervention Name	vYF	YF-VAX
Use	Investigational product	Licensed Active comparator
IMP and NIMP	IMP	IMP
Type	Vaccine	Vaccine
Dose Formulation	Powder and diluent for suspension for injection	Powder and diluent for suspension for injection
Unit Dose Strength	Each single dose of 0.5 mL contains 5 Log $CCID_{50}$/dose of lyophilized vYF-247 attenuated strain of YF virus	Each single dose of 0.5 mL contains at least 4.74 Log plaque-forming units (PFU) of 17D-204 attenuated strain of YF virus
Excipients/Diluent	Diluent for reconstitution: sterile 0.4% sodium chloride solution	Diluent for reconstitution: sterile 0.9% sodium chloride solution
Dosage Levels	0.5 mL per dose	0.5 mL per dose
Number of Doses / Dosing Interval	1 dose at D01	1 dose at D01
Route of Administration	SC injection	SC injection
Site of Administration	Deltoid area in the upper arm	Deltoid area in the upper arm
Sourcing	Provided by the Sponsor	Provided by the Sponsor
Packaging and Labeling	Each dose of the different vaccines (vYF and YF-VAX) will be in an individual box that will be identified by a dose number. Each box will contain a vial with the powder of YF vaccine and either a pre-filled syringe (for vYF vaccine) or a vial (for YF-VAX vaccine) containing the diluent. Each box of vaccine dose will bear both detachable and fixed labels for identification.	
Current/Former Names or Aliases	Not applicable	YF-VAX®
Batch Number	TBD	TBD

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

6.2 Preparation/Handling/Storage/Accountability

Detailed guidance and information are provided in the Operating Guidelines that will be provided to each Investigational site before the start of the study.

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 are provided in the Operating Guidelines.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Randomization and Allocation Procedures

If the participant is eligible for inclusion in the trial (meets the inclusion/exclusion criteria and signs the inform consent form [ICF]), the Investigator will contact the Interactive Response Technology (IRT) to obtain the participant number and the randomized vaccine to administer to the participant at Visit 1.

Randomization will be stratified by site and by age group. Two age groups will be defined: 18 to 45 years[a] and 46 to 60 years[b].

Participants will be randomly assigned to the study vaccine Groups 1 (vYF) or 2 (YF-VAX) in a 2:1 ratio. Site staff will connect to the IRT, enter the identification and security information, and confirm a minimal amount of data in response to IRT prompts. The IRT will then provide the dose number assignment and have the site staff confirm it.

The full detailed procedures will be described in the Operating Guidelines and the IRT manual which will be provided to all sites prior to study start. If the participant is not eligible to participate in the study, then the information will only be recorded on the participant recruitment log with the reason (inclusion, exclusion, or at the Investigator's request).

Participant numbers that are assigned by the IRT consisting of a 12-digit string (a 3-digit country identifier, a 4-digit study center identifier, and a 5-digit participant identifier). The leading number of last 5-digit identifier will be indicator of subsets.

Participant numbers should not be reassigned for any reason. The randomization codes will be kept securely in the IRT. No replacement will be made for randomized participants who terminated the study early.

[a] "18 to 45 years" means from the day of the 18th birthday up to the day before the 46th birthday

[b] "46 to 60 years" means from the day of the 46th birthday up to the day before the 61th birthday

6.3.2 Blinding and Code-breaking Procedures

The VYF02 study is a Phase II, randomized, observer-blind, active-controlled, non-inferiority study to the YF-VAX control vaccine.

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

Investigators, Sponsor, and study staff who conduct the safety assessment and the participant will not know which vaccine is administered.

Only the study staff who prepare and administer the vaccine and are not involved with the safety evaluation ("vaccinator") will know which vaccine is administered. The "vaccinator" or authorized designee will have to ensure that the documents on randomization are stored in a secure place where only he/she has access.

The code may be broken in the event of an AE only when the identification of the vaccine 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 delegate through the IRT system, as explained in the code-breaking procedures described in the Operating Guidelines. Once the emergency has been addressed by the site, the Investigator or a delegate must notify the Sanofi Pasteur Responsible Medical Officer (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 case report form (CRF) is to be completed.

The Institutional Review Boards (IRB)/Independent Ethics Committees (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 Sanofi Pasteur 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 Harmonization (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 vaccine or group assignment) will not be communicated to either the Investigator or the immediate team working on the study, except for the GPV representative.

  by the IDMC if needed to facilitate their assessment of safety.

The code-breaking procedures are described in the Operating Guidelines.

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 noncompliance is documented so that it can be accounted for in the data analyses:

- All study intervention 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

6.5 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 medication(s) of interest beginning on the day of first vaccination. This may include medications of interest that were started prior to the day of vaccination.

Reportable medications will be collected in the CRF from the day of each vaccination to the end of the solicited and unsolicited follow-up period.

Reportable medications include medications that impact or may impact the consistency of the safety information collected after any vaccination and/or the immune response to vaccination. Three standard categories of reportable medications are defined:

- Category 1: medications impacting or that may have an impact on the evaluation of the safety (eg, antipyretics, analgesics, and non-steroidal anti-inflammatory drugs [NSAIDs], systemic steroids/corticosteroids)
- Category 2: 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 Global Clinical Immunology [GCI] department or other testing laboratories, systemic steroids/corticosteroids, immune-suppressors, immune-modulators with immunosuppressive properties, anti-proliferative drugs such as DNA synthesis inhibitors)
- Category 3: medications impacting or that may have an impact on both the safety and the immune response (eg, systemic steroids/corticosteroids)

Dosage and administration route, homeopathic medication, topical and inhaled steroids, as well as topical, ophthalmic, and ear treatments will not be recorded. Topical analgesics should not be applied at the site of vaccination; however, if they are applied inadvertently to the vaccination site, they should be recorded as a Category 1 medication in this specific instance.

