Controlled Study of Immunogenicity and Safety of the Investigational vYF Candidate Vaccine in Comparison to Stamaril® in Adults

Randomized, observer-blind, active-controlled, multi-center, Phase II study conducted in Europe and Asia. This SAP plans the analyses of the VYF03 study in which participants received vYF vaccine or Stamaril vaccine at 18 - 60 years of age.

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	VYF03
Development Phase:	Phase II
Sponsor:	Sanofi Pasteur SA 14 Espace Henry Vallée, 69 007 Lyon, France
Investigational Product(s):	Yellow fever vaccine vYF
Form / Route:	Powder and diluent for suspension for injection / Subcutaneous
Indication For This Study:	Immunogenicity evaluation of the vYF vaccine
Version and Date of the SAP core body part:	Version 4.0, 18JAN2023

Table of Contents

List of Tables **5**

List of Abbreviations **6**

1 Introduction **8**

2 Trial Objectives **9**

2.1 Primary Objective(s) 9

2.2 Secondary Objective(s) 9

2.3 Exploratory Objective(s) 9

3 Description of the Overall Trial Design and Plan **10**

3.1 Trial Design 10

3.2 Trial Plan 11

4 Endpoints and Assessment Methods **14**

4.1 Objectives, Endpoints and Assessment Methods 14

4.2 Derived Endpoints: Calculation Methods 17

4.2.1 Immunogenicity 17

4.2.1.1 Computed Values for Analysis 17

4.2.1.2 Seroprotection 17

4.2.1.3 Seroconversion 17

4.2.1.4 Baseline Serostatus 17

4.2.2 Safety 18

4.2.2.1 Solicited Reactions 19

4.2.2.1.1 Daily Intensity 19

4.2.2.1.2 Maximum Overall Intensity 20

4.2.2.1.3 Presence 20

4.2.2.1.4 Time of Onset 20

4.2.2.1.5 Number of Days of Occurrence During the Solicited Period 21

4.2.2.1.6 Overall Number of Days of Occurrence 21

4.2.2.1.7 Ongoing 21

4.2.2.2 Unsolicited AEs 22

4.2.2.2.1 Presence 22

4.2.2.2.2 Intensity 22

4.2.2.2.3 Last Vaccination 22

4.2.2.2.4 Time of Onset 22
4.2.2.2.5 Duration 23
4.2.2.3 Medically-Attended Adverse Event 23
4.2.2.4 SAEs 23
4.2.2.5 Adverse Events of Special Interest 23
4.2.2.6 Other Safety Endpoints 24
4.2.2.7 Pregnancy 24
4.2.2.8 Action Taken 24
4.2.2.9 Seriousness 24
4.2.2.10 Outcome 24
4.2.2.11 Causal Relationship 24
4.2.2.12 Adverse Events Leading to Study Discontinuation 24
4.2.3 Efficacy 25
4.2.4 Derived Other Variables 25
4.2.4.1 Age for Demographics 25
4.2.4.2 Duration of the Study 25
4.2.4.3 Participant Duration 25

5 Statistical Methods and Determination of Sample Size 25

5.1 Statistical Methods 26
5.1.1 Hypotheses and Statistical Methods for Primary Objective(s) 26
5.1.1.1 Hypotheses 26
5.1.1.2 Statistical Methods 27
5.1.2 Hypotheses and Statistical Methods for Secondary Objective(s) 27
5.1.2.1 Hypotheses 27
5.1.2.2 Statistical Methods 27
5.1.3 Statistical Methods for Exploratory Objective(s) 28
5.2 Analysis Sets 29
5.3 Handling of Missing Data and Outliers 30
5.3.1 Immunogenicity 30
5.3.2 Safety 30
5.3.2.1 Immediate 30
5.3.2.2 Causal Relationship 30
5.3.2.3 Measurements 31
5.3.2.4 Intensity 31
5.3.2.5 Start Date and Stop Date 31
5.3.2.6 Action Taken 31
5.3.3 Efficacy 31
5.4 Interim / Preliminary Analysis 31
5.5 Determination of Sample Size and Power Calculation 32

5.6 Data Review for Statistical Purposes 32
5.7 Changes in the Conduct of the Trial or Planned Analyses 33

6 References List 34

7 Statistical Analysis Plan TLF Shells - Main Outputs 35

List of Tables 36

List of Figures 37

List of Tables

Table 3.1: Overall design 10
Table 3.2: Schedule of activities 11
Table 5.1: Descriptive statistics produced 25

List of Abbreviations

Ab	antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BL	blood sample
CDM	Clinical Data Management
CI	confidence interval
CRF	case report form
CTL	Clinical Team Leader
CSM	Clinical Study Manager
CSR	clinical study report
D	day
DC	diary card
dil	dilution
eCRF	electronic case report form
EIA	enzyme immunosorbent assay
ELISA	enzyme linked immunosorbent assay
EMA	European Medicines Agency
EU	ELISA or EIA unit
FAS	full analysis set
FDA	Food and Drug Administration
FV	flavivirus
GCP	Good Clinical Practice
GM	geometric mean
GMT	geometric mean titer
GMTR	Geometric means of the individual titer ratios
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (application)
ITT	intent-to-treat
IU	international unit
IVRS	interactive voice response system
IWRS	interactive web response system

JE	Japanese encephalitis
LLOD	lower limit of detection
LLOQ	lower limit of quantification
LLN	lower limit of normal
M	Month
MD	missing data
MedDRA	Medical Dictionary for Regulatory Activities
MN	Microneutralization
NA	Not applicable
NSAID	non-steroidal anti-inflammatory drug
PC	phone call
PPAS	per-protocol analysis set
PRNT	Plaque Reduction Neutralization Test
PT	preferred term
PV	Pharmacovigilance
Q1; Q2; Q3	first quartile; second quartile (median); third quartile
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SC	screening
SD	standard deviation
SOC	system organ class (primary)
Sub-PPAS	subgroup-per-protocol analysis set
TLF	table(s), listing(s), and figure(s)
ULOD	upper limit of detection
ULOQ	upper limit of quantification
ULN	upper limit of normal
V	visit
Vac	vaccination
Y	Year
YF	yellow fever
WHO	World Health Organization

1 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.

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, PA, USA) 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.

A safe and efficacious YF vaccine, produced with significantly higher yields than the current ones, to enable the continuation of immunization programs and to provide protection for populations residing in YF endemic or epidemic regions and travelers. 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.

A first study, VYF01, aimed to assess the safety, viremia and immune responses of 3 dosages of vYF and YF-VAX, as a control vaccine, is ongoing in the USA. A second study, VYF02, is designed to assess the non-inferiority of the immune response of the investigational vaccine candidate vYF to the licensed YF-VAX vaccine in adults in the USA.

The proposed third study, VYF03, is a Phase II, randomized, observer-blind, active-controlled (Stamaril) multi-center study to assess the non-inferiority of the immune response, in terms of seroconversion rate 28 days post-vaccine administration of the investigational vaccine candidate vYF to the licensed Stamaril, in adults aged 18 years up to 60 years in Europe (EU). The safety and immunogenicity profile of vYF in a subset of the Chinese population in Asia will also be presented. The study will also assess the immunogenicity profiles (seroprotection rates, geometric mean titers [GMT] and GMT ratios [GMTR]) and the safety profiles of vYF and Stamaril at different timepoints up to 5 years after the vaccine administration.

