NCT02741128

Safety and Immunogenicity of a Tetravalent Dengue Vaccine in HIV-Positive Adults Aged 18 to 50 Years in Brazil

A Phase II, randomized, observer-blind, placebo-controlled, multicenter study in 150 HIV-positive adults, treated with antiretrovirals, previously exposed to dengue, aged 18 to 50 years in Brazil. Subjects will receive 3 injections of CYD dengue vaccine or placebo (0, 6, and 12 months) with a 6-month safety follow-up.

Statistical Analysis Plan (SAP) - Core Body Part

Trial Code:	CYD50
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Sponsor:	Sanofi Pasteur SA 14 Espace Henry Vallée, 69007 Lyon, France Represented by: Sanofi Pasteur Inc. Discovery Drive, Swiftwater, PA 18370-0187, USA
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List of Abbreviations

Ab	antibody
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immune deficiency syndrome
AR	adverse reaction
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
CI	confidence interval
eCRF	electronic case report form
CSR	clinical study report
D	day
DC	diary card
DF	dengue fever
dil	dilution
ELISA	enzyme-linked immunosorbent assay
FAS	full analysis set
FV	flavivirus
GM	geometric mean
GMT	geometric mean titer
GMTR	geometric mean titer ratio
HIV	Human Immunodeficiency Virus
HBsAg	hepatitis B virus antigen
HCV	hepatitis C virus
IVRS	interactive voice response system
IWRS	interactive web response system
JE	Japanese Encephalitits
LLOD	lower limit of detection
LLOQ	lower limit of quantification
M	month
MA	memory aid
MD	missing data
MedDRA	Medical Dictionary for Regulatory Activities
NM	Non-measurable
NR	not-reportable

NS1	non-structural protein 1
PC	phone call
PPAS	per-protocol analysis set
post-Inj	post-Injection
PRNT	plaque reduction neutralization test
RNA	ribonucleic acid
RT-PCR	reverse transcription-polymerase chain reaction
RCDC	reverse cumulative distribution curve
SAE	serious adverse event
SafAS	safety analysis set
SAP	statistical analysis plan
SOC	system organ class (primary)
ULOQ	upper limit of quantification
V	visit
WHO	World Health Organization
WT	wild type
YF	yellow fever

1 Introduction

This is a Phase II study assessing the safety and immunogenicity of the CYD dengue vaccine when administered in Human Immunodeficiency Virus (HIV)-positive adults, previously exposed to dengue, with clinically-stable condition under regular antiretroviral therapy (ART).

Dengue disease is caused by 4 closely related, but antigenically distinct, dengue virus serotypes (1, 2, 3, and 4) of the genus flavivirus (FV). Infection with a dengue virus is usually asymptomatic but can produce a spectrum of clinical illnesses ranging from a non-specific viral syndrome to severe, fatal hemorrhagic disease (1) (2) (3) (4). Dengue fever (DF) is characterized by biphasic fever, headache, and myalgia in various parts of the body, prostration, rash, and lymphadenopathy. Recovery from DF is usually complete in 7 to 10 days (2), but prolonged asthenia is common. Decreases in leukocytes and platelets count are frequent. The incubation period of DF after the mosquito bite averages 4 days (range from 3 to 14 days) (2). According to the World Health Organization (WHO), over 2.5 billion people are now at risk from dengue in more than 100 countries in Africa, the Americas, the Eastern Mediterranean, South-east Asia, and the Western Pacific.

The HIV belongs to the family of retrovirus. It can be transmitted from human to human mostly through sexual intercourses, needle sharing among injecting drug users, and from mother to child during pregnancy (5). Despite advances on complementary fronts, HIV infection remains endemic worldwide, with higher incidence in low-income and middle-income countries, as a consequence of a limited access to health care (Asia, Sub-Saharan Africa, and Latin America). Interactions between HIV and other infectious agents, particularly in tropical regions, have been associated with accelerated HIV/ acquired immune deficiency syndrome (AIDS) disease progression (6). However, the severity and characteristics of dengue and HIV co-infection and the reciprocal impact on disease progression remain elusive because of lack of systematic case-control analysis (7) (8) (9).

Sanofi Pasteur's tetravalent CYD dengue vaccine, using recombinant technology to obtain a live-attenuated vaccine, has been extensively evaluated in subjects from 9 months to 60 years and it has shown a positive benefits/risk balance in subjects aged 9 to 45 years living in endemic areas (10) (11) (12). So far, the CYD dengue vaccine has been tested on healthy subjects, and "at risk" populations have been excluded. As the product has been licensed in a number of countries (commercial name: Dengvaxia®), and as recommended by the WHO, it is now justified to widen clinical studies to all populations that may be exposed to dengue vaccination, and to evaluate whether the vaccine is safe and immunogenic in a population of special interest, such as HIV-positive adults.

It is thus of prime importance to assess whether the dengue vaccine is safe in HIV subjects as dengue and HIV are both endemic in many areas of the world (13) (14) (15) (16). In countries where dengue is endemic and where mass vaccination campaigns may be implemented, there is a need to document the safety in this population as HIV-positive persons could be inadvertently vaccinated with the CYD dengue vaccine. This study will provide data on the use of the vaccine in a HIV-positive population and will be part of the Risk Management Plan. It is also important to assess whether an immunological response mediated by the development of neutralizing antibody

(Ab) levels of HIV-positive subjects injected with the CYD dengue vaccine can be expected. Likely, and as observed with yellow fever (YF) and Japanese Encephalitis (JE) vaccines, the CYD dengue vaccine will trigger an immunological response that is less important than that observed in healthy subjects (17) (18) (19).