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 CRF unless the medication(s) received belongs to one of the pre-listed categories. Medications will not be coded.

6.5.1 Rescue Medicine

Appropriate medical equipment and emergency medications, including epinephrine (1:1 000), must be available on site in the event of an anaphylactic, vasovagal, or other immediate allergic reaction.

6.6 Dose Modification

Not applicable.

6.7 Intervention After the End of the Study

Not applicable.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Not applicable as there is only one vaccination.

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, compliance, or administrative reasons. This is expected to be uncommon.
- The reason for withdrawal should be clearly documented in the source documents and in the CRF: Adverse Event, Lost to Follow-up, Protocol Deviation, or Withdrawal by Participant.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may 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 samples taken and not tested, and the Investigator must document this in the site study records.
- Withdrawn participants will not be replaced. However, all participants enrolled in this study will be followed up for 5 years after vaccine administration. They will be kept in the study (will not be withdrawn) even if they fail to come to one or more of the yearly visits during the 5-year follow-up.

Follow-up of Discontinuations

For participants who have prematurely terminated the study, 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.

For participants where the reason for early termination is lost to follow-up, the site will not attempt to obtain further safety information. See Section 7.3 for definition of “lost to follow-up”.

7.3 Lost to Follow-up

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 and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not 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), or at least to determine his/her health status while fully respecting his/her rights. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 10.1.

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.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

Urine and blood samples will be collected as described in the SoA Table (Section 1.3).

The maximum amount of blood collected from each participant over the 5-year duration of the study, including any extra assessments that may be required, will [redacted] mL, see Table 8.1. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Table 8.1: Blood sampling volume (mL) per visit

Visit Number (V)	V1* Vaccination	V2 (subset of 90 participants only)	V3	V4	V5	V6	V7	V8	V9	V10
Trial timelines (days, months or years)	D01	D11	D15	D29	M6 (D180)	Y1 (D360)	Y2 (D720)	Y3 (D1080)	Y4 (D1440)	Y5 (D1800)
Time windows (days)	NA	+ 2	+ 2	+ 3	± 15	± 15	± 15	± 30	± 30	± 30
Immunogenicity assessments										
[redacted]										
[redacted]										
TOTAL	[redacted]									

NA: not applicable
*3 more mL of blood sample may be collected at V1 in case a HIV test needs to be performed

Guidance and information for the sample collection, preparation, storage, and shipment are provided in the Operating Guidelines.

8.1 Efficacy and Immunogenicity Assessments

8.1.1 Efficacy Assessments

No efficacy data will be obtained in the study.

8.1.2 Immunogenicity Assessments

The primary objective of this study is to demonstrate the non-inferiority of the antibody response in terms of seroconversion rates 28 days after vaccine administration of one dose of vYF administered on D01 compared to the antibody response after one dose of the YF-VAX (control vaccine) administered on D01 in a YF-naïve population. YF-naïve participants (or negative) at baseline correspond to participants with no detectable YF Ab titers before vaccination. YF seronegative at baseline is defined as a titer < LLOQ for the assay (any participant with a baseline

titer ≥ LLOQ will be eliminated from the primary analysis [Per-protocol analysis]). LLOQ determined as 10 (1/dil), also defined the threshold of protection.

Seroconversion is defined as a 4-fold increase in NAb titers, as compared to the pre-vaccination value, while seroprotection is defined as NAb titers ≥ threshold of 10 (1/dil).

The secondary objectives are to describe the immune response to YF in both vaccine groups using YF MN assays before (D01) and after vYF or YF-VAX administration, by determining seroconversion and seroprotection as well as GMT and GMTR in all participants at several timepoints (D11 in a subset only, D29, M6, and yearly from Y1 to Y5).

All secondary objectives will be analyzed depending on the flavivirus status at baseline (YF-naïve and immune, dengue serotypes 1-4 naïve and immune, Zika-naïve and immune, and FV-naïve and immune).

8.1.2.1 Immunogenicity Endpoints

For all objectives, YF antibody assessments will be performed using the YF MN assay.

For the primary objective, seroconversion will be assessed 28 days post-vYF (administered on D01) and post-YF-VAX (administered on D01) in YF-naïve participants.

For the secondary objectives, YF antibody assessments will be performed as follows for each group:

- NAb titers at D01, D11 (subset only), D29, M6, and yearly from Y1 to Y5

Derived endpoints are:

- Seroconversion rates at D11 (subset only) and D29, M6, and yearly from Y1 to Y5

  Seroconversion is defined from M6 onwards as a 4-fold increase in NAb titers: i) as compared to the D01 titers at each time point up to M6; ii) as compared to the last planned previous time point from Y1 onwards
- Seroprotection rates based on participants with antibody titers ≥ 10 (1/dil) at baseline (D01) and at D11 (subset only), D29, M6, and yearly from Y1 to Y5
- GMTRs for D11/D01 (subset only), D29/D01, M6/D01 and yearly ratios.