2 Trial Objectives

2.1 Primary Objective(s)

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 Stamaril control vaccine (administered on D01) in participants enrolled in EU in YF-naïve participants.

2.2 Secondary Objective(s)

Immunogenicity

If the primary objective is reached on D29 with revised time window of +6 days (instead of +3 days, as initially planned in the protocol), the secondary objective 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 Stamaril control vaccine (administered on D01) in participants enrolled in EU in YF-naïve participants, with a time window of +3 days.

To describe the antibody immune responses to YF in both vaccine groups in EU and in Asia before (D01) and after (D11 in a subset of participants only, and D29, M6, and yearly from Y1 to Y5 in all participants) vYF or Stamaril administration.

To describe the immune response to YF in both vaccine group using YF MN assays between D01 and D29 using the D29 +3 days time window in EU YF-naïve participants.

Safety

To describe the safety profile of vYF vaccine in all participants, in EU and in Asia, in comparison to the safety profile of the control Stamaril

2.3 Exploratory Objective(s)

To describe the serological status of FV infection (dengue and Zika in all participants in EU and Asia; Japanese encephalitis [JE] in Asia) in the study population at baseline

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

Table 3.1: Overall design

Type of design	parallel, multi-center
Phase	II
Control method	active-controlled (control = Stamaril) Ratio vYF : Stamaril of 2:1
Study population	healthy adults 18 to 60 years of age
Countries	EU: France, Germany, Spain, Finland Asia: Singapore, Thailand
Level and method of blinding	observer-blind (modified double-blind)
Study intervention assignment method	randomization
IDMC	yes

3.2 Trial Plan

Table 3.2: Schedule of activities

Phase II Study, 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
[redacted]											
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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]											

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; DC: diary card; M: month; MA: memory aid; 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

‡ 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

†† HIV/Hepatitis B/Hepatitis C serology testing at baseline (Visit 1) will be optional depending on local regulatory requirements.

⁑ D29 time window is extended to +6 days instead of +3 days for the purpose of the Statistical analysis of immunogenicity.

+++ The first interim analysis in on safety and immunogenicity up to M6. However, for regulatory purposes, it might be decided to analyze separately the D01-D29 and M6 follow-up periods.

4 Endpoints and Assessment Methods

4.1 Objectives, Endpoints and Assessment Methods

Objectives	Endpoints	Assessment
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 Stamaril control vaccine (administered on D01) in YF-naïve participants enrolled in EU*	Seroconversion rates will be assessed 28 days post-vYF (administered on D01) and post-Stamaril (administered on D01) using a YF microneutralization (MN) assay in participants enrolled in EU 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.	See Section 8.1.2 of the protocol.
Secondary		
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 Stamaril control vaccine (administered on D01) in EU YF-naïve participants with a time window of +3 days. • To describe the antibody immune responses to YF in	• Seroconversion rates will be assessed 28 days (time window of +3 days) post-vYF (administered on D01) and post-Stamaril (administered on D01) in a YF MN assay in EU YF-naïve participants YF antibody assessments will be performed using YF MN assay as	See Section 8.1.2 of the protocol.

Objectives	Endpoints	Assessment
both vaccine groups before (D01) and after vYF or Stamaril administration, on D11 (in a subset† of participants only), D29, M6, and yearly from Y1 to Y5 in all participants	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 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 • 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. 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)	
• To describe the immune response to YF in both vaccine groups using YF MN assays between D01 and D29 using the D29 +3 days time window in EU YF-naive participants.	• Seroconversion rates at D29 • Seroprotection rates at baseline (D01) and at D29 • Geometric means of the individual titers ratios for D29/D01	

Objectives	Endpoints	Assessment
Safety • To describe the safety profile of the vYF vaccine in comparison to the safety profile of the control Stamaril • 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‡	• 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 solicited • 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, up to 28 days after vaccination • Presence of any SAEs and AESIs, up to 6-month after vaccination • Presence of related SAEs and all deaths from D01 to 5 years after vaccination	See Section 8.1.2 of the protocol.
Exploratory		
To describe the serological status of FV infection (dengue and Zika in all participants in EU and Asia; JE in Asia) in the study population at baseline	• NAb levels against FV infection (dengue and Zika in all participants in EU and Asia; JE in Asia) on a blood sample taken at baseline	See Section 8.1.2 of the protocol.

AESI: adverse event of special interest; D: day; eCRF: electronic case report form; FV: flavivirus; GMT: geometric means of titers; GMTR: geometric means of titer ratios; M: month; MN; microneutralization; NAb: neutralizing antibody; 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.
‡ 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 in EU 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.
A subset of the first 60 participants enrolled at some sites in Asia (40 participants in Group 1 and 20 participants in Group 2) will provide an additional post-vaccination blood sample on D11 to assess the immune response elicited by both vaccines in terms of NAb titers

4.2 Derived Endpoints: Calculation Methods

4.2.1 Immunogenicity

4.2.1.1 Computed Values for Analysis

In order to appropriately manage extreme values (< lower limit of quantification [LLOQ] and ≥ upper limit of quantification [ULOQ]) for analysis purposes, the following computational rule is applied to the values provided in the clinical database for each blood sample drawn: For the computation of GMTs, any titer reported as < LLOQ will be converted to a value of LLOQ/2.

- For calculation of proportion of participants with NAb titers ≥ threshold of 10 (1/dil), a titer reported as < LLOQ will be converted to a value of LLOQ/2.
- For calculating geometric mean of titer ratio (GMTR), < LLOQ will be converted to LLOQ/2 for a numerator and < LLOQ will be converted to LLOQ for a denominator. If both numerator and denominator are < LLOQ, then both will be converted in the same way so that titer ratio=1.
- Any titer reported as > ULOQ will be converted to ULOQ.

4.2.1.2 Seroprotection

See Section 4.1 (or Section 8.1.2 of the protocol).

4.2.1.3 Seroconversion

See Section 4.1 (or Section 8.1.2 of the protocol).

4.2.1.4 Baseline Serostatus

The baseline serostatus (eg, YF naïve participants and YF immune, Dengue naïve and Dengue immune, Zika naïve and Zika immune in EU and Asia; JE-naïve and immune in Asia) is defined as the presence of antibodies (Abs) in the baseline blood sample collected at Visit 1 (V01) in the present study from all participants.

YF naïve participants are participants with baseline YF NAb value below the threshold for protection [< 10 (1/dil)]. If the NAb value is ≥ 10 (1/dil) then the YF immune indicator will be " Immune". Otherwise, the baseline YF serostatus will be classified as "Undetermined".

Dengue serostatus at baseline will be determined using a Dengue Plaque Reduction Neutralization Test (PRNT) assay for dengue serotypes 1 to 4. The serostatus of dengue is computed based on values of dengue NAb titers against each of the four serotypes at V01. If the NAb value is positive (≥ 10 [1/dil]) for any serotype, then the dengue immune indicator will be "Immune". Else if the NAb value is not positive (<10 [1/dil]) and non-missing for all four serotypes (ie, all of the titers planned to be measured at baseline must be available, and valid [not coded "NR" in the serology database] then the dengue immune indicator will be "Naive". Otherwise, the baseline serostatus will be classified as "Undetermined".