In order to pursue the development of the CYD dengue vaccine, the present study will descriptively assess the safety and the immunogenicity of the CYD dengue vaccine in a HIV-positive population. It will involve 150 HIV-positive adults treated with ART (aged 18 to 50 years) who will receive either 3 injections of CYD dengue vaccine or placebo at 0, 6, and 12 months.

2 Trial Objectives

2.1 Primary Objective

Safety

To describe the safety of each injection of CYD dengue vaccine in HIV-positive adults previously exposed to dengue.

2.2 Secondary Objectives

Immunogenicity:

- To describe the humoral immune response to each dengue serotype at baseline and 28 days after each injection of CYD dengue vaccine in HIV-positive adults previously exposed to dengue.

Safety

- To detect the CYD dengue vaccinal viremia post-Injection (post-Inj) 1 in HIV-positive adults previously exposed to dengue.
- To describe changes in CD4 count and HIV ribonucleic acid (RNA) viral load after each injection of CYD dengue vaccine in HIV-positive adults previously exposed to dengue.

2.3 Observational Objective

Immunogenicity

- To describe the FV (dengue, YF and Zika) serological status in the study population at baseline.

3 Description of the Overall Trial Design and Plan

3.1 Trial Design

This is a multicenter, observer-blind, randomized, placebo-controlled, Phase II study of the CYD dengue vaccine in 150 HIV-positive adults (18 to 50 years) in Brazil. Potential participants fulfilling all inclusion criteria, including a previous exposure to dengue according to a Rapid Diagnosis Test (RDT) or a dengue IgG enzyme-linked immunosorbent assay (ELISA), will be enrolled. Subjects will receive 3 injections of either CYD dengue vaccine or placebo at 0, 6, and 12 months. The enrollment of subjects will be carried out in two steps, including an early safety data review before the second step.

Subjects HIV-positive and previously exposed to dengue according to RDT or ELISA will be randomized in a 2:1 ratio into 1 of 2 groups:

- Group 1 (N=100): subjects will receive 3 doses of CYD dengue vaccine (live, attenuated, dengue serotype 1, 2, 3, 4 virus)
- Group 2 (N=50): subjects will receive 3 doses of placebo (NaCl 0.9%)

Each subject will have her / his dengue serostatus confirmed using both dengue PRNT and anti-NS1 IgG assay on the pre-injection blood sample. Subjects who are dengue-positive by RDT or ELISA at Screening Visit and dengue-negative by PRNT (sample collected before the first injection [at Visit 1] and assayed before second injection) will be considered as not previously exposed. Therefore, they will not receive any further injections and will be followed for safety until 6 months after the last dose. In addition, if they received the vaccine, provisions for timely access to medical care will be offered for 10 years after the last dose, according to IDMC prior recommendations.

All subjects are planned to be included in safety and immunogenicity analysis set. Blood samples will be taken at the Screening Visit (serology, hematology and biochemistry) if such a visit is required, and at several other time points throughout the study for baseline dengue, YF, and Zika serological status, CYD dengue vaccine immunogenicity, dengue vaccinal viremia post-Inj 1, and HIV status monitoring assessments, depending on the time points.

The duration of each subject's participation in the study will be approximately 18 months.

At the end of the trial, subjects will be informed on whether they received the CYD dengue vaccine or placebo. For those who received placebo, and who have a prescription, the CYD dengue vaccine will be offered free of charge by Sanofi Pasteur through the study doctor, in accordance with the Brazilian laws and with vaccine indication in Brazil. This will be a decision between the subject and the study doctor since the vaccine offered will not be part of the trial.

3.2 Trial Plan

An overview of assessments and study vaccinations is provided in Table 3.1 Study procedures.

Each potential subject will sign and date the ICF. In addition to the Screening Visit, all included subjects will attend 8 study visits, will receive 4 follow-up phone calls, and will be contacted 6 months after the last vaccination for a safety follow-up.

Vaccination

All subjects will receive 3 injections of either CYD dengue vaccine or placebo at Day (D) 0, Month (M) 6, and M12.

Blood sampling

A number of immunological (hepatitis B virus antigen [HBsAg], hepatitis C virus [HCV] Abs), hematological (hemoglobin, hematocrit, platelet count, white blood cells count), and biochemical (aspartate aminotransferase [AST], alanine aminotransferase [ALT], urea and creatinine) parameters will be assessed at screening (unless the tests have already been performed as part of routine follow-up within the 4-week time window). The subject's dengue serostatus will be determined by RDT or ELISA during the Screening Visit.

Dengue, YF, and Zika baseline status will be assessed at D0.

Dengue vaccinal viremia will be assessed at D7 and D14 post-Inj 1.

Dengue neutralizing antibody (Ab) levels will be assessed at baseline (V01; prior to Inj 1) and 28 days after each injection.

If no HIV viral load and CD4 count results are available prior to each injection (ie, tests have not been performed within 2 months before injection visit), tests will be performed to ensure that results are available at the time of injection visit.

HIV viral load and CD4 count will be assessed 28 days after each injection. In case an increase in HIV viral load (plasma HIV-1 RNA > 1000 copies/mL 28 days post-injection after having been undetectable [< 50 copies/mL] pre-injection) or a decrease in CD4 count (decrease greater than 30% 28 days post-injection compared to the pre-injection value) is observed, a second blood sample is to be taken 4 weeks later for confirmation, as it is current local practice to confirm abnormal and significant deterioration of HIV-condition related results (20).

Collection of safety data

Safety data will be collected following each injection. Clinical site personnel will record immediate AEs that occur within the 30 minutes after injection. Subjects will record in the diary card (DC) information about solicited injection site reactions from D0 to D7 post-injection, about solicited systemic reactions from D0 to D14 post-injection, and unsolicited AEs occurring up to 28 days post-injection. Information on serious adverse events (SAEs) will be reported throughout the study. Serious and non-serious adverse events of special interest (AESIs) will be collected in defined time windows according to the type of AESI.