The corresponding parameters are seroconversion rate, seroprotection rate, GMT, and GMTR

Data will be analyzed depending on FV immune status at baseline (FV-naïve and immune: YF-naïve and immune, Dengue serotypes 1-4 naïve and immune, Zika-naïve and immune, and JE-naïve and immune in participants enrolled in Asia)

8.1.2.2 Immunogenicity Assessment Methods

YF MN Method Description (all Participants, visits V1 and V4 to V10 for the main cohort, and visits V1, V2, and V4 to V10 for the subset of participants)

YF NAb titers will be measured using a MN assay. Serial, 2-fold dilutions of serum to be tested (previously heat-inactivated) are mixed with a constant concentration of the YF vaccinal strain 17D. The mixtures are inoculated into wells of a 96-well microplate with permissive Vero cells

and incubated for 2 days. A reduction in virus infectivity (viral antigen production) due to neutralization by antibody present in serum samples is detected by enzyme linked immunosorbent assay (ELISA). After washing and fixation, YF viral antigen production in cells is detected by successive incubations with a flavivirus-specific mAb, horse radish peroxidase anti-mouse immunoglobulin G (IgG) conjugate, and a chromogenic substrate. The resulting optical density is measured using a microplate reader. The reduction in YF virus infectivity as compared to that in the virus control wells constitutes a positive neutralization reaction indicating the presence of NAbs in the serum sample. The method was qualified by assessing precision, specificity, LLOQ, and dilutability. To verify the LLOQ of 10, a panel of 17 additional human serum samples diluted in a negative serum targeting a titer of ½ of the LLOQ to exactly the LLOQ was tested 11 times by 2 qualified analysts in 2 independent assay runs. This data supports that the LLOQ of 10 was verified for the YFV MN assay and LOD can be considered as equivalent to LLOQ (LOD = LLOQ):

- LLOQ determined as 10 (1/dil) with the MN assay defines the threshold of protection; a subject presenting with detectable Ab (≥ LLOQ) is considered as protected against YF virus
- As LOD = LLOQ, YF-naïve population, or YF negative population, corresponds to participants with no pre-existing Ab titers ie, no detectable as below LLOQ equal to 1:10. Those participants are given a value equal to half LLOQ, ie, 5 (1/dil)
- Seroconversion is defined as having at least a 4-fold increase of Ab titers as compared to baseline (pre-vaccination value); Sanofi Pasteur would like to consider this 4-fold increase in Ab titers for both participants with or without pre-existing Ab titers:
    - For participants assigned with a value at baseline of 10 (LLOQ) or more, 1/dil, seroconversion means values of 40 (1/dil), or more post-vaccination.
    - For participants with a nominal value of 5 (half LLOQ) 1/dil assigned to baseline YF seronegative participants, this means that seroconversion requires an increase to at least a titer of 20 (1/dil) on day 28 post-vaccination.

The assay was deemed suitable for its intended use to quantitate YF NAb in human serum. Laboratory technicians conducting the immunogenicity assays will be blinded to the group to which each participant was assigned.

The YF MN assay will be performed at Sanofi Pasteur GCI, Swiftwater, Pennsylvania, or at a qualified contract laboratory for GCI.

Zika MN method description (all participants, samples from V1)

Zika NAbs will be measured using a MN assay. Serial, 2-fold dilutions of serum to be tested (previously heat-inactivated) are mixed with a constant concentration of Zika virus. The mixtures are inoculated in duplicate into wells of a 96-well microplate with permissive Vero cells. After adsorption, cells are incubated for 4 days. A reduction in virus infectivity (viral antigen production) due to neutralization by antibody present in serum samples is detected by ELISA. After washing and fixation, Zika viral antigen production in cells is detected by successive incubations with flavivirus-specific mAb, horseradish peroxidase goat anti-mouse IgG conjugate, and a chromogenic substrate. The resulting optical density is measured using a microplate reader.

The reduction in Zika virus infectivity as compared to that in the virus control wells constitutes a positive neutralization reaction indicating the presence of NAbs in the serum sample (13). The LLOQ of the assay is 10 (1/dil).

Dengue PRNT method description (all participants, samples from V01)

Dengue neutralizing Ab levels will be measured by plaque reduction neutralization test (PRNT) (using parental dengue virus strains of CYD dengue vaccine constructs) by Sanofi Pasteur GCI, Swiftwater, USA (or outsourced with a GCI selected external laboratory). Serial, 2-fold dilutions of serum to be tested (previously heat-inactivated) are mixed with a constant challenge-dose of each dengue serotype 1, 2, 3 or 4 (expressed as PFU/mL). The mixtures are inoculated into wells of a microplate with confluent Vero cell monolayers. After adsorption, cell monolayers are incubated for a few days. A reduction in virus infectivity due to neutralization by Ab present in serum samples is detected. The reported value (end point neutralization titer) represents the highest dilution of serum at which ≥ 50% of dengue challenge virus (in plaque counts) is neutralized when compared to the negative control wells which represents the 100% virus load. The endpoint neutralization titers are presented as continuous values. The LLOQ of the assay is 10 (1/dil). The PRNT assay data will be used for the baseline serostatus analyses.

The Zika microneutralization assay and the dengue PRNT method assay will be performed at Sanofi Pasteur GCI, Swiftwater, Pennsylvania, or at a qualified contract laboratory for GCI.

NAbs against other flaviviruses from participant may be assessed during the course of study analysis if deemed appropriate. The same methodology will be used for other viruses.

8.2 Safety Assessments

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

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

At each visit, the Investigator or a delegate will perform physical examination and will ask the participant about any solicited reactions (D01 to D14) and unsolicited AEs (D01 to D29) recorded in the DC, as well as about any other AEs that may have occurred since the previous visit. All relevant data will be transcribed into the CRF according to the instructions provided by the Sponsor.

In addition, a subset of 90 participants will be assessed for biosafety (hematology and biochemistry) on D01 and then on D11.

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.

8.2.2 Physical Examinations

At each visit, the Investigator or a delegate will perform a clinical examination[a]. 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 (see Section 10.3.5.1.1 for more details).

No other vital signs (eg, blood pressure, pulse rate) will be collected in the CRF.

8.2.4 Clinical Safety Laboratory Assessments

Urine pregnancy testing will be performed in women of childbearing potential before vaccination (D01) and repeated on D29.