Zika serostatus will be determined using a Zika microneutralization test for serum samples obtained at baseline. Zika immune samples were defined as having a Zika antibody titer of ≥ 100 (1/dil) (1). If the NAb value is not positive (< 100 [1/dil]) and non-missing (ie, the titers planned to be measured at baseline must be available, and valid [not coded "NR" in the serology database]), then the Zika immune indicator will be "Naive". Otherwise, the baseline Zika serostatus will be classified as "Undetermined".

JE serostatus will be determined using a JE PRNT assay for serum samples obtained at baseline. JE immune samples are defined as having a JE antibody titer of ≥ 10 (1/dil). If the NAb value is not positive (< 10 [1/dil]) and non-missing (ie, the titers planned to be measured at baseline must be available, and valid [not coded "NR" in the serology database]), then the JE immune indicator will be "Naive". Otherwise the baseline JE serostatus will be classified as "Undetermined".

Flavivirus immune participants at baseline are defined as participants either immune to YF or immune to Dengue or immune to Zika at baseline (as well as JE in Asia). Flavivirus naive participants at baseline are defined as participants naïve to YF and naive to Dengue and naive to Zika at baseline (as well as JE in Asia). Otherwise the baseline Flavivirus serostatus will be classified as "Undetermined".

4.2.2 Safety

The following terms are generally used in safety tables:

- AE: Adverse event includes immediate, solicited, and unsolicited (including non-serious and serious adverse events)
- Adverse Event of Special Interest (AESI): Is one of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. The following AESIs have been defined for VYF03 based upon the prior experience with YF vaccines:
    - Serious hypersensitivity/allergic reactions
    - Organ failure/serious viscerotropic events
    - Serious neurologic events

- Adverse Reaction (AR): Corresponds to related AE to the study vaccine, unless otherwise specified.
- Immediate: Unsolicited systemic AE checked "Yes" in the field of "immediate (within 30 minutes from the vaccination)" by the investigator in the case report form (CRF).
- Medically-Attended Adverse Event (MAAE): New onset or a worsen of a condition that prompts the participant or participant's parent/guardian to seek unplanned medical advice at a physician's office or Emergency Department.
- Solicited reaction: Event pre-listed in the CRF, and which occurred during the solicited period
- Unsolicited AE: AE recorded in the CRF as Unsolicited Systemic Events or Unsolicited Injection Site Reactions.
- Unsolicited injection site reactions are to be considered as related to the vaccine injection and therefore analyzed as ARs.
- Unsolicited AEs occurring before or after the defined period will be presented in a separate listing.
- SAE: Unsolicited AE considered serious by the investigator (reconciled with Global Pharmacovigilance database).

4.2.2.1 Solicited Reactions

Solicited injection site reaction will be collected within 7 days after vaccination.

Solicited systemic reactions will be collected within 14 days after vaccination.

4.2.2.1.1 Daily Intensity

All daily records for solicited reactions will be derived into daily intensity according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing (Unknown).

For measurable injection site reactions:

- None: > 0 to < 25 mm
- Grade 1: ≥ 25 to ≤ 50 mm
- Grade 2: ≥ 51 to ≤ 100 mm
- Grade 3: > 100 mm

For Fever:

- None: < 38.0°C or <100.4°F
- Grade 1: ≥ 38.0°C to ≤ 38.4°C or ≥100.4°F to ≤ 101.1°F
- Grade 2: ≥ 38.5°C to ≤ 38.9°C or ≥ 101.2°F to ≤ 102.0°F
- Grade 3: ≥ 39.0°C or ≥ 102.1°F

For the derivation of daily intensities, the following sequential steps will be applied:

1) Solicited reactions (except Fever/Pyrexia) with CRF presence recorded as "No" and with all daily records missing (Unknown) then all daily intensities will be derived as None.
2) For non-measurable solicited reactions, daily intensities will correspond to daily records reported in the clinical database. For measurable solicited reactions the daily measurements reported in the clinical database will be converted based upon the intensity scales defined in the protocol; this assumes a reaction that is too large to measure (non-measurable, "NM") is Grade 3. Note the intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (eg, swelling measurement > 0 mm but < 25 mm in adults).

Note: The maximum intensity on the ongoing period is derived from the record of the maximum intensity/measurement after the end of the solicited period following the rule described above.

4.2.2.1.2 Maximum Overall Intensity

Maximum overall intensity is derived from the daily intensities computed as described in Section 4.2.2.1.1 and is calculated as the maximum of the daily intensities over the period considered.

Note: The maximum intensity could be considered "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (eg, swelling measurement > 0 mm but < 25 mm in adults).

4.2.2.1.3 Presence

Presence is derived from the maximum overall intensity over the time period considered:

- None: No presence
- Grade 1, Grade 2, or Grade 3: Presence
- Missing or Unknown: Missing presence

Participants with at least one non-missing presence for a specific endpoint will be included in the analysis. Conversely, those without a non-missing presence will not be included in the analysis of the endpoint.

The time period is displayed as follows:

- Injection site reactions: D1-D4, D5-D8, D9 or later
- Systemic reactions: D1-D4, D5-D8, D9-D15, D16 or later.

4.2.2.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.2.2.1.1. It corresponds to the first day with intensity of Grade 1, Grade 2, or Grade 3.

Note: If a reaction is not continuous (ie, reaction occurs over two separate periods of time intervened by at least one daily intensity Missing or None) then the time of onset is the first day of the first occurrence.

Time of onset period is displayed as follows:

- Injection site reactions: D1-D4, D5-D8
- Systemic reactions: D1-D4, D5-D8, D9-D15.

4.2.2.1.5 Number of Days of Occurrence During the Solicited Period

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.2.2.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of presence on the solicited period with a specified intensity may also be derived.

Number of days of occurrence during the solicited period will be displayed by categories as follows:

- Injection site reactions: 1-3 days, 4-7 days, 8 days
- Systemic reactions: 1-3 days, 4-7 days, 8-14 days, 15 days

4.2.2.1.6 Overall Number of Days of Occurrence

If a reaction is ongoing at the end of the solicited period, then the overall number of days of occurrence is derived from the daily intensities and the end date of the reaction after the end of the solicited period. The overall number of days of presence is:

- (End date – investigational vaccination date) + (number of days of presence within the solicited period) - length of the solicited period + 1

If the end date is missing or incomplete (contains missing data), the overall number of days of presence will be considered as Missing.

Overall number of days of occurrence will be displayed by category (range) as follows:

- Injection site reactions: 2-3 days, 4-7 days, 8 days or more, missing end date
- Systemic reactions: 2-3 days, 4-7 days, 8-14 days, 15 days or more, missing end date

4.2.2.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.2.2.1.1 and the maximum intensity on the ongoing period. The investigator's ongoing flag is not used because the measurement would determine the ongoing status of the reaction.

- Ongoing: if the last daily intensity of the solicited period is at least Grade 1 and the maximum intensity on the ongoing period is at least Grade 1
- Not ongoing: if the last daily intensity of the solicited period is None or the maximum intensity on the ongoing period is None.
- Missing: all other conditions (in this case, it is not included in the denominator of the ongoing analysis in the safety tables).

4.2.2.2 Unsolicited AEs

4.2.2.2.1 Presence

An observation will be considered an event if it has at least a verbatim term and is not a Grade 0 intensity event.

Grade 0 events will not be included in safety analysis but will be included in separate listings.