DCs will be provided to subjects to collect information on SAEs in-between injections (ie, from 28 days to 6 months post-Inj 1; and from 28 days to 6 months post-Inj 2). A memory aid (MA) will be provided to subjects to help them record SAEs during the 6 months safety follow-up (from

28 days post-Inj 3 to 6 months after last injection). Subjects are to contact the Investigator (within the first 5 days after fever onset) in case of hospitalization for suspected dengue disease at any time during the study for virological confirmation of the disease.

Clinical site personnel will review the safety data with the subjects during post-injection visits.

Table 3.1: Table of Study Procedures

Phase II Trial: a Screening Visit (Scr.), 8 Visits (V), and 5 Phone Calls (PC); 3 Injections; 7 to 9 Blood Samples; 18-month duration per subject

Visit (V) and Phone Call (PC) Number	Scr.*	V01*	V02	V03	V04	V05	PC1	PC2	V06	V07	PC3	PC4	V08	6-month Follow-up†
Trial Timelines Injection (Inj); Day (D); Month (M)	-D28 to –D0	Inj 1 (D0)	Inj 1 +7D	Inj 1 +14D	Inj 1 +28D	Inj 2 (M6)	Inj 2 +7D	Inj 2 +14D	Inj 2 +28D	Inj 3 (M12)	Inj 3 +7D	Inj 3 +14D	Inj 3 +28D	Last Inj +6 months
Time Windows (Days)			+3	+3	+14	±20	+3	+3	+14	±20	+3	+3	+14	+30
Phone calls							X†	X†			X†	X†		X†
Informed Consent	X													
Inclusion/Exclusion Criteria	X	X												
Demography/Body Stature		X												
Significant Medical History	X	X												
History of dengue infection/vaccination, YF vaccination, or Zika	X	X												
Physical/Clinical Examinations‡	X	X				X	†	†		X	†	†		†
Temperature§		X				X				X				
IRT Contact	X	X				X				X				
Randomization		X												
Concomitant Therapy**		X	X	X	X	X			X	X			X	
Urine Pregnancy Test††		X				X				X				
Contraindications						X				X				
Blood Sampling														
Screening tests‡‡	X													
Previous exposure to dengue using RDT or dengue ELISA §§	X													
FV status (dengue, YF, and Zika)***		BL1												
Dengue neutralizing Abs***		BL1			BL4				BL5				BL6	
Dengue vaccinal viremia			BL2	BL3										
CD4 count and HIV Viral Load†††		†††			BL4‡‡‡	†††			BL5‡‡‡	†††			BL6‡‡‡	

Visit (V) and Phone Call (PC) Number	Scr.*	V01*	V02	V03	V04	V05	PC1	PC2	V06	V07	PC3	PC4	V08	6-month Follow-up†
Trial Timelines Injection (Inj); Day (D); Month (M)	-D28 to –D0	Inj 1 (D0)	Inj 1 +7D	Inj 1 +14D	Inj 1 +28D	Inj 2 (M6)	Inj 2 +7D	Inj 2 +14D	Inj 2 +28D	Inj 3 (M12)	Inj 3 +7D	Inj 3 +14D	Inj 3 +28D	Last Inj +6 months
Time Windows (Days)			+3	+3	+14	±20	+3	+3	+14	±20	+3	+3	+14	+30
Virological confirmation of dengue by NS1 Ag ELISA and/or WT dengue RT-PCR		All acute febrile illness with diagnosis of dengue requiring hospitalization within the first 5 days after fever onset, occurring after the first visit (V01) and until the end of the 6-month safety follow-up												
Injection		Inj. 1				Inj 2				Inj 3				
30-Min. Observation Period – Collection of immediate events		X				X				X				
Injection Site Reactions & Systemic Events Assessment		Solicited injection site reactions will be collected for Days 0–7 after each injection. Solicited systemic reactions will be collected for Days 0–14 after each injection. Unsolicited events will be collected for Days 0-28 after each injection.												
Diary Card (DC)§§§ Provided Checked Collected		DC1	DC1	DC1	DC2 DC1 DC1	DC3 DC2 DC2			DC4 DC3 DC3	DC5 DC4 DC4			DC5 DC5	
Memory Aid (MA)§§§ Provided													MA	
Termination Record****													X	
SAEs and Serious AESIs††††	‡‡‡‡	SAEs from the first visit (V01) and until the end of the 6-month safety follow-up; AESIs in defined time windows according to the type of AESI												

* Serology, hematology and biochemistry results, as well as all other information collected as part of the screening of potential subjects will be captured in the source document. Inclusion/exclusion criteria, significant medical history, history of dengue infection/vaccination, of YF infection/vaccination, and of Zika infection, physical/clinical examinations, CD4 count and HIV viral load results will be captured in the CRF at V01 for eligible subjects. The Screening Visit and Visit 1 can be simultaneous for subjects tested positive by RDT and whose tests have been performed in appropriate time windows (within 4 weeks before injection for hepatitis serology, hematology, and biochemistry; within 2 months for CD4 count and HIV viral load) as part of the subject's routine follow-up.

† A follow-up visit can be arranged depending on the information provided during the phone call, at the Investigator's discretion. In the case of the 6-month follow-up phone call, this can be anticipated to perform the 6 months follow up after the last vaccination in case of early termination.

‡ A full physical/clinical examination will be conducted on each vaccination visit (before vaccine injection), and at the Investigator's discretion if at the time of other visits, based on the health status of the subject for the other visits.

§ Subject's temperature is to be measured before each injection, and at the Investigator's discretion at the time of other visits, if necessary based on the health status of the subject for the other visits. Temperatures will be recorded in source document only.

