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

Randomized, observer-blind, active-controlled, multi-center, Phase II study conducted in the USA. This SAP plans the analyses of the VYF02 study in which participants received vYF vaccine or YF-VAX vaccine at 18 - 60 years of age.

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	VYF02
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 3.0, 05 August 2022

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List of Abbreviations

Ab	antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate transaminase
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
EDC	electronic data capture
EIA	enzyme immunosorbent assay
ELISA	enzyme linked immunosorbent assay
EMA	European Medicines Agency
EU	European Union
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
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
PSO	Product Safety Officer
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
WBC	White blood cell
WHO	World Health Organization
Y	Year
YF	yellow fever

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 who will spend time in these areas, is therefore required. 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.

The proposed study, VYF02, is a Phase II, randomized, observer-blind, active-controlled (YF-VAX) 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 YF-VAX, in adults aged 18 years up to 60 years in the USA. 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 YF-VAX 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 YF-VAX control vaccine (administered on D01) 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, 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 YF-VAX control vaccine (administered on D01) in YF-naïve participants, with a time window of +3 days (as initially planned in the protocol).

To describe the immune response to YF in both vaccine groups using YF microneutralization (MN) assays before (D01) and after (D11 in a subset only, D29, M6, and yearly from Y1 to Y5) vYF or YF-VAX administration.

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 YF-naïve participants.

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.

2.3 Exploratory Objective(s)

To describe the serological status of FV infection (dengue and Zika) 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 = YF-VAX) ratio 2:1 (vYF : YF-VAX)
Study population	healthy adults aged 18-60 years

Country	USA
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, 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											

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**
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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**
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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**
[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

⁑ 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 is on safety and immunogenicity up to D29 only.

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 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 days 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 YF-VAX control vaccine (administered on D01) in YF-naïve participants with a time window of +3 days. • To describe the immune response to YF in both vaccine groups using YF MN assays before (D01)	• Seroconversion rates will be assessed 28 days (time window of +3 days) post-vYF (administered on D01) and post-YF-VAX (administered on D01) in a YF MN assay in YF-naïve participants YF antibody assessments will be performed using YF MN assay as follows for each group:	See Section 8.1.2 of the protocol.

Objectives	Endpoints	Assessment
and after (D11 in a subset† only, D29, M6, and yearly from Y1 to Y5) vYF or YF-VAX administration	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 • 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).	
• 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 YF-naïve participants.	• Seroconversion rates at D29 • Seroprotection rates at baseline (D01) and at D29 • Geometric means of the individual titers ratios for D29/D01	
Safety		See section 8.2 of the protocol

Objectives	Endpoints	Assessment
• 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 up to 28 days after vaccination and AESIs up to 6-months 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 • 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	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 titer; GMTR: geometric means 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.

4.2 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) 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".

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".

Flavivirus immune participants at baseline are defined as participants either immune to YF or immune to Dengue or immune to Zika at baseline. Flavivirus naive participants at baseline are defined as participants naïve to YF and naive to Dengue and naive to Zika at baseline. 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 VYF02 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).
- Biological safety results (biochemistry and hematology for subset of subjects only): Hematology and biochemistry out-of-range test results will be summarized at D01 and D11 for participants in the subset.

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 be not 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 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 vaccination 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 Biological Safety Tests

The evaluation of biological safety parameters will consist in assessing whether each parameter is within or outside normal range and depending on the parameters, according to severity. Normal ranges for each biological parameter will be provided by the study centers and will be displayed in the listings. Biological safety endpoints will be assessed on whether or not they reach the pre-defined intensity thresholds. The pre-defined intensity thresholds are shown in Table 4.1.

Table 4.1: 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

4.2.2.7 Other Safety Endpoints

4.2.2.7.1 Pregnancy

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

4.2.2.7.2 Action Taken

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

4.2.2.7.3 Seriousness

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

4.2.2.7.4 Outcome

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

4.2.2.7.5 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.

4.2.2.7.6 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 Derived Other Variables

4.2.3.1 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.

4.2.3.2 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.

4.2.3.3 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® Version 9.4 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 Analysis 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 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.