4.2.2.2.2 Intensity

Intensity will be derived according to the following classification: None, Grade 1, Grade 2, Grade 3, or Missing

If the unsolicited AE is measurable and its preferred term is part of the list of solicited reactions, then the measurement is derived based upon and following the same rule of the intensity scales defined in the protocol for that measurable injection site or systemic reaction. Note the intensity could be considered as "None" (not a reaction) in the analysis despite being considered a reaction by the investigator (eg, swelling measurement >0 mm but < 25 mm in adults).

Intensity for the other unsolicited AEs will correspond to the value reported in the CRF.

The maximum intensity corresponds to the highest intensity for a unique term.

4.2.2.2.3 Last Vaccination

Last vaccination before an unsolicited AE is derived from the start date of the unsolicited AE provided in the CRF and is calculated as follows:

- If an unsolicited AE has a complete start date and different to any of the vaccination dates, the start date is used to determine the last vaccination before the unsolicited AE

If the start date is missing or partially missing, or equal to any vaccination date, then the visit number in the "Appeared after Visit" or similar field, is used to determine the last vaccination before the unsolicited AE.

4.2.2.2.4 Time of Onset

Time of onset is derived from the start date of the unsolicited AE and the date of last vaccination as described in Section 4.2.2.1.1:

Time of Onset = start date of the unsolicited AE - date of last vaccination before the unsolicited AE + 1.

The time of onset is considered as missing only if one or both dates are missing or partially missing.

The unsolicited AEs will be analyzed "Within 28 days" after each vaccination, which corresponds to AEs with a time of onset between 1 and 29 days. An AE with missing time of onset will be

considered to have occurred just after the last vaccination (computed according to the Section 4.2.2.2.4), so will be included in these tables.

Time of onset period is displayed as D1-D4, D5-D8, D9-D15, D16 or later, and Missing.

Note: Unsolicited AE that occurred before vaccination (negative time of onset) or with a time of onset higher than defined above will not be included in analysis but will be listed separately.

4.2.2.2.5 Duration

Duration is derived from the start and end dates of the unsolicited AE:

Duration = End date of unsolicited AE - start date of unsolicited AE + 1.

The duration is considered as missing only if one or both of the start and end dates of the unsolicited AE is missing or partially missing.

Duration will be displayed by categories as 1-3 days, 4-7 days, 8-14 days, 15 days or more, missing.

4.2.2.3 Medically-Attended Adverse Event

An event will be considered as an MAAE if "Yes" is checked for "Is the event an MAAE?" in the CRF.

MAAE will be analyzed during the following time periods:

- Within 28 days after a vaccination
- During the period from 29 days after the vaccination 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)

4.2.2.4 SAEs

An event will be considered as a serious event if "Yes" is checked for "Serious" in the CRF.

SAEs will be analyzed throughout the study using the following periods:

- Within 28 days after a vaccination
- During the period from 29 days after the injection until the last participant contact at M6
- During the study for related SAEs (ie, all related SAEs occurred during the study)

4.2.2.5 Adverse Events of Special Interest

An event will be considered as an AESI if "Yes' is checked for "Is the event an AESI?" in the CRF.

AESIs will be analyzed throughout the study using the following periods:

- Within 28 days after a vaccination
- During the period from 29 days after the injection until the last participant contact at M6

4.2.2.6 Other Safety Endpoints

4.2.2.7 Pregnancy

This information will not be included in the analysis but will be listed separately. No derivation or imputation will be done.

4.2.2.8 Action Taken

This information will be summarized as collected, including missing observations. No derivation or imputation will be done.

4.2.2.9 Seriousness

This information will be summarized as collected. No derivation or imputation will be done.

4.2.2.10 Outcome

This information will be summarized as collected. No derivation or imputation will be done.

4.2.2.11 Causal Relationship

This information will be summarized as collected in the field "Relationship to study vaccine". Missing causal relationship will be handled as described in Section 5.3.2.2 Relationship to study procedure is only presented in the listing.

4.2.2.12 Adverse Events Leading to Study Discontinuation

This information will be summarized as collected. A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation before the end of active phase.

In general, the items that are counted are:

- Disposition table: A participant who, on the "Completion at End of Study" form question "What was the participant's status?" has "Adverse Event" checked.
- Safety overview table: A participant who has either on the "Completion at End of Study" form, question" What was the participant's status?" has "Adverse Event" checked or lists a solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" checked that is at least Grade 1 or missing and is within the time period indicated.

System Organ Class (SOC)/Preferred Term (PT) table: A solicited AE that has "Caused Study Termination" checked that is at least Grade 1 or an unsolicited AE that has "Caused Study Discontinuation" checked that is at least Grade 1 or missing and is within the time period indicated.

4.2.3 Efficacy

Not applicable

4.2.4 Derived Other Variables

4.2.4.1 Age for Demographics

Considering the Sanofi convention of date of birth collection, the age of a participant at the date of informed consent signature/visit 1 will be entered in the electronical CRF.

4.2.4.2 Duration of the Study

The durations are computed in days as follows:

Latest date of all participants (termination date, last visit date, date of last contact) - earliest date of all participants (date of visit V01) + 1.

4.2.4.3 Participant Duration

The duration of a participant participation in the study is computed as follows:

Maximum (Visit dates, Termination date, Follow-up date, Last contact date) - V01 date + 1.

5 Statistical Methods and Determination of Sample Size

The statistical analyses will be performed under the responsibility of the Sponsor's Biostatistics platform using SAS® 9.4 Version software or later.

The results of the statistical analysis will be available in the final clinical study report (CSR).

For descriptive purposes, the following statistics will be presented:

Table 5.1: Descriptive statistics produced

Baseline characteristics and follow-up description	**Categorical data**	Number of participants. Percentage of participants.
	Continuous data	Mean, standard deviation (SD), quartiles, minimum, and maximum.
Clinical safety results	**Categorical data**	Solicited: Number and percentage (95% CIs) of participants. Unsolicited: Number and percentage (95% CIs) of participants, and number of events.
Immunogenicity results	**Categorical data (seroprotection, seroconversion, cutoff)**	Number and percentage (95% CIs) of participants.
	Continuous data **(titer / data†)**	Log10: Mean and standard deviation. Anti-Log10 (work on Log10 distribution, and anti-Log10 applied): Geometric mean, 95% CI of the geometric mean, quartiles, minimum, and maximum. Graphical representation by Reverse Cumulative Distribution Curve (RCDC).

The CI for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (2), ie, using the inverse of the beta integral with SAS®.

For immunogenicity results, assuming that Log10 transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI will be calculated on Log10 (titers / data) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom), then antilog transformations will be applied to the results of calculations, in order to provide geometric means (GMs) and their 95% CI.

GM is defined as follows:

$$GM = \left(\prod_{i=1}^{n} y_i \right)^{1/n} = 10^{\wedge} \left(\frac{1}{n} \sum_{i=1}^{n} \log_{10}(y_i) \right)$$

where $(y_1, y_2, \ldots, y_n)$ are the observed titers or other data where applicable for each participant. Rounding rules on descriptive statistics will follow the Sanofi Pasteur standard technical guideline ("Conventions for the Presentation of Descriptive Statistics").

5.1 Statistical Methods

5.1.1 Hypotheses and Statistical Methods for Primary Objective(s)

5.1.1.1 Hypotheses

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

The objective is to demonstrate that the humoral response in terms of seroconversion of vYF (Group 1) is non-inferior to the humoral response of Stamaril (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(Stamaril) ≤ - δ
- H1 (Alternative hypothesis): p(vYF) - p(Stamaril) > - δ

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

Where p(vYF) and p(Stamaril) are the proportion of participants with seroconversion. Seroconversion is defined as a 4-fold increase in NAb titers as compared to pre-vaccination value.