**	Concomitant therapy will be collected for Days 7, 14 and 28 days post-Injection 1 as well as before and 28 days after Injection 2 and Injection 3.
††	In all female subjects, result of urine pregnancy test should be confirmed as negative before each vaccine injection.
‡‡	Screening tests will be performed at local laboratory within 1 and 4 weeks before the first vaccination. These tests will include: serology (HBsAg, HCV Ab), hematology (hemoglobin, hematocrit, platelet count, white blood cells count), and biochemistry (AST, ALT, urea and creatinine). HBsAg and HCV tests will not be performed in case the information is already available in subject's medical history. If serology, hematology, and biochemistry results are available and were obtained within 4 weeks before first injection, tests do not need to be performed again.
§§	Tests will be performed sequentially. RDT will be performed first, and IgG ELISA will only be performed on subjects who tested negative for RDT. Subjects who previously tested negative by RDT can be re-screened using dengue IgG ELISA.
***	Blood sample to be collected before vaccine injection.
†††	Pre-injection HIV viral load and CD4 count will come from routine periodical tests of subjects as per local guidelines. For subjects for whom CD4 count is not part of the routine periodical follow-up as per guidelines, the Investigator will assess CD4 count to ensure that results are available at the time of Visit 1. Likewise, if CD4 count is not available before Inj 2 and Inj 3 (for checking contraindication) the Investigator will assess CD4 count to ensure that results are available at the time of Inj 2 and Inj 3. Pre-injection CD4 count test should be performed within 2 months before the corresponding vaccination visit.
‡‡‡	If an increase in HIV viral load (plasma HIV-1 RNA increase > 1000 copies/mL 28 days post-injection after having been undetectable [< 50 copies/mL] pre-injection) or a decrease in CD4 count (decrease in CD4 count greater than 30% assessed 28 days post-injection compared to pre-injection value), another blood sample is to be taken 4 weeks later for confirmation.
§§§	DCs are used for the collection of solicited and unsolicited AEs and concomitant medication. DC2 and DC4 are used for the collection of medical events and/or hospitalization and medications at the time of the event in the period between V04 and V05 and V06 and V07, respectively. Each DC is to be reviewed and collected by the site at the following visit. The MA is used for the collection of medical events and/or hospitalization and medications at the time of the event for 6 months after the third injection. The caller will ascertain whether any SAEs occurred since the last contact. During the follow-up period, subjects will be instructed to contact the clinical site if they are hospitalized or experience an AE that might be considered serious.
****	Termination record will be checked either during a planned study visit or a phone call.
††††	Serious AESIs will be reported after each injection in defined time windows as follows: serious hypersensitivity/allergic reactions occurring within 7 days, serious viscerotropic disease occurring within 30 days, serious neurotropic disease occurring within 30 days; hospitalized suspected dengue disease will be reported during the entire study. Non-serious AESIs (ie, hypersensitivity / allergic reactions) will be reported within 7 days after each injection.
‡‡‡‡	SAEs related to study procedures (from Screening Visit to V01) will be reported on paper form; at V01, all SAE information for eligible subjects reported on paper SAE form should be transcribed into the EDC system. From V01 until the end of the safety follow-up, all SAEs and AESIs in defined time windows according to the type of AESI will be documented in the EDC.

4 Endpoints and Assessment Methods

4.1 Primary Endpoints and Assessment Methods

See Section 9.1 of the protocol.

4.2 Secondary Endpoints and Assessment Methods

See Section 9.2 of the protocol.

4.3 Observational Endpoints and Assessment Methods

See Section 9.3 of the protocol.

4.4 Derived Endpoints: Calculation Methods

4.4.1 Safety

Terms used in the clinical safety tables to describe the safety events are specified below:

- AE: Adverse event; includes immediate, solicited, and unsolicited including non-serious and serious adverse events.
- AR: Adverse reaction; adverse reaction corresponds to a related AE.
- Immediate: Unsolicited systemic AE checked "immediate (within 30 minutes from the vaccination)" by the investigator in the case report form (CRF).
- Solicited reaction: Event pre-listed in the CRF, and which occurred during the solicited period (period is usually 0 to 7 days for injection site reactions and 0 to 14 days for systemic reactions post-vaccination).
- Unsolicited AE: AE recorded in the CRF as Immediate Unsolicited Systemic Events or Unsolicited Systemic Events or Unsolicited Injection Site Reactions.
- Unsolicited injection site reactions are always considered as related to the vaccine injection and analyzed as ARs.
- SAE: Unsolicited AE considered serious by the investigator.
- Hospitalized virologically-confirmed dengue case: Hospitalized suspected dengue disease is defined as an acute febrile illness with diagnosis of dengue requiring hospitalization (inpatient care). The confirmatory dengue diagnosis is performed through virological detection (eg, dengue non-structural protein 1[NS1], dengue reverse transcription-polymerase chain reaction [RT-PCR]).

4.4.1.1 Solicited Reactions

4.4.1.1.1 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.

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

1) Solicited reactions (except Fever/Pyrexia) with an investigator presence recorded as "No" and with all daily records missing 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 Section 9.1.1.3.2 of the protocol; this assumes a reaction that is too large to measure (non-measurable [NM]) is Grade 3.

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.

4.4.1.1.2 Maximum Intensity

Maximum intensity is derived from the daily intensities computed as described in Section 4.4.1.1.1 and is calculated as the maximum of the daily intensities over the period considered.

Note: The maximum intensity could be considered as "None" (ie, not a reaction) in the analysis despite being considered a reaction by the Investigator (eg, Injection site erythema measurement > 0 mm and < 25 mm).

4.4.1.1.3 Presence

Presence is derived from the maximum intensity on the period considered:

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

Subjects 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.