Blood samples will be taken on D01 and D11 in a subset of 90 participants for the determination of biochemistry (ALT, AST, CPK, alkaline phosphatase, bilirubin, creatinine, CRP) and hematology (RBC count, hemoglobin, hematocrit, MCV, platelets count, WBC count, quantitative differential counts) parameters.

8.2.5 Viremia/Vaccinemia

Viremia will not be evaluated in this study.

8.3 Adverse Events and Serious Adverse Events

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 (see Section 7).

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 vaccination to ensure their safety.

The post-vaccination observation period should be documented in the source document.

[a] In case the D15 visit is replaced by a phone call, the physical examination will not be performed.

Reactogenicity

Solicited injection site reactions will be collected from the day of vaccination (D01) until 7 days after vaccination (D08).

Solicited systemic reactions will be collected from the day of vaccination (D01) until 14 days after vaccination (D15).

The solicited injection site reactions and systemic reactions that are pre-listed in the diary cards 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 (D01) until 28 days after vaccination (D29).

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 up to D29 as part of the unsolicited AEs; up to M6 post-vaccination as part of the SAE (Serious MAAE) and at any time during the study as part of SAEs that are related or fatal (serious related or fatal MAAE).

Adverse Events of Special Interest (AESIs)

AESIs will be collected from D01 to Month 6, and serious AESIs will be collected as SAEs.

See Section 8.3.6 for the list of AESIs.

SAEs

Information on SAEs will be collected and assessed throughout the study, from inclusion at D01 until 6 months after vaccination, and related SAEs and death will be collected throughout the study, up to 5 years after vaccination. However, before the first study intervention administration, only SAEs related to study procedures are to be collected.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will not be recorded on the AE section of the case report book (CRF).

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 AE or SAE 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 Diary cards (DCs), specifically designed for this study by the Sponsor and provided to the study sites, will be given to study participants for the recording of daily safety information.

These diary cards 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 an authorized designee will interview the participants to collect the information recorded in the diary card or memory aid and will attempt to clarify anything that is incomplete or unclear. All clinical study information gathered by the study site will be reported electronically by the Investigator or authorized designee using a web based CRF. Any information that was not documented in the diary card will first be captured in the source document and then reported electronically.

The 6-month follow-up will be done by interviewing participants either during a visit or over the telephone using a questionnaire to capture SAEs and serious AESIs, if applicable.

The method of recording, evaluating, and assessing causal relationship of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

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

Unless a participant refuses further contact, each participant who experiences an AE (whether serious or non-serious) during the study must be followed until the condition resolves, becomes stable, or becomes chronic (even after the end of the participant's participation in the study) if *either* of the following is true:

- The AE is considered by the Investigator to be related to the study intervention administered
- The AE caused the discontinuation of the participant from the study or from vaccination

The Investigator will inform the Sponsor of the date of final disappearance of the event or the date of "chronicity" establishment.

8.3.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a 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.
- For all studies except those investigating medical devices Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

- 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.

8.3.5 Pregnancy

Pregnancy is an exclusion criterion for enrollment in this study, but a participant could potentially become pregnant during her participation.

Details of all pregnancies in female participants which started within the minimal period of requested contraception (from 4 weeks before to 4 weeks after study intervention administration) will be collected by the Investigator and recorded in the Pregnancy CRF. 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. Any data collected after CRF lock will be transmitted to the pharmacovigilance department on the paper form.

- If a pregnancy is reported, the Investigator should inform the Sponsor within 1 month of learning of the pregnancy and should follow the procedures outlined in Appendix 10.4.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse Events of Special Interest

The following AESIs have been defined for this clinical development program based upon the prior experience with YF vaccines:

Serious hypersensitivity/allergic reactions

- Organ failure/serious viscerotropic[a] events (YEL-AVD)
- Serious neurologic[b] events (YEL-AND)

The scope of AESIs is larger than the scope of corresponding potential risks, and eligible events are considered AESI even if they are considered unrelated to the vaccination. AESIs will be assessed as per appropriate Brighton Collaboration and/or Advisory Committee on Immunization Practices (ACIP) definitions. Specific guidelines are provided to the Investigator to help in the detection and evaluation of AEs that may raise suspicion of potential vaccine viscerotropism or

[a] As defined in Brighton collaboration criteria for viscerotropic disease, including but not limited to: liver dysfunction (AST and ALT ≥ 3xULN or total bilirubin ≥ 1.5xULN); renal impairment (blood urea nitrogen or creatinine ≥ 1.5 x ULN if no history of renal disease, or ≥ 1.5 x patient's baseline if history of renal disease); thrombocytopenia < 100 000/µl; CPK ≥ 5xULN; respiratory failure; requirement for vasopressor drugs to maintain systolic blood pressure etc.

[b] As defined in ACIP criteria for neurologic and neurotropic disease, including but not limited to: focal neurologic dysfunction (ataxia, aphasia, paresis etc.), new onset of seizure, aseptic meningitis, encephalopathy, encephalitis, autoimmune disease with central (ADEM) or peripheral (GBS) nervous system involvement.

neurotropism (see "Operating Guidelines for Assessing Viscerotropic and Neurotropic Adverse Events in studies using YF vaccines").

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 Treatment of Overdose

Since the study intervention is administered by a health care professional and it is in a single dose vaccine administration at the first visit, it is unlikely that overdose by injection occurs.

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

1) Contact the Medical Monitor immediately
2) Closely monitor the participant for any AE/SAE
3) Document the quantity of the excess of the overdose in the source documents

8.5 Pharmacokinetics

Pharmacokinetics parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

No other biomarkers than those described in the immunogenicity assessments section (Section 8.1.2) or the biosafety assessment (Section 8.2.4) are evaluated in this study.

8.9 Immunogenicity Assessments

See Section 8.1.2.