In the last version of the protocol (version 4.0 approved on 1st July 2021), the D29 visit is to be performed with a time window of +3 days; a blood sample BL0003 has to be taken at the D29 visit.

However, the timing for the Phase II non-inferiority VYF03 study has been complicated by COVID epidemic waves and vaccination campaigns; when non-COVID work was resuming at Investigational sites, these studies were competing against other studies. As a direct consequence, the enrolments were delayed and longer than expected. Considering that the planned sample size was likely to be not reached, the Applicant worked on a mitigation plan based on the number of

evaluable subjects (derived from the attrition rate used for the statistical hypotheses) consisting of extending the time window of the D29 post-vaccination visit (initially defined as D29 +3 days) with a proposal to extend up to D29 +6 days as the immune responses should not be impacted by this extension. The analyses with a revised time window for the D29 visit +6 days will be presented as the primary analysis of 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 Stamaril (administered on D01) in EU YF-naïve participants. If the primary objective is reached, in secondary objective, the originally planned analysis of the non-inferiority of the antibody response on D29 with a time window of +3 days will be presented too on the EU YF-naïve participants only and completed with a descriptive analysis in terms of seroconversion, seroprotection, GMT and GMTR.

5.1.1.2 Statistical Methods

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 (3) for seroconversion rates.

5.1.2 Hypotheses and Statistical Methods for Secondary Objective(s)

5.1.2.1 Hypotheses

No hypotheses will be tested. Descriptive statistics will be presented.

5.1.2.2 Statistical Methods

Immunogenicity:

Analyses will be performed 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:

- GMT for each vaccine group
- Seroconversion rates: number and percentage of participants in each vaccine group converted with neutralizing antibody titer 4-fold increased compared to D01 up to M6: D11 (subset only) compared to D01, D29 compared to D01, M6 compared to D01; and yearly from Y1 to Y5 compared with the latest planned timepoint: Y1 compared to M6, Y2 compared to Y1, Y3 compared to Y2, Y4 compared to Y3, Y5 compared to Y4
- Within-group GMTR for each vaccine group post-vaccination injection, compared to D01 (D11/D01 [subset only], D29/D01, M6/D01 and yearly ratios: Y1/M6, Y2/Y1, Y3/Y2, Y4/Y3, Y5/Y4

- Number and percentage of participants (seroprotection rates) in each vaccine group with antibody titer ≥ 10 (1/dil) at baseline (D01) and at D11 (subset only†), D29, M6, and yearly from Y1 to Y5
- Distribution of titers against YF at each time point and corresponding RCDC

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.

Complementary immunogenicity analysis based on the planned analysis on D29 with a time window of +3 days will be performed on a sub-population of the Per-Protocol Analysis Set:

- Non-inferiority analysis of the antibody response on D29
- GMT for each vaccine group
- Seroconversion rates: number and percentage of participants in each vaccine group converted with neutralizing antibody titer 4-fold increase compared to the previous time point, at D29 compared to D01
- Within-group GMTR for each vaccine group D29 post-vaccination injection, compared to D01
- Number and percentage of participants (seroprotection rates) in each vaccine group with antibody titer ≥ 10 (1/dil) at baseline (D01) and at D29

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 (2) for proportions.

5.1.3 Statistical Methods for Exploratory Objective(s)

Analyses will be performed on the Randomized Set.

- GMT of NAb levels against FV infection (dengue, Zika, and JEV) for each vaccine group at baseline

5.2 Analysis Sets

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 is recruited in Asia • 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 sample at 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.
Subgroup-Per-Protocol Analysis Set (sub-PPAS)	Subset of the PPAS. Participant will be excluded from the sub-PPAS if they did not provide the post-dose serology on Day 29 Visit (D28 after vaccination) in the proper time window of original protocol (D29 +3 days).

The PPAS will be used for the analysis for the primary objectives. Immunogenicity analyses in secondary objectives will be performed on FAS and a complementary analysis will be provided on sub-PPAS. Demographic and baseline characteristics will be presented on the PPAS and FAS.

The SafAS will be used for the description of clinical safety.

Randomized participants will be used for various standard population tables including duration of the study, disposition of participants and deviations and exploratory objective.

The subset will be used to describe additional neutralizing Ab levels in this subset.

5.3 Handling of Missing Data and Outliers

5.3.1 Immunogenicity

No imputation of missing values and no search for outliers will be performed. LLOQ and ULOQ management will be performed as described above.

5.3.2 Safety

Generally, no replacement will be done for Safety Missing Data and Outliers.

5.3.2.1 Immediate

For unsolicited systemic AEs, a missing response to the “Immediate” field is assumed to have occurred after the 30-minute surveillance period and will not be imputed.

5.3.2.2 Causal Relationship

By convention, all events reported at the injection site (either solicited or unsolicited) will be considered as related to the administered product and then referred to as reactions. In a same way,

all solicited systemic events pre-listed in the CRF are also considered as related to vaccination and will be considered as reactions.

- For unsolicited systemic AE, missing relationship will be considered as related to study vaccine at the time of analysis.
- If relationship to concomitant vaccine is collected, missing relationship to concomitant vaccine for unsolicited systemic AE will be considered as related to concomitant vaccine.

The missing relationship to study procedures for SAEs will not be imputed.

5.3.2.3 Measurements

For solicited reactions, missing measurements will be handled as described in Section 4.2.2.1.1.

5.3.2.4 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.2.2.1.1. For unsolicited AEs, missing intensities will remain missing and will not be imputed.

5.3.2.5 Start Date and Stop Date

Missing or partially missing start dates or end dates for unsolicited AEs (including SAEs) will remain missing and not be imputed. If the start date is missing or partially missing, the time of onset will be considered to be missing. Nevertheless, unsolicited AEs with missing time of onset will be included in analyses according to the last vaccination (computed according to the Section 4.2.2.2.3),. If either the start date or end date is missing or partially missing, the duration will be considered missing.

Missing or partially missing end dates for ongoing solicited AEs will remain missing and not be imputed.

5.3.2.6 Action Taken

Missing actions taken will remain missing and not be imputed.

5.3.3 Efficacy

Not applicable.

5.4 Interim / Preliminary Analysis

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

The first interim analysis will be performed on immunogenicity results and safety data obtained up to the 6-month follow-up visit with all available data collected, cleaned and locked. However, for regulatory purposes, it might be decided to analyze separately the D01-D29 and M6 follow-up periods. This planned analysis will require the unblinding of data. Once the interim database lock

has been conducted, the trial statistician will break the blind and will conduct the statistical analysis.

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).

In addition, the first interim analysis will be performed on immunogenicity and safety data gathered on all EU participants enrolled and followed up, even in case the submission/approval in Asian countries and/or the recruitment of participants of Chinese origin is delayed as compared to that in EU. As a consequence, an interim CSR might be produced to present the analysis on participants enrolled in EU only.

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

5.5 Determination of Sample Size and Power Calculation

The sample size is based on the primary objective and on the safety secondary objectives.
A total of 690 participants are expected to be enrolled in the study, using a 2:1 repartition (460 participants in the vYF group, with 380 in EU and 80 in Asia, and 230 participants in the Stamaril group, 190 in EU and 40 in Asia).