4.4.1.1.4 Time of Onset

Time of onset is derived from the daily intensities computed as described in Section 4.4.1.1.1. 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 will be displayed by period as follows:

- Injection site reactions (D0-D7): D0-D3, D4-D7
- Systemic reactions (D0-D14): D0-D3, D4-D7, D8-D14

4.4.1.1.5 Number of Days of Occurrence

Number of days of occurrence over the period considered is derived from the daily intensities computed as described in Section 4.4.1.1.1. It corresponds to the number of days with daily intensities of Grade 1, Grade 2, or Grade 3. Number of days of occurrence 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 category (range) as follows:

- Injection site reactions (D0-D7): 1-3 days, 4-7 days, 8 days
- Systemic reactions (D0-D14): 1-3 days, 4-7 days, 8-14 days, 15 days

4.4.1.1.6 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 stop date of the reaction after the end of the solicited period. The overall number of days of occurrence is:

- (stop date – last vaccination date) + (number of days of occurrence within the solicited period) – length of the solicited period + 1

If the stop date is missing or incomplete (contains missing data [MD]), the overall number of days of occurrence will be considered as Missing.

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

- Injection site reactions (D0-D7): 2-3 days, 4-7 days, ≥8 days, missing
- Systemic reactions (D0-D14): 2-3 days, 4-7 days, 8-14 days, ≥15 days, missing

4.4.1.1.7 Ongoing

Ongoing is derived from the last daily intensity of the solicited period computed as described in Section 4.4.1.1.1 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).

4.4.1.2 Unsolicited AEs

An observation will be considered as an event if it has at least a verbatim term and is not a Grade 0 intensity event. Grade 0 events should be included in the listing "Unsolicited adverse events not included in the safety analysis".

4.4.1.2.1 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 than the intensity scales defined in the protocol for that measurable injection site or systemic reaction.

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.

4.4.1.2.2 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 the vaccination date, 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

4.4.1.2.3 Time of Onset

Time of onset is derived from the start date of the unsolicited AE and the date of last vaccination:

- start date of the unsolicited AE - date of previous vaccination

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

The unsolicited AEs will be analyzed "Within 28 days", which corresponds to AEs with a time of onset between 0 and 28 days after vaccination or missing. An AE with missing time of onset will be considered to have occurred just after the vaccination indicated by the visit number, so will be included in these tables.

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.

Time of onset will be displayed by period as follows: D0-D3, D4-D7, D8-D14, ≥ D15 and Missing.

4.4.1.2.4 Duration

Duration is derived from the start and stop dates of the unsolicited AE provided in the clinical database:

- stop date of unsolicited AE – start date of unsolicited AE + 1.

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

Duration will be displayed by period as follows: 1-3 days, 4-7 days, 8-14 days, 15 days or more, Missing.

4.4.1.3 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 each injection
- Between 28 days after last injection and next injection
- During the 6-month follow-up period (ie, from 28 days after last injection until the last subject contact)
- During the study (ie, all SAEs occurred during the study)

4.4.1.4 AESIs

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 each injection
- Between 28 days after last injection and next injection
- During the 6-month follow-up period (ie, from 28 days after last injection until the last subject contact)
- During the study (ie, all AESIs occurred during the study)

4.4.1.5 Other Safety Endpoints

4.4.1.5.1 Pregnancy

This information will not be included in the analysis, but will be listed separately as collected.

4.4.1.5.2 Action Taken

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

4.4.1.5.3 Seriousness

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

4.4.1.5.4 Outcome

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

4.4.1.5.5 Causality

The information will be summarized as collected. Missing causality (relationship) will be handled as described in Section 5.3.1.2. Relationship to study procedure is only presented in the listing.

4.4.1.5.6 AEs Leading to Study Discontinuation

A flag is available in the clinical database for all AEs in order to identify AEs leading to discontinuation.

The items that are counted are:

- Disposition table: A subject who has, on the "Completion at End of Study" form question "What was the participant's status?" has "Adverse Event" checked
- Safety overview table: A subject 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)/PT frequency 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

4.4.1.5.7 Virologically-confirmed Dengue Infection

Virologically-confirmed dengue infection is defined as positive if the positive dengue screen RT-PCR (ie, >=lower limit of quantification [LLOQ]) result and/or the positive Dengue NS1 enzyme-linked immunosorbent assay (ELISA) result (ie, sample ratio >1) and/or positive Simplexa™ dengue RT-PCR result (ie, "DETECT" for any serotype).

For Dengue NS1 antigen ELISA, sample ratios of <0.5, >=0.5 to <=1.0, and >1 will be indicative of negative, equivocal, and positive results, respectively.

4.4.1.5.8 Viremia

The following viremia endpoints will be calculated:

- For all subjects: presence of detectable (>= lower limit of detection [LLOD]) or quantified (>= LLOQ) dengue vaccinal viremia (Yes, No, Missing) (by YF RT-PCR method).
- For subjects with a positive YF RT-PCR (ie, >=LLOD): presence of detectable (>=LLOD) or quantified (>= LLOQ) serotype-specific vaccine viremia (Yes, No, Missing) for each of the four serotype (by CYD RT-PCR method).

4.4.1.5.9 CD4 Count

The standardization of CD4 count will be performed using the International System Units if different units appear (eg, if more than one laboratory is involved).