8.10 Medical Resource Utilization and Health Economics

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

9 Statistical Considerations

All statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics Platform using the Statistical Analysis Software (SAS) at least version 9.4 (SAS Institute, Cary, NC, USA).

A detailed Statistical Analysis Plan (SAP) will be written before the database lock. Based on the protocol, the SAP will describe all analyses to be performed as well as statistical tables, and listings.

9.1 Statistical Hypotheses

Primary objective:

A non-inferiority approach will be used to compare the post-vaccination seroconversion rates of vYF and YF-VAX groups in YF-naïve participants. Details on statistical methods are provided in Section 9.4.

Secondary and observational objectives:

No hypotheses will be tested. The analyses will be descriptive.

9.2 Sample Size Determination

The sample size is based on the primary objective and on the safety secondary objectives.
A total of 570 participants are expected to be enrolled in the study, using a 2:1 repartition (380 in vYF and 190 in YF-VAX).

Considering a potential attrition rate of [redacted], such sample size would provide 456 evaluable participants with 304 participants enrolled in Group 1 (vYF) and 152 in Group 2 (YF-VAX). This will give [redacted] power (Farrington and Manning formula) to declare the non-inferiority of Group 1 (vYF) versus Group 2 (YF-VAX) based on seroconversion rate of [redacted] at D29 after a single dose of the investigational or control vaccine, assuming:

A one-sided alpha level of [redacted]

A non-inferiority margin δ of [redacted]

The subset sample size has been arbitrarily set to 90 participants, in which 60 participants will be enrolled in Group 1 and 30 participants will be enrolled in Group 2.

9.3 Populations for Analyses

The following populations are defined:

Population	Description
Randomized	All participants with data in the CRF.

Full analysis set (FAS)	Subset of randomized participants who received at least 1 dose of the study vaccine or control vaccine and had a valid post-vaccination blood sample result. Participants will be analyzed according to the intervention to which they were randomized.
Safety Analysis Set (SafAS)	Participants who have received at least 1 dose of the study vaccines. All participants will have their safety analyzed according to the vaccine they actually received. Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).
Per-protocol analysis set (PPAS)	Subset of the FAS. Participants presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS: Participant is not YF-naïve Participant did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria. 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 Non-availability of other critical measurements for the primary analysis: • Baseline serology sample was not collected in the protocol-specified time window or the serology sample was not drawn • Participant did not provide the post-dose serology sample on Day 29 visit (D28 after vaccination) in the proper time window or the blood sample was not drawn • Participant received any therapy / medication / vaccine which could inhibit the immune response until the time point considered for the analysis (Day 29, Visit 4). In addition to the reasons listed above, participants will also be excluded from the PPAS if their baseline or post-vaccination serology on D29 (Visit 4) did not produce a valid test result (ie, results for all antigens are missing or out-of-range). This list may not be exhaustive. The above protocol deviations leading to exclusion from the PPAS may be detailed and completed if necessary, in the SAP following a data review. The PPAS definition

	will be finalized before the database lock (and code-breaking if applicable) In the event of a local or national immunization program with a eg, pandemic influenza vaccine, any other vaccine as needed, participants who receive 1 or more doses of eg, a pandemic influenza vaccine, or the vaccine listed above at any time during the study will not be withdrawn from the study.

9.4 Statistical Analyses

The SAP will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

Primary analyses will be performed on the Per-Protocol Analyses Set.

The objective is to demonstrate that the humoral response (in terms of seroconversion) of vYF (Group 1) is non-inferior to YF-VAX (Group 2) 28 days after a single dose in YF-naïve participants.

The percentages of participants with seroconversion 28 days after vaccination will be used to compare responses between Group 1 and Group 2 with the following hypotheses:

- H0 (Null hypothesis): $p(vYF)-p(YF\text{-}VAX) \leq -\delta$
- H1 (Alternative hypothesis): $p(vYF)-p(YF\text{-}VAX) > -\delta$

Where δ the non-inferiority margin is set to 5%.

Where p(vYF) and p(YF-VAX) are the proportion of participants with seroconversion. Seroconversion is defined as a fourfold increase in NAb titers as compared to pre-vaccination value.

The non-inferiority will be demonstrated if the lower limit of the 2-sided 95% confidence interval (CI) of the difference between the 2 percentages is > -5%.

The CI of the difference in percentages will be computed using the Wilson score method without continuity correction as quoted by Newcombe (14) for seroconversion rates.

9.4.2 Secondary Endpoints

The statistical analysis for secondary objectives will be descriptive.

Immunogenicity:

Analyses will be performed per vaccine group on the Full Analyses Set.

The immunogenicity parameters will be described per vaccine group. Immunogenicity analyses will be provided on participants by YF serostatus and by FV serostatus.

The following parameters will be analyzed:

- GMTs for each vaccine group
- Seroconversion rates using previous timepoint as reference: number and percentage of participants in each vaccine group converted with neutralizing antibody titer 4-fold increase compared to the previous time point, at D11 compared to D01 (subset only), at D29 compared to D01, at M6 compared to D01, at Y1 compared to M6, at Y2 compared to Y1, at Y3 compared to Y2, at Y4 compared to Y3, at Y5 compared to Y4
- Within groups, GMTRs for each vaccine group post-vaccination injection, compared to D01 (D11/D01 [subset only], D29/D01, M6/D01 and then yearly ratios: Y1/M6, Y2/Y1, Y3/Y2, Y4/Y3, Y5/Y4 (see Section 8.1.2.1)
- Number and percentage of participants (seroprotection rates) in each vaccine group with antibody titers $\geqslant$ 10 (1/dil) at baseline (D01) and at D11 (subset only), D29, M6, and yearly from Y1 to Y5

The 95% CIs will be calculated using:

- The normal approximate method for GMTs and GMTRs
- The exact binomial distribution for percentages (Clopper-Pearson's method, quoted by Newcombe)

Assuming that log10 transformation of the titers/ratios follows a normal distribution, first, the mean and 95% CI will be calculated on log10 (titers/ratios) using the usual calculation for normal distribution, then antilog transformations will be applied to the results of calculations, to compute GMTs/GMTRs and their 95% CIs.