In EU, 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 (Stamaril). This will give >[redacted]% power (Farrington and Manning formula) to declare the non-inferiority of Group 1 (vYF) versus Group 2 (Stamaril) based on seroconversion rates 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 sizes have been arbitrarily set to 90 participants in EU and 60 participants in Asia, in which 60 and 40 participants will be enrolled in Group 1 in EU and Asia, respectively, and 30 and 20 participants will be enrolled in Group 2, in EU and Asia, respectively.

5.6 Data Review for Statistical Purposes

A review of the data has been anticipated through the data review process led by data management before database lock. This review of the data included a statistical review.

5.7 Changes in the Conduct of the Trial or Planned Analyses

In the last version of the protocol (version 4.0 approved on 1st July 2021), the D29 visit is to be performed with a time window of +3 days; a blood sample BL0003 has to be taken at the D29 visit.

However, the timing for the Phase II non-inferiority VYF02 study has been complicated by COVID epidemic waves and vaccination campaigns; when non-COVID work was resuming at Investigational sites, these studies were competing against other studies. As a direct consequence, the enrolments were delayed and longer than expected. Considering that the planned sample size was likely to be not reached, the Applicant worked on a mitigation plan based on the number of evaluable subjects (derived from the attrition rate used for the statistical hypotheses) consisting of extending the time window of the D29 post-vaccination visit (initial defined as D29 +3 days) with a proposal to extend up to D29 +6 days, as the immune responses should not be impacted by this extension. The analyses with a revised time window for the D29 visit +6 days will be presented as the primary analysis of 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 Stamaril control vaccine (administered on D01) in EU YF-naïve participants. If the primary objective is reached, in secondary objective, the originally planned analysis of the non-inferiority of the antibody response on D29 with a time window of +3 days will be presented too and completed with a descriptive analysis in terms of seroconversion, seroprotection, GMT and GMTR.

Moreover, by contrast to the analyses defined in the protocol, the first interim analysis will be performed on safety and immunogenicity data gathered from D01 to M6 (instead of D29 for immunogenicity data). However, for regulatory purposes, it might be decided to analyze separately the D01-D29 and M6 follow-up periods.

Finally, in the last version of the protocol (version 4.0 approved on 1st July 2022), the randomization is stratified by age group and by country. However, an error of stratification factor was done, and each participant was randomized by age group and by site instead of country. A repartition of randomized participant by site will be provided to assess the balance between both vaccine groups.

6 References List

1 Nascimento EJM, Bonaparte MI, Luo P, Vincent TS, Hu B, George J, et al. Use of a Blockade-of-Binding ELISA and Microneutralization Assay to Evaluate Zika Virus Serostatus in Dengue-Endemic Areas. Am. J. Trop. Med. Hyg. 2019:101(3):708-715.

2 Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods, Statistics in Medicine, (1998) 17, 857-872.

3 Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998; 17(8):873-90.

7 Statistical Analysis Plan TLF Shells - Main Outputs

This section remains optional and may be completed if necessary (e.g if the SAP is planned to be submitted to Health Authority). It should present the shells of the main outputs planned for the statistical analysis. For instance, it may cover the analyses planned for the primary objective(s). These outputs may not match the key tables that will be identified by the clinical team. The full TLF shells will be presented in a different document; the TLF numbering in this document may not match the TLF numbering in the full TLF shells but generally the table numbering in the full TLF shells should be used for the statistical analysis. The two documents (core body+TLF) should be finalized 8 weeks before the database lock.

List of Tables

Table 7.1: Non-inferiority of the percentage participants achieving seroconversion 28 days after one dose YF vaccination in YF-naive participants enrolled in EU- Microneutralization assays - Per-Protocol Analysis Set 38

Table 7.2: Summary of geometric means of titers and geometric means of individual titer ratios of antibody against YF virus by YF status at baseline - Microneutralization assays - Full Analysis Set 39

Table 7.3: Summary of geometric means of titers and geometric means of individual titer ratios of antibody against YF virus by FV status at baseline - Microneutralization assays - Full Analysis Set 41

Table 7.4: Summary of percentages of participants achieving seroconversion after one dose YF vaccination by YF status at baseline - Microneutralization assays - Full Analysis Set 43

Table 7.5: Summary of percentages of participants achieving seroconversion after one dose YF vaccination by FV status at baseline - Microneutralization assays - Full Analysis Set 44

Table 7.6: Summary of percentages of participants achieving seroprotection after one dose YF vaccination by YF status at baseline - Microneutralization assays - Full Analysis Set 45

Table 7.7: Summary of percentages of participants achieving seroprotection after one dose YF vaccination by FV status at baseline - Microneutralization assays - Full Analysis Set 46

Table 7.8: Safety overview after a vaccine injection - Safety Analysis Set 47

Table 7.9: Summary of solicited reactions within 7 or 14 days after a vaccine injection - Safety Analysis Set 49

List of Figures

Figure 7.1: Reverse cumulative distribution curves for YF virus at each timepoint in participants with YF immune status at baseline - Microneutralization assays - Full Analysis Set 50

Figure 7.2: Reverse cumulative distribution curves for yellow YF at each timepoint in participants with YF naive status at baseline - Microneutralization assays - Full Analysis Set..... 51

Figure 7.3: Reverse cumulative distribution curves for YF virus at each timepoint in participants with FV immune status at baseline - Microneutralization assays - Full Analysis Set 51

Figure 7.4: Reverse cumulative distribution curves for YF virus at each timepoint in participants with FV naive status at baseline - Microneutralization assays - Full Analysis Set:..... 51

Table 7.1: Non-inferiority of the percentage participants achieving seroconversion 28 days after one dose YF vaccination in YF-naive participants enrolled in EU- Microneutralization assays - Per-Protocol Analysis Set

vYFv (N=xxx)			Stamaril (N=xxx)			vYF - Stamaril		Non-inferiority
n/M	Seroconversion rate (%)	95% CI (2-sided)	n/M	Seroconversion rate (%)	95% CI	Difference (%)	95% CI (2-sided)	
###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)	##.#	(##.#, ##.#)	Yes/No

n: Number of participant s who achieve a yellow fever vaccination seroconversion.

M: Number of participant s with available data for the endpoint.

Seroconversion: for a participant with a 4-fold increase in NAb titers as compared to the pre-vaccination value

The non-inferiority will be demonstrated if the lower limit of the 2-sided 95% CI is > -5%.