In the last version of the protocol (version 4 approved on 16th February 2022), 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 +6days 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 YF-VAX control vaccine (administered on D01) in 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 YF-naïve population only and completed with a descriptive analysis in terms of seroconversion, seroprotection, GMT and GMTR.

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 Analysis 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 using previous timepoints 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-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.

Biological safety results (biochemistry and hematology for subset of subjects only):

Hematology and biochemistry out-of-range test results will be summarized at D01 and D11 after vaccination for participants in the subset. The hematology and biochemistry laboratory parameters at baseline and Day 11 visit will also be summarized in the form of a table showing the number of subjects with values over time according to the intensity grading scales. Shift tables for hematology and biochemistry laboratory parameters with reference ranges will present the number (%) of subjects with laboratory results with Grade 1, Grade 2 and Grade 3 (see Table 4.1) at Day 11 visit relative to baseline by vaccine group including total values. Parameters to be presented will be biochemistry (ALT, AST, CPK, alkaline phosphatase, bilirubin, creatinine, CRP), and hematology (RBC count, hemoglobin, hematocrit, MCV, platelets count, WBC count,

and quantitative differential count [neutrophils, lymphocytes, monocytes, eosinophils, basophiles]) on Day 01 visit and Day 11 visit.

Subjects with abnormal intensity grade will be presented for the hematology and biochemistry listings. The results will be displayed in their original units.

5.1.3 Statistical Methods for Exploratory Objective(s)

Analyses will be performed on the Randomized participants:

- GMT of NAb levels against FV infection (dengue and Zika) 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 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.
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 and biological safety parameters 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.

5.4 Interim / Preliminary Analysis

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 D29 visit and safety data obtained up to the 6-month follow-up visit with all available data collected, cleaned and locked. 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).

Final statistical 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 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.

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 approved on 16th February 2022), 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 +6days 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 YF-VAX control vaccine (administered on D01) in 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 D29 (instead of M6 for safety data).

6 References List

1 Eduardo J. M. Nascimento, Matthew I. Bonaparte, Ping Luo, Timothy S. Vincent, Branda Hu, James K. George, Germán Áñez, Fernando Noriega, Lingyi Zheng and James W. Huleatt. "Use of a Blockade-of-Binding ELISA and Microneutralization Assay to Evaluate Zika Virus Serostatus in Dengue-Endemic Areas" Am. J. Trop. Med. Hyg., 101:708-715, 2019.

2 Newcombe R.G., 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

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

vYFv (N=xxx)			YF-VAX (N=xxx)			vYF – YF-VAX		Non-inferiority
n/M	Seroconversion rate (%)	95% CI	n/M	Seroconversion rate (%)	95% CI	Difference (%)	95% CI	
###/###	##.#	(##.#; ##.#)	###/###	##.#	(##.#; ##.#)	##.#	(##.#, ##.#)	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 fourfold 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=###)			YF-VAX (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=###)			YF-VAX (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 in the baseline sample; naive for participants without quantified (< LLOQ) neutralizing Abs against YF, with no Ab quantified against any of the four dengue serotypes and Zika 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	vYFv (N=xxx)			YF-VAX (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 fourfold 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	vYFv (N=xxx)			YF-VAX (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 fourfold 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 in the baseline sample; naive for participants without quantified (< LLOQ) neutralizing Abs against YF, with no Ab quantified against any of the four dengue serotypes and Zika 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)			YF-VAX (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)			YF-VAX (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 in the baseline sample; naive for participants without quantified (< LLOQ) neutralizing Abs against YF, with no Ab quantified against any of the four dengue serotypes and Zika in the baseline sample.

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

Period/ Participants experiencing at least one:	vYF (N=###) n/M	%	(95% CI)	YF-VAX (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	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
Serious AESI						
Non-serious AESI	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
MAAE	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
During 6-month* follow-up period						
SAE	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
Death	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
Serious AESI	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
Non-serious AESI						
Serious MAAE	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
During the study						
SAE	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
Related SAE						
Death	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)
Serious related or fatal MAAE	###/###	##.#	(##.# ; ##.#)	###/###	##.#	(##.# ; ##.#)

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

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

*During the period from 29 days after the injection until the last participant contact at M6

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

	vYF (N=###)			YF-VAX (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

Table 7.10: Abnormality and/or intensity for Biochemistry parameters measurements at D01 and D11 – Subset

