Official Protocol Title:	A Phase 2, Randomized, Double-Blind, Multicenter, Safety and Immunogenicity Clinical Bridging Study to Compare V181 (Dengue Quadrivalent Vaccine rDENVΔ30 [live, attenuated]) to Butantan Dengue Vaccine (Butantan-DV) in Healthy Adults 18 to 50 Years of Age in Brazil
NCT number:	NCT05710224
Document Date:	23-Aug-2024

Title Page

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Protocol Title: A Phase 2, Randomized, Double-Blind, Multicenter, Safety and Immunogenicity Clinical Bridging Study to Compare V181 (Dengue Quadrivalent Vaccine rDENVΔ30 [live, attenuated]) to Butantan Dengue Vaccine (Butantan-DV) in Healthy Adults 18 to 50 Years of Age in Brazil

Protocol Number: 002-04

Compound Number: V181

Sponsor Name:

Instituto Butantan
(hereafter called the Sponsor)

Legal Registered Address:

Sponsor Address
Av. Vital Brasil, 1500, Butantã
São Paulo – SP [São Paulo] 05503-900 – Brasil

Study Executor:

Merck Sharp & Dohme LLC
(hereafter called MSD)

126 East Lincoln Avenue
P.O. Box 200
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

ANVISA	25351019896/2021-84

Approval Date: 23 August 2024

Sponsor Signatory

Typed Name:
Title:

Date

MSD is executing the study. MSD contact information can be found in the Investigator Trial File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 04	23-AUG-2024	CCI [redacted]
Amendment 03	23-AUG-2022	To extend the contraception requirements from 4 weeks after administration of study intervention to 90 days after administration of study intervention.
Amendment 02	28-JUL-2021	To change the comparison of dengue virus-neutralizing antibody seroconversion rates for V181 and Butantan-DV from a secondary study objective to a primary study objective.
Amendment 01	19-FEB-2021	Correction of errors in the Study Interventions table (Table 1).
Original Protocol	21-DEC-2020	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendment:

CCI [redacted]

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 3, Hypotheses, Objectives, and Endpoints	CCI [redacted]	CCI [redacted]

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1.3.1, Study Procedures for All Participants	The note for visit windows was changed to a letter footnote.	To align with addition of new footnote for flaviviruses.
	Added a footnote on collection of previous exposure to other flaviviruses and previous receipt of other flavivirus vaccines, for those participants remaining in the study	To ensure collection of additional medical history to explore the prior exposure to other flaviviruses circulating in Brazil and previous vaccination information to explore prior vaccination to other flaviviruses.
Section 4.2.1.3	Added brief rationale for new exploratory objective and endpoint.	Refer to Section 3 rationale.
Section 8.1.5, Medical History	Added text for collection of participant's history of any other flavivirus infection(s) at any time prior to Day 1, for those participants remaining in the study	Refer to Section 1.3.1 rationale.
Section 8.1.6.1, Prior Medications	Added text for collection of participant's history of vaccination for any other flavivirus infection(s) at any time prior to Day 1, for those participants remaining in the study	Refer to Section 1.3.1 rationale.
Section 8.2.4, CCI [redacted]	CCI [redacted]	Refer to Section 3 rationale.

Section Number and Name	Description of Change	Brief Rationale
Section 9.4.1, Immunogenicity and Viremia Endpoints	Added bullet point for new exploratory endpoint.	Refer to Section 3 rationale.
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2, Randomized, Double-Blind, Multicenter, Safety and Immunogenicity Clinical Bridging Study to Compare V181 (Dengue Quadrivalent Vaccine rDENVΔ30 [live, attenuated]) to Butantan Dengue Vaccine (Butantan-DV) in Healthy Adults 18 to 50 Years of Age in Brazil

Short Title: Phase 2 Bridging Study of V181 to Butantan Dengue Vaccine in Healthy Adults

Acronym: V181-002

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

The following objectives and endpoints will be evaluated in healthy participants 18 to 50 years of age (inclusive) in low dengue-endemic areas in Brazil.

Primary Objectives	**Primary Endpoints**
- To compare the dengue virus-neutralizing antibody geometric mean titers (GMTs) for each of the 4 dengue serotypes at Day 28 postvaccination for participants administered V181 versus Butantan-DV **Hypothesis (H1):** V181 is non-inferior to Butantan-DV for each of the 4 dengue serotypes based on GMTs at Day 28 postvaccination. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI of the GMT ratio [V181 versus Butantan-DV] to be greater than 0.67 for each dengue serotype).	- Dengue virus-neutralizing antibody titers for each of the 4 dengue serotypes as measured by virus reduction neutralization test (VRNT)