Safety:

Safety results will be described per vaccine groups on the SafAS. The main parameters for the safety endpoints will be described by 95% CIs of point estimates, calculated using the exact binomial distribution from Clopper-Pearson's method quoted by Newcombe (15) for proportions.

9.4.3 Exploratory Endpoints

Exploratory endpoints are NAb levels against FV infection (dengue and Zika) in a blood sample taken at baseline.

9.5 Interim Analyses

Interim Analyses

Six statistical analyses will be performed on data obtained from all participants.

The first interim analysis will be performed on the immunogenicity results obtained up to the D29 visit and safety data obtained up to the 6-month follow-up visit, then the successive interim analyses will be performed on data collected up to Y1 visit and not yet analyzed, then every year on the data gathered at each yearly visit up to 4 years after YF vaccine administration; these

results will be presented in an interim clinical study report (CSR) (immunogenicity data up to D29 and safety data up to M6) or CSR addendum (up to Y4).

Final Analysis

The final analysis will be performed at the end of the follow-up (5 years after YF vaccine injection).

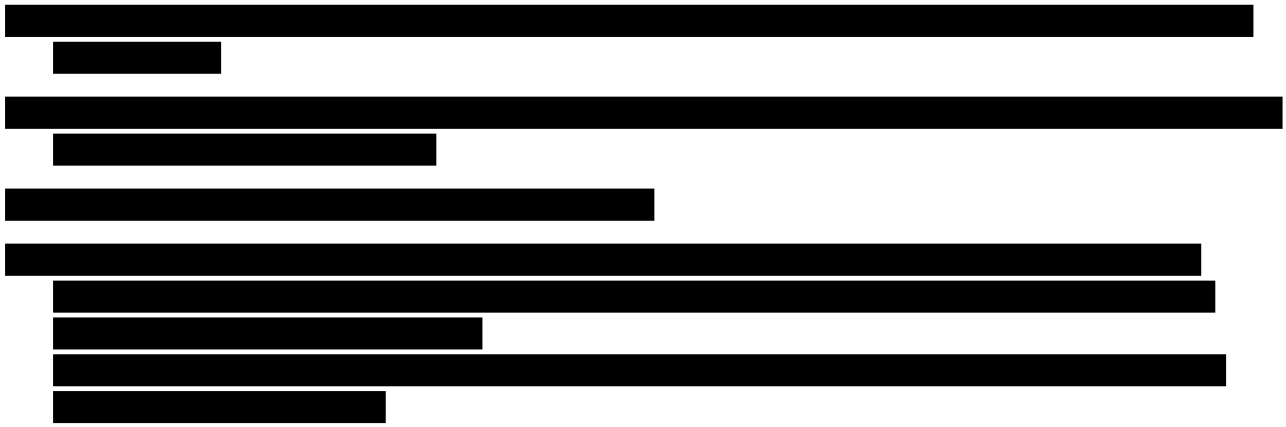
The SAP will describe the planned interim analyses in greater detail.

Ongoing Safety Surveillance

This study will not include an early safety data review. However, participant safety will be continuously monitored by the Sponsor's internal safety review committee: Safety Management Team (SMT) which includes safety signal detection at any time during the study.

This SMT led by the Global Safety Officer (GSO) includes core representatives from the Global Pharmacovigilance (GPV) Department and from the Clinical Department. The SMT is empowered to recommend a pause in recruitment while it investigates any potential signal or concern.

The enrollment will be paused if one of the following pausing/halting criteria that could potentially constitute an unreasonable and significant risk for study participants occurs:



The study can be resumed if investigations conclude that there is no unreasonable and significant risk for study participants.

9.6 Data Monitoring Committee (DMC)

An independent DMC (IDMC) will be utilized throughout this study, composed of external independent experts in relevant clinical specialties and at least one biostatistician knowledgeable about statistical methods for clinical trials and sequential analysis of study data.

The committee will periodically assess the progress of the clinical study, all safety data, and will recommend to Sanofi Pasteur whether to continue, modify, or stop the study. The IDMC will make recommendations to the Sponsor on a medical and ethical basis.

In case of safety concern raised by the IDMC, the Sponsor will decide whether further vaccine administration should be temporarily halted as a precautionary measure while investigating the potential safety signal.

For details on IDMC, refer to Appendix 10.1.5.

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, protocol amendments, 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
- The Investigator 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 (in addition to summaries required from the Sponsor).
  - 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.

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), and all other applicable local regulations

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 to the participant or his/her legally authorized representative and answer all questions regarding 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, Health Insurance Portability and Accountability Act (HIPAA) requirements, 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(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Recruitment Procedures
Potential participants will be recruited from a pool of volunteers who meet site-specific screening requirements.
Prior to enrollment, the Investigator, or a designee will complete the informed consent procedures with potentially eligible participants. After the participant has signed the ICF and (if applicable) after the participant has signed the assent form, and following confirmation by the Investigator that the participant has satisfied all inclusion / exclusion criteria, eligible participants will be included in the study and randomized by the Interactive Web Response Technology (IVRS/IWRS). They will provide their initial blood sample and will be vaccinated according to their IRT assigned study groups.

10.1.4 Data Protection and Future Use of Stored Samples

- All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR. 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 (eg, on African-American population for the FDA).
- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; 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 local data protection law. 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.
- 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.
- Participant data will be used for this study and in support of the whole drug development program for the Investigational Product, including negotiations with payers and publication of results.