Change in CD4 count after each injection will be calculated in percentages (%) for the derivation of decrease in CD4 count as

$$\frac{\text{CD4 count prior to vaccination} - \text{CD4 count post vaccination}}{\text{CD4 count prior to vaccination}} \times 100\%$$

The following CD4 count indicators will be derived after each injection:

- Decrease in CD4 count > 30% post-injection compared to the pre-injection values (ie, percentage change in CD4 count > 30%), not explained by non-adherence to ART and not explained by any other possible etiology: Yes, if the decrease in CD4 count > 30%, otherwise No, when pre- and post-injection CD4 counts are valid and not missing; Missing if either pre- or post-injection count is missing or non-valid.
- Confirmed decrease in CD4 count > 30% post-injection compared to the pre-injection values (ie, percentage change in CD4 counts > 30 %), not explained by non-adherence to ART and not explained by any other possible etiology: Yes if the second test taken 4 weeks after the first (ie, approximately 2 months post-injection) also shows a decrease in CD4 > 30%, otherwise No, if pre- and the two post-injection CD4 counts are valid and not missing; Missing if there are missing or non-valid pre- or post-injection CD4 counts in the first or second test.

4.4.1.5.10 HIV viral load

The following HIV viral load indicators will be derived after each injection:

- Increase in HIV viral load: Yes, if plasma HIV-1 RNA < 50 copies/mL pre-injection and > 1000 copies/mL post-injection, not explained by non-adherence to ART and not explained by any other possible etiology, otherwise No, if pre- and post-injection HIV viral load are valid and not missing; Missing if either pre- or post-injection HIV viral load is missing or non-valid.
- Confirmed increase in HIV viral load: Yes, if plasma HIV-1 RNA < 50 copies/mL pre-injection and > 1000 copies/mL post-injection, not explained by non-adherence to ART and not explained by any other possible etiology and a second test taken 4 weeks after the first (ie,

approximately 2 months post-injection) also shows plasma HIV-1 RNA > 1000 copies/mL, otherwise No, if pre- and post-injection HIV viral load are valid and not missing; Missing if there is missing or non-valid pre- or post-injection HIV viral load value in the first or second test.

4.4.2 Immunogenicity

4.4.2.1 Computed Values for Analysis

For the computation of geometric mean titers (GMTs), a titer reported as < LLOQ will be converted to a value of 0.5 LLOQ.

For calculating titer ratio (geometric mean titer ratio [GMTR]), < LLOQ will be converted to 0.5 LLOQ 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.

There is no upper limit of quantification (ULOQ) with the plaque reduction neutralization test (PRNT) method planned.

4.4.2.2 Calculation Rules for the "at least X serotype(s)" Tables

The criteria below will be computed for each subject and visit as soon as at least one of the 4 dengue serotype results is different from missing or not-reportable (NR) (ie, coded no result in the serology database):

- Number and percentage of subjects with antibody titer ≥ 10 (1/dilution [dil]) against at least 1, 2, 3, or 4 serotypes with the parental dengue virus strains.
- Number and percentages of subjects with antibody titer ≥ various titer thresholds (1/dil) against at least 1, 2, 3, or 4 serotypes with the parental dengue virus strains.

Titer(s) ≥ to a threshold for at least X serotype(s) with parental dengue virus strains is computed as a Yes/No/Missing variable (note: in the case no titer is available the variable will be missing). If at least X among the 4 serotype titers meet the threshold considered then the variable is derived to "Yes", otherwise if at least one titer is available and does not meet the threshold the variable is derived to "No". For the percentage calculation, all the subjects with at least one titer available regardless of the serotype will be considered in the denominator.

4.4.2.3 Baseline FV (dengue, YF, and Zika) Status

Baseline FV status is defined as the presence of neutralizing Abs against YF virus and/or Zika virus and/or positive Anti-NS1 ELISA result in the blood sample collected at V01 before vaccination in the present study from all subjects.

- **Immune**: subjects with quantified (>= LLOQ) neutralizing Abs against YF virus, and/or Zika virus (>=100), and/or positive Anti-NS1 ELISA result.
- **Non-immune**: subjects without quantified (< LLOQ) neutralizing Abs against YF and without Ab against Zika (<100) and negative Anti-NS1 ELISA result. To be classified in this

category, the titer results at baseline must be available and valid, ie, not coded 'NR' in the serology database.

- **Missing**: subjects with all the titer values missing.
- **Undetermined**: subjects do not meet the criteria for at least one of the above three categories,eg, a subject with a value < LLOQ against YF virus and/or Zika virus (<100) and/or negative Anti-NS1 ELISA result and non-valid titer results (ie, 'Missing' or coded 'NR' in the serology database).

Similarly, the following baseline statuses with 3 identical categories (ie, Immune, Non-immune and Missing) are defined for:

- Baseline dengue status: considering Anti-NS1 IgG
- Baseline YF status: considering neutralizing Abs against YF
- Baseline Zika status: considering neutralizing Abs against Zika

The LLOQ for YF and Zika and dengue neutralizing Abs is 10 (1/dil). Positive Anti-NS1 is defined as ≥ 9 ELISA unit/mL.

4.4.3 Efficacy

Not applicable.

4.4.4 Derived Other Variables

4.4.4.1 Age for Demographics

The age of a subject is the age computed automatically in the eCRF, and presented as an integer.5

4.4.4.2 Duration of a Subject in the Trial

The duration of a subject in the study is computed as follows: Maximum (date of visit, date of term form, follow-up date, date of last contact) – date of V01 +1.

4.4.4.3 Duration of the Study

The duration of the study is computed in days as follows: Latest date of all subjects (termination date, last visit date, date of last contact) – earliest date of all subjects (date of visit V01) +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 final analysis will be conducted once the 6-month safety data have been collected and the final database lock has occurred. No statistical adjustment is necessary because no hypotheses will be tested.