- To compare the dengue virus-neutralizing antibody seroconversion rates for each of the 4 dengue serotypes at Day 28 postvaccination for participants administered V181 versus Butantan-DV **Hypothesis (H2):** V181 is non-inferior to Butantan-DV for each of the 4 dengue serotypes based on seroconversion rates at Day 28 postvaccination. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI of the difference in the seroconversion rates [V181 minus Butantan-DV] to be greater than -0.1 for each dengue serotype).	- Dengue virus-neutralizing antibody titers for each of the 4 dengue serotypes as measured by VRNT
- To evaluate the safety and tolerability of V181 and Butantan-DV with respect to the proportion of participants experiencing vaccine-related serious adverse events (SAEs)	- Vaccine-related SAEs from Day 1 through Day 28 postvaccination
Secondary Objective	**Secondary Endpoint**
- To evaluate the safety and tolerability of V181 and Butantan-DV with respect to the proportion of participants experiencing solicited AEs	- Solicited injection-site AEs from Day 1 through Day 5 postvaccination - Solicited systemic AEs from Day 1 through Day 28 postvaccination

Overall Design:

Study Phase	Phase 2
Primary Purpose	Prevention
Indication	Prevention of dengue disease in toddlers, children, and adults in endemic areas, as well as travelers to endemic areas
Population	Healthy adults 18 to 50 years of age
Study Type	Interventional
Intervention Model	Parallel This is a multisite study
Type of Control	Active Control Without Placebo
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Sponsor MSD Investigator Participants
Estimated Duration of Study	MSD estimates that the study will require approximately 22 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact. For purposes of analysis and reporting, the overall study ends when MSD receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

Number of Participants:

Approximately 1240 participants will be randomized in this study.

Intervention Groups and Duration:

Intervention Groups	

Arm Name	Intervention Name	Dosage Level/ Unit Dose Strength	Vaccine Regimen	Route of Admin.	Use
V181 Group	V181	CCI [redacted]	Single dose at Visit 1	SC	Test Product
Butantan-DV Group	Butantan-DV	CCI [redacted]	Single dose at Visit 1	SC	Test Product

Admin=administration; DV=dengue vaccine; PFU=plaque forming unit; SC=subcutaneous

Total Number of Intervention Groups/ Arms	2
Duration of Participation	Each participant will participate in the study for approximately 12 months from the time the participant provides documented informed consent through the final contact.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

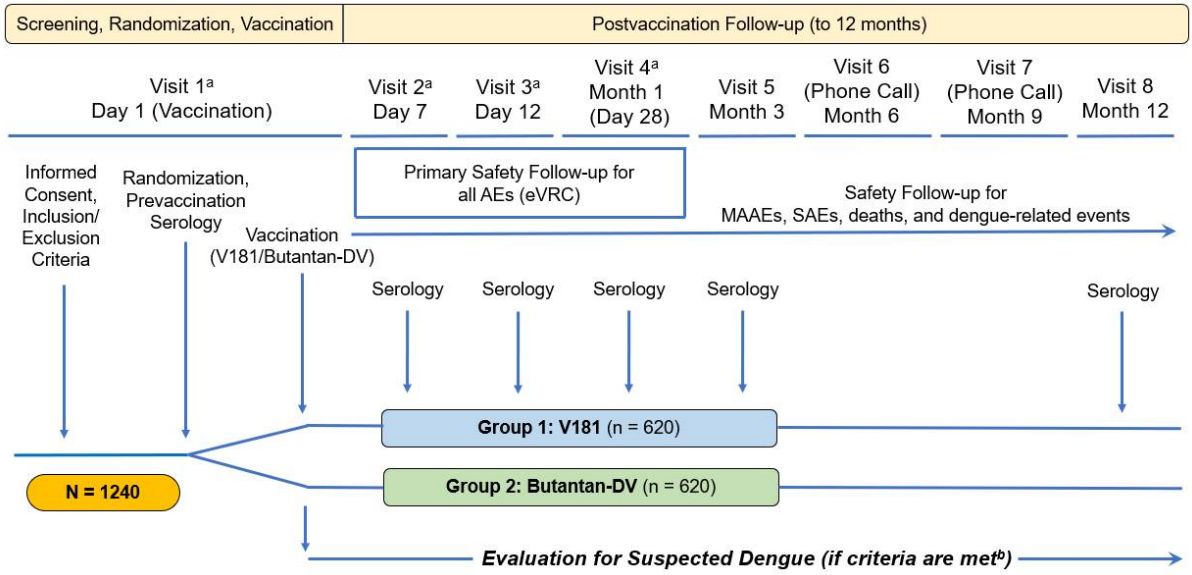
Study Accepts Healthy Volunteers: Yes

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 V181-002 Study Design



eVRC=electronic Vaccination Report Card; MAAE=medically attended adverse event; N=number of participants; n=number of participants in vaccination group; SAE=serious adverse event.