Table 7.2: Summary of geometric means of titers and geometric means of individual titer ratios of antibody against YF virus by YF status at baseline - Microneutralization assays - Full Analysis Set

YF status		vYF (N=###)			Stamaril (N=###)		
	Time point/ratio	M	GM	(95% CI)	M	GM	(95% CI)
Immune	V01 (Pre-inj)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	V02 (V01+10D)*	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	V04 (V01+28D)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	V05 (V01+6M)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	V06 (V01+1Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	V07 (V01+2Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	V08 (V01+3Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	V09 (V01+4Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	V10 (V01+5Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	Ratio V02 (V01+10D)/ V01 (Pre-inj)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	Ratio V04 (V01+28D)/ V01 (Pre-inj)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	Ratio V05 (V01+6M)/ V01 (Pre-inj)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	Ratio V06 (V01+1Y)/ V05 (V01+6M)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	Ratio V07 (V01+2Y)/ V06 (V01+1Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	Ratio V08 (V01+3Y)/ V07 (V01+2Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	Ratio V09 (V01+4Y)/ V08 (V01+3Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	Ratio V10 (V01+5Y)/ V09 (V01+4Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
Naïve	…						

* Subset only

M: Number of participant s available for the endpoint

YF status: Immune for participants with quantified (≥ LLOQ) neutralizing Abs against YF; naive for participants without quantified (< LLOQ) neutralizing Abs against YF in the baseline sample

Table 7.3: Summary of geometric means of titers and geometric means of individual titer ratios of antibody against YF virus by FV status at baseline - Microneutralization assays - Full Analysis Set

FV status		vYF (N=###)			Stamaril (N=###)		
	Time point/ratio	M	GM	(95% CI)	M	GM	(95% CI)
Immune	V01 (Pre-inj)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	V02 (V01+10D)*	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	V04 (V01+28D)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	V05 (V01+6M)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	V06 (V01+1Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	V07 (V01+2Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	V08 (V01+3Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	V09 (V01+4Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	V10 (V01+5Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	Ratio V02 (V01+10D)/ V01 (Pre-inj)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	Ratio V04 (V01+28D)/ V01 (Pre-inj)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	Ratio V05 (V01+6M)/ V01 (Pre-inj)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	Ratio V06 (V01+1Y)/ V05 (V01+6M)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	Ratio V07 (V01+2Y)/ V06 (V01+1Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	Ratio V08 (V01+3Y)/ V07 (V01+2Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	Ratio V09 (V01+4Y)/ V08 (V01+3Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
	Ratio V10 (V01+5Y)/ V09 (V01+4Y)	###	###.#	(###.#; ###.#)	###	###.#	(###.#; ###.#)
Naïve	…						

* Subset only

M: Number of participant s available for the endpoint

Flavivirus status: Immune for participants with quantified (≥ LLOQ) neutralizing Abs against YF, and/or against at least one dengue serotype, and/or Zika ≥ 100 (1/dil) in the baseline sample, and/or JE in Asia; naive for participants without quantified (< LLOQ) neutralizing Abs against YF, with no Ab quantified against any of the four dengue serotypes, Zika < 100 (1/dil) and JE in Asia; in the baseline sample.

Table 7.4: Summary of percentages of participants achieving seroconversion after one dose YF vaccination by YF status at baseline - Microneutralization assays - Full Analysis Set

YF status	Time point	vYF (N=xxx)			Stamaril (N=xxx)		
			Seroconversion rate			Seroconversion rate	
		n/M	(%)	95% CI	n/M	(%)	95% CI
Immune	V02 (V01+10D)/ V01 (Pre-inj)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V04 (V01+28D)/ V01 (Pre-inj)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V05 (V01+6M)/ V01 (Pre-inj)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V06 (V01+1Y)/ V05 (V01+6M)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V07 (V01+2Y)/ V06 (V01+1Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V08 (V01+3Y)/ V07 (V01+2Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V09 (V01+4Y)/ V08 (V01+3Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V10 (V01+5Y)/ V09 (V01+4Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
Naive	…						

n: Number of participant s who achieve a yellow fever vaccination seroconversion.

M: Number of participant s with available data for the endpoint.

Seroconversion: For a participant with a 4-fold increase in NAb titers as compared to the previous timepoint value

YF status: Immune for participants with quantified (≥ LLOQ) neutralizing Abs against YF; naive for participants without quantified (< LLOQ) neutralizing Abs against YF in the baseline sample.

Table 7.5: Summary of percentages of participants achieving seroconversion after one dose YF vaccination by FV status at baseline - Microneutralization assays - Full Analysis Set

FV status	Time point	vYF (N=xxx)			Stamaril (N=xxx)		
			Seroconversion rate			Seroconversion rate	
		n/M	(%)	95% CI	n/M	(%)	95% CI
Immune	**V02 (V01+10D)/ V01 (Pre-inj)**	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V04 (V01+28D)/ V01 (Pre-inj)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V05 (V01+6M)/ V01 (Pre-inj)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V06 (V01+1Y)/ V05 (V01+6M)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V07 (V01+2Y)/ V06 (V01+1Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V08 (V01+3Y)/ V07 (V01+2Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V09 (V01+4Y)/ V08 (V01+3Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V10 (V01+5Y)/ V09 (V01+4Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
Naive	**…**						

n: Number of participant s who achieve a yellow fever vaccination seroconversion.

M: Number of participant s with available data for the endpoint.

Seroconversion: For a participant with a 4-fold increase in NAb titers as compared to the previous timepoint value

Flavivirus status: Immune for participants with quantified (≥ LLOQ) neutralizing Abs against YF, and/or against at least one dengue serotype, and/or Zika ≥ 100 (1/dil) in the baseline sample, and/or JE in Asia; naive for participants without quantified (< LLOQ) neutralizing Abs against YF, with no Ab quantified against any of the four dengue serotypes and Zika < 100 (1/dil) and JE in Asia; in the baseline sample.

Table 7.6: Summary of percentages of participants achieving seroprotection after one dose YF vaccination by YF status at baseline - Microneutralization assays - Full Analysis Set

YF status	Time point	vYFv (N=xxx)			Stamaril (N=xxx)		
		n/M	Seroprotection rate (%)	95% CI	n/M	Seroprotection rate (%)	95% CI
Immune	**V01 (Pre-inj)**	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V02 (V01+10D)*	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V04 (V01+28D)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V05 (V01+6M)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V06 (V01+1Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V07 (V01+2Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V08 (V01+3Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V09 (V01+4Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V10 (V01+5Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
Naive	**…**						

*Subset only.

n: Number of participant s who achieve a yellow fever vaccination seroprotection.

M: Number of participant s with available data for the endpoint.

Seroprotection: Participants with antibody titer ≥ 10 (1/dil)

YF status: Immune for participants with quantified (≥ LLOQ) neutralizing Abs against YF; naive for participants without quantified (< LLOQ) neutralizing Abs against YF in the baseline sample.

Table 7.7: Summary of percentages of participants achieving seroprotection after one dose YF vaccination by FV status at baseline - Microneutralization assays - Full Analysis Set

FV status	Time point	vYFv (N=xxx)			Stamaril (N=xxx)		
		n/M	Seroprotection rate (%)	95% CI	n/M	Seroprotection rate (%)	95% CI
Immune	**V01 (Pre-inj)**	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V02 (V01+10D)*	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V04 (V01+28D)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V05 (V01+6M)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V06 (V01+1Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V07 (V01+2Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V08 (V01+3Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V09 (V01+4Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
	V10 (V01+5Y)	###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)
Naive	**…**						

*Subset only.

n: Number of participant s who achieve a yellow fever vaccination seroprotection.

M: Number of participant s with available data for the endpoint.

Seroprotection: Participants with antibody titer ≥ 10 (1/dil)

Flavivirus status: Immune for participants with quantified (≥ LLOQ) neutralizing Abs against YF, and/or against at least one dengue serotype, and/or Zika ≥ 100 (1/dil) in the baseline sample, and/or JE in Asia; naive for participants without quantified (< LLOQ) neutralizing Abs against YF, with no Ab quantified against any of the four dengue serotypes and Zika < 100 (1/dil) and JE in Asia; in the baseline sample.