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 subjects. Percentage of subjects.
	Continuous data	Mean, standard deviation, quartiles, minimum, and maximum.
Clinical safety results	**Categorical data (AEs)**	Solicited: Number and percentage (95% CIs) of subjects. Unsolicited: Number and percentage (95% CIs) of subjects, and number of events.
	Categorical data (decrease in CD4 count, increase in HIV viral load, virologically-confirmed dengue case)	Number of subjects Percentage of subjects
Viremia	**Categorical data**	Number and percentage of subjects with a detectable or quantified viremia (possibly 95% CI of the percentage of the subjects)
	Continuous data	Mean, standard deviation, minimum and maximum (possibly median and quartiles) on quantified viremia data.
Immunogenicity results	**Categorical data (cutoff)**	Number and percentage (95% CIs) of subjects.
	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 confidence interval (CI) for the single proportion will be calculated using the exact binomial method (Clopper-Pearson method, quoted by Newcombe (21), 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 subject. 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

For descriptive purposes, the statistics presented on Table 5.1 will be produced.

5.1.1.1 Hypotheses

No hypotheses will be tested.

5.1.1.2 Statistical Methods

All analyses will be descriptive. Safety will be assessed after each and any dose of CYD Dengue vaccine.

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

The analysis of safety will address the number and percentage of subjects with injection site or systemic AEs until 28 days following each injection (solicited systemic reactions from D0 to D14, solicited injection site reactions from D0 and D7 and unsolicited AEs until D28, including AESIs and immediate unsolicited AEs, ie, occurring within 30 minutes after each vaccination).

Solicited reactions will be described according to their intensity and according to time of onset, number of days of occurrence, action taken, and according to whether they lead to trial discontinuation.

Unsolicited AEs will be described by Medical Dictionary for Regulatory Activities (MedDRA) SOC and preferred term definition according to their relationship, severity, time to onset, leading to study discontinuation and duration.

Serious and non-serious AESIs (in defined time windows according to the type of AESI) and SAEs (throughout the trial; including the 6-month follow-up) will be described by MedDRA SOC and preferred term, outcome, seriousness and relationship to vaccination.

The number and percentage of subjects with a hospitalized suspected dengue cases virologically-confirmed at any time throughout the trial after the injection will be described.

5.1.2 Hypotheses and Statistical Methods for Secondary Objectives

5.1.2.1 Hypotheses

No hypotheses will be tested.

5.1.2.2 Statistical Methods

For descriptive purposes, the statistics presented on Table 5.1 will be produced.

The proportion of subjects with a detected and quantified CYD dengue vaccinal viremia (ie, above the detection level) whatever the serotype (as assessed by YF RT-PCR) and for each of the four dengue serotypes (by serotype-specific CYD RT-PCR method) after the first CYD dengue vaccine injection will be presented at V02 and V03.

Number of subjects and percentages having a decrease in CD4 > 30% post-injection compared to pre-injection values and confirmed decrease in CD4 > 30% after each injection, not explained by non-adherence to ART and not explained by any other possible etiology, as well as an increase in HIV viral load post-injection and confirmed increase in HIV viral load (ie, plasma HIV-1 RNA < 50 copies/mL pre-injection and > 1000 copies/mL post-injection) for each injection, not explained by non-adherence to ART and not explained by any other possible etiology will be presented.

Analysis of dengue neutralizing antibody levels will be performed in each vaccine group before first injection (at baseline) and 28 days after each injection using:

- GMTs against each serotype with the parental dengue virus strains
- GM of individual titer ratio (GMTR) against each serotype with the parental dengue virus strains (post-Injection 1/pre-Injection 1, post-Injection 2/pre-Injection 1, and post-Injection 3/pre-Injection 1)
- Number and percentage of subjects ≥ 10 (1/dil) against each dengue serotype with the parental dengue virus strains at each available time point
- Number and percentage of subjects ≥ 10 (1/dil) against at least 1, 2, 3, or 4 dengue serotypes with the parental dengue virus strains at each available time point
- Number and percentage of subjects ≥ various titer thresholds (1/dil) against each dengue serotype with parental dengue virus strains at each available time point
- Number and percentage of subjects ≥ various titer thresholds (1/dil) for at least 1, 2, 3, or 4 serotypes with parental dengue virus strains at each available time point
- Distribution of titers against each of the 4 serotypes with parental dengue virus strains at each available time point and corresponding RCDCs
- Number and percentage of subjects immune and non-immune to YF, dengue, Zika and FV statuses at baseline

5.1.3 Statistical Methods for Observational Objectives

5.1.3.1 Hypotheses

No hypotheses will be tested.

5.1.3.2 Statistical Methods

For descriptive purposes, the statistics presented on Table 5.1 will be produced for neutralizing Ab levels (measured by YF PRNT) against FV (dengue, YF and Zika) at baseline.

5.1.4 Complementary Outputs

Analyses of the immunogenicity and safety by baseline YF, dengue, Zika and FV statuses respectively will be provided in Appendix 15 of the clinical study report (CSR).

Immunogenicity analyses

- Summary of GMTs and GMTRs against each serotype with the parental dengue virus strains
- Number and percentage of subjects ≥ 10 (1/dil) against each dengue serotype with the parental dengue virus strains at each available time point
- Number and percentage of subjects ≥ 10 (1/dil) against at least 1, 2, 3, or 4 dengue serotypes with the parental dengue virus strains at each available time point

Safety analyses

- Safety overview
- Summary of solicited reactions and unsolicited AEs
- Solicited reactions and unsolicited AEs/ARs by maximum intensity
- Unsolicited AEs/ARs and Immediate AEs by MedDRA SOC and preferred terms
- Overview of SAEs

COVID-19

Impact of COVID-19 pandemic on study conduct and disposition of participants impacted by COVID-19 pandemic situation will be summarized in tables on all participants and listed in Appendix 16 of the CSR.

If more than 10% of randomized participants are impacted by COVID-19, and still evaluable for immunogenicity/safety timepoints, additional analyses in impacted/non-impacted participants will be done on main immunogenicity and safety endpoints.