- Any unused part of the serum samples will be securely stored at the Sanofi Pasteur serology laboratory (GCI) up to 25 years after the end of the study. These samples 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.
- The other biological samples collected to qualify the participant for inclusion in the study or to monitor his/her health are dedicated for immediate use. In case they 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.
- In addition, participants will be asked to indicate in the ICF whether they will permit the future use of any unused stored serum samples for other tests. If they refuse permission, the samples will not be used for any testing other than that directly related to this study. If they agree to this use, they will not be paid for giving permission. Anonymity of samples will be ensured. 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 or infectious diseases, or to improve existing tests or develop new tests to assess vaccines. Human genetic tests will never be performed on these samples without specific individual informed consent.

10.1.5 Committees Structure

This study will not include an early safety data review. However, participant safety will be continuously monitored by the Sponsor.

Moreover, an IDMC will be set up for VYF02.

10.1.6 Dissemination of Clinical Study Data

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.

10.1.7 Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRF 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.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (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).
- 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.
- 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.

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, diary cards, medical and hospital records, screening logs, informed consent / assent 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.

Detailed guidance and information are provided in the Operating Guidelines that will be provided to the Investigational site before the start of the study.

10.1.9 Study and Site Start and Closure

Details on which clinical supplies are provided by the Sponsor or the site are described in the Operating Guidelines.

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

The Sponsor 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:

- 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 recruitment of participants by the Investigator
- Discontinuation of further study intervention development

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

A urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) will be performed before vaccination at D01 (Visit 1) and at D29 (Visit 4). Pregnancy Testing is compulsory at V01 since pregnant women cannot be included in this study.

Biosafety parameters (hematology and biochemistry in a subset on D01 and D11) will be determined at the site local laboratory; laboratory values will be reported in the CRF and data categorized according to the toxicity grading scale presented in Appendix 10.3.5.2.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind the study will not be reported to Investigational sites until the study has been unblinded.

10.3 Appendix: Adverse Events: 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 conditions 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 which 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.

Note: any AEs at and around the NIMP injection / administration site regardless of its nature and onset is to be reported as unsolicited systemic AE since it does not occur at and around the IMP injection/administration site.

Adverse Event of Special Interest (AESI):

An adverse event of special interest (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.

For more detailed instructions on safety data collection, refer to the Sanofi Pasteur Safety Guideline.

Medically Attended AE (MAAE)

An MAAE is a new onset or a worsening of a condition that prompts the participant or participant's parent/legally acceptable representative 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 pediatric check-ups, follow-up visits of chronic conditions with an onset prior to entry in the study, and solicited reactions.

They are collected up to D29 as any other unsolicited AEs, up to M6 post-vaccination as any other SAE in case of a serious MAAE, and at any time during the study in case of a serious related or fatal MAAE.

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) which 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 not be immediately life-threatening or result in death or hospitalization but 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 or convulsions or development of intervention dependency or intervention abuse, new onset diabetes or autoimmune disease or suspected transmission of any infectious agent via an authorised 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 participant's 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 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).
- Details regarding SAE reporting can be found in the Operating Guidelines.

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: [redacted]
  - In PDF format to the following e-mail address, using a method of transmission that includes password protection: [redacted]
  - By express mail, to the following address: Global Pharmacovigilance, Sanofi Pasteur SA, 14 Espace Henry Vallée, F-69367 Lyon cedex 07, France

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 is provided in the Operating Guidelines. 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 10.1: Solicited injection site reactions: terminology, definitions, and intensity scales

CRF term (MedDRA lowest level term [LLT])	Injection site pain	Injection site erythema	Injection site swelling
Diary card term	Pain	Redness	Swelling
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
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. **Diary card:** Grade 1: No interference with usual activities Grade 2: Some interference with usual activities Grade 3: Significant; prevents usual activities	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

MedDRA: Medical Dictionary for Regulatory Activities

* For the scale will be provided in the CRF and the intensity will be transcribed from in the diary card. For other injection site reactions (erythema and swelling), 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 10.2: Solicited systemic reactions: terminology, definitions, and intensity scales

CRB term (MedDRA lowest level term [LLT])	Fever	Headache	Malaise	Myalgia
Diary card 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	**CRB:** 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.	**CRB:** 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.	**CRB:** 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: ≥ 38.5°C to ≤ 38.9°C, **or** ≥ 101.2°F to ≤ 102.0°F	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 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 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: ≥ 39.0°C **or** ≥ 102.1°F	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.	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.	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.
		Diary card:	**Diary card:**	**Diary card:**
		Grade 1: No interference with usual activities	Grade 1: No interference with usual activities	Grade 1: No interference with usual activities
		Grade 2: Some interference with usual activities	Grade 2: Some interference with usual activities	Grade 2: Some interference with usual activities
		Grade 3: Significant; prevents usual activities	Grade 3: Significant; prevents usual activities	Grade 3: Significant; prevents usual activities

MedDRA: Medical Dictionary for Regulatory Activities

* For all reactions (except fever), the scale will be provided in the CRF and the intensity will be transcribed from the diary card. For fever, will be recorded 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. 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 DC 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 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 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.
  - Diary card: No interference with usual activities.
- 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.
  - Diary card: Some interference with usual activities.
- 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.
  - Diary card: Significant; prevents usual activities.

10.3.5.2 Tables for Laboratory Abnormalities

The pre-defined intensity thresholds for laboratories abnormalities are shown in Table 10.3.