[a] Participants who report rash onset from Day 1 through Day 28 postvaccination should contact the site promptly to ensure that the rash is assessed by the investigator within 72 hours of onset. If rash assessment cannot occur at a planned visit (Visit 2, 3, or 4) within 72 hours of the participant's rash onset, then the rash should be assessed by the investigator at an unscheduled visit.

[b] Participants who experience protocol-specified fever (axillary temperature of ≥37.8°C) for ≥2 consecutive days postvaccination at any time during the study should schedule an initial evaluation for suspected dengue as soon as possible and no later than 8 days after the second day of protocol-specified fever.

1.3 Schedule of Activities

1.3.1 Study Procedures for All Participants

Study Period	Screening/ Randomization/ Intervention			Follow-up (through Month 12 postvaccination)							Notes
Visit Number:	1			2	3	4	5	6	7	8	
Scheduled Day/Month	Day 1			Day 7	Day 12	Day 28	Month 3	Month 6 Phone Call	Month 9 Phone Call	Month 12	
Visit Window Permitted [a]	Pre-Dose	Dose	Post-Dose	±2 days D5-D9	±2 days D10-D14	+14 days D28-D42	±14 days D76-D104	±14 days D166-D194	±14 days D256-D284	±14 days D346-D374	
Screening Procedures											
Informed Consent	X										Consent must be obtained PRIOR to any study procedures, including screening.
Assignment of Screening Number	X										
Participant Identification Card	X										
Inclusion/ Exclusion Criteria	X										
Medical History [b]	X										
Prior [b]/Concomitant Medications/ Vaccines Review	X			X	X	X	X	X	X	X	After V4, report only concomitant medications associated with SAEs or dengue events, or receipt of any investigational or approved dengue vaccine (Section 6.6).
Urine Pregnancy Test (WOCBP only)	X										Performed by site/local laboratory. WOCBP must have negative result prior to vaccination.

Study Period	Screening/ Randomization/ Intervention			Follow-up (through Month 12 postvaccination)							Notes
Visit Number:	1			2	3	4	5	6	7	8	
Scheduled Day/Month	Day 1			Day 7	Day 12	Day 28	Month 3	Month 6 Phone Call	Month 9 Phone Call	Month 12	
Visit Window Permitted [a]	Pre-Dose	Dose	Post-Dose	±2 days D5-D9	±2 days D10-D14	+14 days D28-D42	±14 days D76-D104	±14 days D166-D194	±14 days D256-D284	±14 days D346-D374	
Serum hCG (WOCBP only)	X										Serum hCG is tested only if the urine pregnancy test is inconclusive.
Baseline Dengue Serostatus POC Screening Assay	X										Result must be dengue seronegative to proceed with randomization. See Section 8.1.8.
Randomization/Vaccination											
Assignment of Randomization Number	X										
Study Vaccine Administration		X									
Provide Electronic Device or Configure Participant's Own Electronic Device for eVRC Data Collection			X								Study-site personnel will train participant on use of eVRC.
Immunogenicity Procedures											
Serum Samples for Dengue Antibody Titers (VRNT)	X					X	X			X	Day 1 blood sample must be collected prior to vaccination.
Safety Procedures											
Full Physical Examination Including Height and Weight	X										See Section 8.3.1.

Study Period	Screening/ Randomization/ Intervention			Follow-up (through Month 12 postvaccination)							Notes
Visit Number:	1			2	3	4	5	6	7	8	
Scheduled Day/Month	Day 1			Day 7	Day 12	Day 28	Month 3	Month 6 Phone Call	Month 9 Phone Call	Month 12	
Visit Window Permitted [a]	Pre-Dose	Dose	Post-Dose	±2 days D5-D9	±2 days D10-D14	+14 days D28-D42	±14 days D76-D104	±14 days D166-D194	±14 days D256-D284	±14 days D346-D374	
Vital Signs	X										See Section 8.3.2.
Postvaccination Safety Observation			X								Observe participant for at least 30 minutes following vaccination for any immediate reactions. See Section 8.3.3.
AE/SAE Review	X			X	X	X	X	X	X	X	• After V4, report only MAAEs, SAEs, deaths, and dengue-related events. • Rashes with onset D1 through D28 postvaccination should be evaluated by the investigator within 72 hours of onset (Section 8.3.5).
Review eVRC Data with Participant				X	X	X					
Collect Electronic Device From Participant						X					For participants who were provided an electronic device.
Viremia											
Blood for Viremia Testing (RT-PCR)				X	X						There must be at least 2 days between V2 and V3.

AE=adverse event; D=day; eVRC=electronic Vaccination Report Card; hCG=human chorionic gonadotropin; MAAE=medically attended adverse event; POC=point of care; RT-PCR=reverse transcription polymerase chain reaction; SAE=serious adverse event; V=visit; VRNT=virus reduction neutralization test; WOCBP=women of childbearing potential.