5.2 Analysis Sets

Five analysis sets will be used: The Per-Protocol Analysis Set (PPAS), the Full Analysis Set (FAS), the Safety Analysis Set (SafAS), the Screened Subjects set, and the Randomized Subjects set.

5.2.1 Full Analysis Set

The FAS is defined as the subjects who received either CYD dengue vaccine or placebo and had blood sample drawn and valid post-injection serology results (ie, a result different from "not-reportable" ["NR"] or missing, for at least one dengue serotype).

Subjects will be analyzed by the vaccine treatment group to which they were randomized.

5.2.2 Per-Protocol Analysis Set

The PPAS is a subset of the FAS. The subjects presenting with at least one of the following relevant protocol deviations will be excluded from the PPAS:

- Subject did not meet all protocol-specified inclusion criteria or met at least one of the protocol-specified exclusion criteria
- Subject did not complete the vaccination schedule
- Subject 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
- Subject did not receive vaccine in the proper time window
- Subject did not provide post-dose serology sample in the proper time window or a post-dose serology sample was not drawn
- Subject received a protocol-prohibited medication (see protocol Section 6.7)
- Subject's post-injection serology sample did not produce a valid test result (ie, a result different from "NR" or missing, for at least one dengue serotype)
- Subject had other protocol violations that affected the subject's immune response, as determined by the clinical team before locking the database.

Subjects will remain in the corresponding population as long as they do not meet one of the above criteria.

5.2.3 Safety Analysis Set

The SafAS is defined as those subjects who have received study vaccine and for which safety data are scheduled to be collected. All subjects will have their safety analyzed after each dose according to the vaccine they actually received. For the analysis at any dose, subjects will be analyzed according to the treatment received at the first dose.

Safety data recorded for a vaccine received out of the protocol design will be excluded from the analysis (and listed separately).

5.2.4 Other Analysis Set(s)

Screened subjects: all subjects with a Screening Visit.

Randomized subjects: a randomized subject is a subject for whom an injection group has been allocated.

5.2.5 Populations Used in Analyses

The SafAS will be used for the description of clinical safety data. Subjects will be analyzed according to the product they actually received.

The immunogenicity analyses will be performed on the PPAS and will be confirmed on the FAS.

Screened subjects and randomized subjects will be used for various standard population tables including duration of the study, disposition of participants and deviations. Demographic and baseline characteristics will be presented on the PPAS, FAS and SafAS.

5.3 Handling of Missing Data and Outliers

5.3.1 Safety

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

5.3.1.1 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.

5.3.1.2 Causality

Missing causality (relationship) for unsolicited AEs and SAEs will be considered at the time of analysis as related to vaccination. The missing relationship to study procedures for SAEs will not be imputed.

5.3.1.3 Measurements

Missing measurement (for temperature or length) will not be replaced.

5.3.1.4 Intensity

For solicited reactions, missing intensities will be handled as described in Section 4.4.1.1.1. For unsolicited AEs, missing intensities will remain missing and will not be imputed.

5.3.1.5 Start Date and Stop Date

Missing or partially missing start dates for unsolicited AEs will remain missing and not be imputed. If the start 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 visit number collected in “Appeared after visit” or similar field. If either the start date or end date is missing or partially missing, the duration will be considered missing.

Missing or partially missing stop dates for AEs (solicited reactions and unsolicited AEs) will remain missing and not be imputed.

5.3.1.6 Action Taken

Missing actions taken will remain missing and not be imputed.

5.3.2 Immunogenicity

No imputation of missing values and no search for outliers will be performed. LLOQ and ULOQ management will be performed as described in Section 4.4.2.1.

5.3.3 Efficacy

Not applicable.

5.4 Interim / Preliminary Analysis

No interim analysis will be performed as stated in section 5.7. A final analysis will be conducted once the 6-month safety data have been collected and the final database lock has occurred. No statistical adjustment is necessary because no hypotheses will be tested.

5.5 Determination of Sample Size and Power Calculation

The objective of the trial is to provide descriptive safety and immunogenicity results and therefore the sample size is arbitrarily set to 100 subjects for the CYD Dengue Vaccine Group and 50 subjects for the Placebo Group. There is a 95% probability of observing an event that has a true incidence rate of 3% for the CYD Dengue Vaccine Group.

5.6 Data Review for Statistical Purposes

A treatment blind 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.

In the context of this study (ie, HIV-positive adults), a blinded early safety data review will be performed when the first 20 subjects have received the first injection and have provided safety data for Days 0-14 post-first injection on the following safety endpoints:

- Immediate (within 30 minutes) AEs
- Solicited injection site and systemic reactions
- Unsolicited AEs reported as related by the investigator within 14 days after the first injection
- SAEs and AESIs (including serious and non-serious AESIs)

5.7 Changes in the Conduct of the Trial or Planned Analyses

Subjects had other protocol violations that affected the subject's immune response (as determined by the clinical team before locking the database) has been added as one of the criteria for the PPAS definition in Section 5.2.2 taking the study population being HIV-positive adults treated with ARTs into account.

The age computed automatically in the eCRF, and presented as an integer.

The Sponsor decided to add a second test, with a higher sensitivity, ie, an ELISA (Anti-Dengue IgG ELISA commercialized by Euroimmun) to screen potential study participants. Both tests are very specific. The two tests will be performed sequentially. RDT will be performed first, and IgG ELISA will only be performed on subjects who tested negative for RDT. These changes are presented in details in Section 3.

Some endpoints derivation were updated in Section 4.4.1.2.2, 4.4.1.5.6 and 5.3.1.5 per latest Safety Task Force Guideline 8.0.

No interim analysis on data obtained up to Day 28 after the last injection of the last subject will be performed. The full trial results will be released in once in the final CSR.

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