Table 10.3: Intensity grading scale for laboratories abnormalities

Laboratory Endpoint	Unit	Grade 1	Grade 2	Grade 3
Creatinine	mg/dL	1.5 – 1.7	1.8 – 2.0	> 2.0
CPK	mg/dL	1.25 – 1.5 x ULN	1.6 – 3.0 x ULN	> 3.0 x ULN
Alkaline phosphate – increase by factor		1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	> 3.0 x ULN
Liver Function Tests – ALT, AST increase by factor		> 1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	≥ 5.0 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test, increase by factor		1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	> 1.5 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor		1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	> 2.0 x ULN
Hemoglobin (Female)	gm/dL	11.0 – 12.0	9.5 – 10.9	< 9.5
Hemoglobin (Female) change from baseline value	gm/dL	Any decrease – 1.5	1.6 – 2.0	> 2.0
Hemoglobin (Male)	gm/dL	12.5 – 13.5	10.5 – 12.4	< 10.5
Hemoglobin (Male) change from baseline value	gm/dL	Any decrease – 1.5	1.6 – 2.0	> 2.0
WBC Increase	cell/mm^3	10 800 – 15 000	15 001 – 20 000	> 20 000
Decrease in WBC	cells / mm^3	2 500 – 3 500	1 500 – 2 499	< 1 500
Decrease in Lymphocytes	cells / mm^3	750 – 1 000	500 – 749	< 500
Decrease in Neutrophils	cells / mm^3	1 500 – 2 000	1 000 – 1 499	< 1 000
Decrease in Platelets	cells / mm^3	125 000 – 140 000	100 000 – 124 000	< 100 000
Eosinophils –	cell/mm^3	650 – 1 500	1 501 – 5 000	> 5 000

ULN: Upper Limit of Normal
LLN: Lower Limit of Normal
WBC: white blood cell
ALT: alanine aminotransferase
AST: aspartate transaminase

10.3.6 Visit to the Center in the Event of Severe (Grade 3) Fever, or Suspicion of Neurotropic Disease or Acute Viscerotropic Disease Within 28 Days of Vaccination

Participants will be instructed to inform (or to visit) the study site if participants develop severe (Grade 3) fever (≥ 39.0°C).

In the event of specific clinical symptoms (severe [Grade 3] fever, or suspicion of neurotropic diseases or acute viscerotropic diseases) within 28 days of vaccination, specimen (blood, body fluid or tissue samples) might be collected to support the diagnosis according to the local practice. The Investigator or authorized designee will:

- Perform a physical examination (including body temperature) and collect information in the source document
- Collect blood by venipuncture for assessment of biological safety[a] and detection of YF viremia
- Collect cerebrospinal fluid (CSF) for cultures and virological/bacterial research, when required
- Collect suspected diagnosis
- Treatment will be given according to local practices and standards by local HCPs
- Information collected at this visit will be recorded in the eCRF

In case a neurotropic disease or acute viscerotropic disease is suspected, it is strongly recommended that the Investigator follows the guidelines for the assessment of viscerotropic and neurotropic AEs. On the basis of the severity of the symptoms reported, the Investigator will decide whether body fluid or tissue samples may need to be collected to support the differential diagnosis or vaccine causality. YEL-AVD and YEL-AND will be reported as SAEs. Events suggestive of YEL-AND and YEL-AVD will be assessed as per ACIP case definition criteria.

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

[a] Biological Safety assessed at local laboratory

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.

COLLECTION OF PREGNANCY INFORMATION

Female Participants who become pregnant

The Investigator will only collect pregnancy information on any female participant who becomes pregnant while participating in this study with an estimated conception date within the 28 days before or after study vaccination. The initial information together with the contraceptive method if any will be recorded on the appropriate form and submitted to the Sponsor within 1 month of learning of a participant's pregnancy.

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 not be required for longer than 4 weeks 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.

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.

A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.

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.

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[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [b]
• Bilateral tubal occlusion
• 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.*
• **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[c] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[c] – 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[d] 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)[c]
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. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.
d) Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 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.

10.6 Appendix: Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	adverse events
AESI	adverse events of special interest
ALT	alanine aminotransferase
AR	adverse reactions
AST	aspartate transaminase
BL	blood sampling
CDISC	Clinical Data Interchange Standards Consortium
CDP	clinical development plan
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	case report form
CSR	clinical study report
D	day
DC	diary card
DENV	Dengue virus
DMC	Data Monitoring Committee
DoD	Department of Defense
DRC	Democratic Republic of Congo
ELISA	enzyme linked immunosorbent assay
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FV	flavivirus
GCI	Global Clinical Immunology
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMT	geometric mean titer
GMTR	geometric means of the individual titer ratios

GPV	Global Pharmacovigilance
HCP	Health Care Provider
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonization
ICVP	International Certificate of Vaccination or Prophylaxis
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committees
IgG	immunoglobulin G
IHR	International Health Regulations
IMP	investigational medicinal product
IRB	Institutional Review Boards
IRT	Interactive Response Technology
LLN	lower limit of normal
LLOQ	lower limit of quantitation
M	month
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
MN	microneutralization
NAb	neutralizing antibody
NIMP	non- investigational medicinal product
PPAS	per-protocol analysis set
RMO	Responsible Medical Officer
RNA	Ribonucleic acid
SAE	serious adverse events
SafAS	safety analysis set
SAP	statistical analysis plan
SC	subcutaneous

SmPC	Summary of Product Characteristics
SoA	schedule of activities
SUSAR	Suspected unexpected serious adverse reactions
ULN	upper limit of normal
V	visit
VAC	vaccination
WBC	white blood cell
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential
Y	year
YEL-AND	YF vaccine-associated neurotropic disease
YEL-AVD	YF vaccine-associated viscerotropic disease
YF	yellow fever

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12 Sponsor Signature Page

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Approve & eSign	[redacted] Clinical [redacted]