Parameter	Subject experiencing at least one abnormality at:	vYF (N=###) n/M	vYF (N=###) %	YF-VAX (N=###) n/M	YF-VAX (N=###) %
Liver Function Tests – ALT increase by factor	V01 (Pre-inj)				
	Intensity				
	Grade 1	###/###	#.#	###/###	#.#
	Grade 2	###/###	#.#	###/###	#.#
	Grade 3	###/###	#.#	###/###	#.#
	Out of normal range	###/###	#.#	###/###	#.#
	V02 (V01+10d)	…			
	…				
Liver Function Tests – AST increase by factor	…				
Creatine phosphokinase (mg/dL)	…				
Alkaline phosphatase - increase by factor	…				
Bilirubin – when accompanied by any increase in Liver Function Test, increase by factor	…				
Bilirubin – when Liver Function Test is normal; increase by factor					
Creatinine (mg/dL)	…				

C-reactive protein	**V01 (Pre-inj)**				
	Out of normal range	###/###	#.#	###/###	#.#
	V02 (V01+10d)				
	Out of normal range	###/###	#.#	###/###	#.#

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

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

Table 7.11: Abnormality and/or intensity for Hematology parameters measurements at D01 and D11 - Subset

Parameter	Subject experiencing at least one abnormality at:	vYF (N=###) n/M	%	YF-VAX (N=###) n/M	%
RBC (cell/mm^3)	V01 (Pre-inj)				
	Out of normal range	###/###	#.#	###/###	#.#
	V02 (V01+10d)	…			
	…				
Hematocrit (%)	…				
Mean corpuscular volume [MCV]	…				
Monocytes (cell/mm^3)	…				
Basophiles (cell/mm^3)	…				
Hemoglobin (gm/dL)	V01 (Pre-inj)				
	Intensity				
	Grade 1	###/###	#.#	###/###	#.#
	Grade 2	###/###	#.#	###/###	#.#
	Grade 3	###/###	#.#	###/###	#.#
	Out of normal range	###/###	#.#	###/###	#.#
	V02 (V01+10d)	…			
Hemoglobin change from baseline value	…				
WBC increase (cell/mm3)	…				

Decrease in WBC (cell/mm3)	
Decrease in Neutrophils (cell/mm^3)	…
Decrease in Lymphocytes (cell/mm^3)	…
Eosinophils (cell/mm^3)	…
Decrease in Platelets (cell/mm^3)	…

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

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

Table 7.12: Evolution of the intensity for Biochemistry parameters after vaccine injection - Subset

			vYF (N=###) Baseline				YF-VAX (N=###) Baseline			
			Grade 1	Grade 2	Grade 3	Total	Grade 1	Grade 2	Grade 3	Total
Parameter	**Visit**	**Intensity**	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**
Liver Function Tests – ALT increase by factor	**V02 (V01+10d)**	Grade 1	##	##	##	##	##	##	##	##
		Grade 2	##	##	##	##	##	##	##	##
		Grade 3	##	##	##	##	##	##	##	##
		Total	##	##	##	##	##	##	##	##
Liver Function Tests – AST increase by factor	…									
Creatine phosphokinase (mg/dL)	…									
Alkaline phosphatase - increase by factor	…									
Bilirubin – when accompanied by any increase in Liver Function Test, increase by factor	…									
Bilirubin – when Liver Function Test is normal; increase by factor	…									
Creatinine (mg/dL)	…									
…	..									