Table 7.8: Safety overview after a vaccine injection - Safety Analysis Set

Period/ Participants experiencing at least one:	vYF (N=###) n/M	%	(95% CI)	Stamaril (N=###) n/M	%	(95% CI)
Within 30 minutes after vaccine injection						
Immediate unsolicited AE	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
Immediate unsolicited AR	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
Solicited reaction within solicited period after vaccine injection	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
Solicited injection site reaction	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
Solicited systemic reaction	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
Within 28 days after vaccine injection						
Unsolicited AE	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
Unsolicited AR	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
AE leading to study discontinuation	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
SAE	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
Death	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
AESI	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
MAAE	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
During 6-month follow-up period						
SAE	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
Death	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
AESI	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
MAAE	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
During the study						
SAE	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
Death	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
AESI	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
MAAE	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)

n: number of participants experiencing the endpoint listed in the first column
M: number of participants with available data for the relevant endpoint
AR: Reactions related to study vaccine

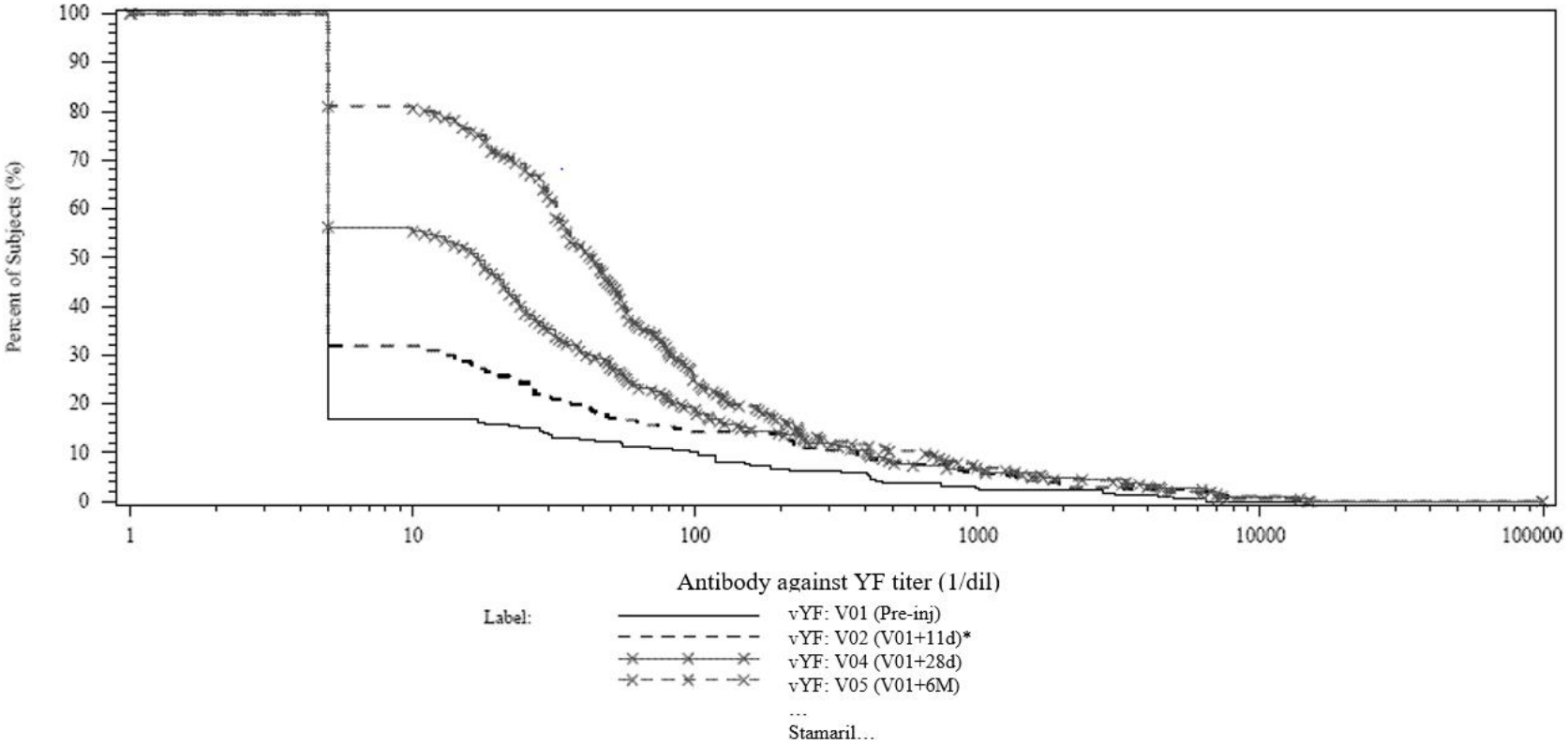
Table 7.9: Summary of solicited reactions within 7 or 14 days after a vaccine injection - Safety Analysis Set

	vYF (N=###)			Stamaril (N=###)		
Participants experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Solicited reaction	###/###	###.#	(###.#; ###.#)	###/###	###.#	(###.#; ###.#)
Grade 3 solicited reaction	###/###	###.#	(###.#; ###.#)	###/###	###.#	(###.#; ###.#)
Solicited injection site reaction	###/###	###.#	(###.#; ###.#)	###/###	###.#	(###.#; ###.#)
Grade 3 injection site reaction	###/###	###.#	(###.#; ###.#)	###/###	###.#	(###.#; ###.#)
Solicited systemic reaction	###/###	###.#	(###.#; ###.#)	###/###	###.#	(###.#; ###.#)
Grade 3 systemic reaction	###/###	###.#	(###.#; ###.#)	###/###	###.#	(###.#; ###.#)

n: number of participants experiencing the endpoint listed in the first column

M: number of participants with available data for the relevant endpoint

Figure 7.1: Reverse cumulative distribution curves for YF virus at each timepoint in participants with YF immune status at baseline - Microneutralization assays - Full Analysis Set



*Subset only.

<Instructions: This is a template, this will have 18 curves. The Y-axis represents percentage of participants having at least that level of serotype, and the scale is from 0% to 100%. The X axis represents the titers of the serotype.>

<Label present in this order:

vYF: V01 (Pre-inj); vYF: V02 (V01+10D)*; vYF: V04 (V01+28D); vYF: V05 (V01+6M); vYF: V06 (V01+1Y); vYF: V07 (V01+2Y); vYF: V08 (V01+3Y); vYF: V09 (V01+4Y); vYF: V10 (V01+5Y)

Stamaril: V01 (Pre-inj); Stamaril: V02 (V01+10D)*; Stamaril: V04 (V01+28D); Stamaril: V05 (V01+6M); Stamaril: V06 (V01+1Y); Stamaril: V07 (V01+2Y); Stamaril: V08 (V01+3Y); Stamaril: V09 (V01+4Y); Stamaril: V10 (V01+5Y)>

Figure 7.2: Reverse cumulative distribution curves for yellow YF at each timepoint in participants with YF naive status at baseline - Microneutralization assays - Full Analysis Set

*Subset only.

< Same shell as previous one>

Figure 7.3: Reverse cumulative distribution curves for YF virus at each timepoint in participants with FV immune status at baseline - Microneutralization assays - Full Analysis Set

*Subset only.

< Same shell as previous one>

Figure 7.4: Reverse cumulative distribution curves for YF virus at each timepoint in participants with FV naive status at baseline - Microneutralization assays - Full Analysis Set:

*Subset only.

< Same shell as previous one>