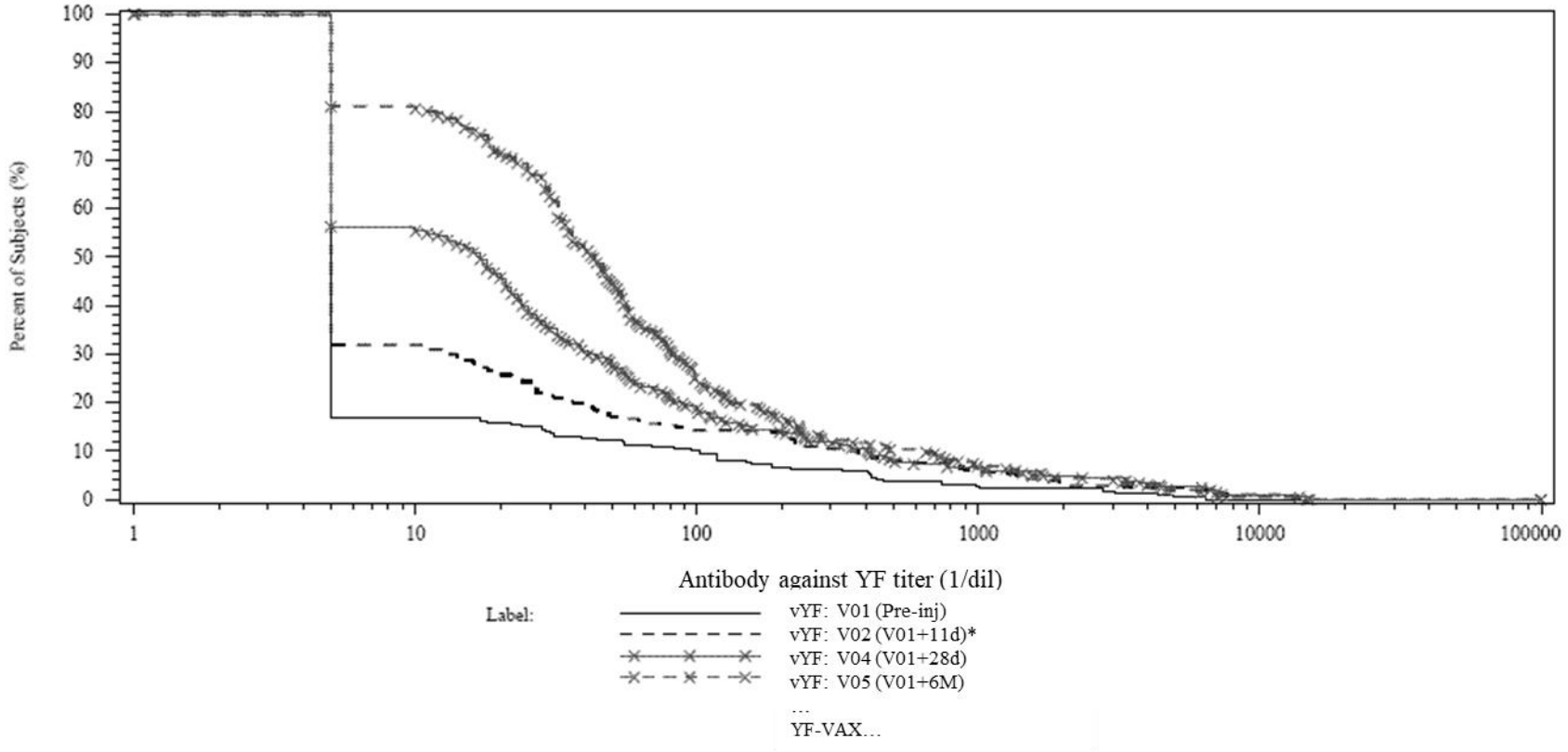
n: number of subjects with available data for the relevant endpoint

Table 7.13: Evolution of the intensity for Hematology parameters after vaccine injection – Subset

			vYF (N=###) Baseline				YV-VAX (N=###) Baseline			
			Grade 1	Grade 2	Grade 3	Total	Grade 1	Grade 2	Grade 3	Total
Parameter	**Visit**	**Intensity**	**n**	**n**	**n**	**n**	**n**	**n**	**n**	**n**
Hemoglobin (gm/dL)	**V02 (V01+10d)**	Grade 1	##	##	##	##	##	##	##	##
		Grade 2	##	##	##	##	##	##	##	##
		Grade 3	##	##	##	##	##	##	##	##
		Total	##	##	##	##	##	##	##	##
WBC increase (cell/mm3)	…									
Decrease in WBC (cell/mm3)										
Decrease in Neutrophils (cell/mm^3)										
Decrease in Lymphocytes (cell/mm^3)										
Eosinophils (cell/mm^3)										
Decrease in Platelets (cell/mm^3)										
…										

n: number of subjects 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)

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

Figure 7.2: Reverse cumulative distribution curves for YF virus 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>