[a] To calculate subsequent visit windows, assume that 1 month equals to 30 days.

[b] For those participants remaining in the study at the time of Amendment 04, the investigator will also inquire about the participant's history of any other flavivirus infection(s) and any other flavivirus vaccination, at any time prior to Vist 1 (Day 1) (see Section 8.1.5 and Section 8.1.6.1).

1.3.2 Study Procedures for Participants With Suspected Dengue

Procedures at Unscheduled Visits (Full Duration of Study)	**Acute Initial Evaluation Visit** Participants who experience protocol-specified fever (axillary temperature of ≥37.8°C) for ≥2 consecutive days postvaccination at any time during the study should schedule an acute visit as soon as possible and no later than 8 days after the second day of protocol-specified fever.	**Convalescent Follow-up Visit** 14 to 28 Days After Acute Initial Evaluation Visit If the investigator assesses a case as dengue or possible/probable dengue, a convalescent follow-up visit is to occur 14 to 28 days after the acute visit to collect information about the severity and recovery from the febrile illness.	Notes
Study Procedures			
Clinical evaluation for dengue	X	X	Investigators will conduct a clinical evaluation using the 2009 WHO Dengue Guidelines. See Section 10.3.6.
Directed physical examination	X	X	See Section 8.3.1.
Vital signs	X	X	See Section 8.3.2.
Concomitant medications/vaccines review	X	X	After Day 28 postvaccination (V4), report only concomitant medications associated with SAEs or dengue events, or receipt of any investigational or approved dengue vaccine. See Section 6.6.
Safety Evaluations			
AEs/SAEs review	X	X	After Day 28 postvaccination (V4), report MAAEs and SAEs (regardless of causality), deaths (due to any cause), and dengue-related events (regardless of seriousness).

Procedures at Unscheduled Visits (Full Duration of Study)	**Acute Initial Evaluation Visit** Participants who experience protocol-specified fever (axillary temperature of ≥37.8°C) for ≥2 consecutive days postvaccination at any time during the study should schedule an acute visit as soon as possible and no later than 8 days after the second day of protocol-specified fever.	**Convalescent Follow-up Visit** 14 to 28 Days After Acute Initial Evaluation Visit If the investigator assesses a case as dengue or possible/probable dengue, a convalescent follow-up visit is to occur 14 to 28 days after the acute visit to collect information about the severity and recovery from the febrile illness.	Notes
Specimen Collection			
Serum sample for DENV detection by quantitative serotype-specific RT-PCR	X		A participant may have an acute visit on the first day of protocol-specified fever if they choose; however, if the fever persists on the second consecutive day, the participant must return for a second serum sample collection no later than 8 days after the second day of protocol-specified fever. See Section 8.3.6.
Serum sample for DENV antigen detection by NS1 ELISA	X		

AE=adverse event; DENV=dengue virus; ELISA=enzyme-linked immunosorbent assay; MAAE=medically attended adverse event; NS=non-structural protein; RT-PCR=reverse transcription polymerase chain reaction; SAE=serious adverse event; V=visit; WHO=World Health Organization

2 INTRODUCTION

The dengue quadrivalent vaccine rDENVΔ30 (live, attenuated), hereafter referred to as V181, is a dengue vaccine that is being developed by Merck Sharp & Dohme LLC (hereafter referred to as MSD) in collaboration with Instituto Butantan (hereafter referred to as Sponsor or Butantan) for the prevention of dengue disease in individuals at risk of exposure by living in or traveling to dengue-endemic areas. V181 is also known as dengue Live-Attenuated Tetravalent Vaccine (LATV) in some preclinical and Phase 1 studies.

Similarly to V181, the parental viruses for the Butantan-DV were initially developed by NIH. V181, Butantan-DV, and the NIH dengue LATV TV003 are analogous quadrivalent formulations as they all have the same parental strains, similar amounts of each attenuated virus strains per dose, are produced using similar methods, and have the same antigenic composition.

The Sponsor of the study is Butantan, and the study will be conducted by MSD in collaboration with the Sponsor in a manner consistent with the MSD Code of Conduct for Clinical Trials (Section 10.1.1).

2.1 Study Rationale

The purpose of this study is to demonstrate that V181 and Butantan-DV have a comparable safety and immunogenicity profile in healthy participants 18 to 50 years of age in Brazil. The age range of 18 to 50 years was selected in order to include healthy adults with intact immune systems capable of optimal immune responses in this study that includes hypothesis-driven primary immunogenicity objectives. Differences are not expected in immunogenicity by age subgroup within this study population. To avoid the impact of pre-existing immunity on the immune responses induced postvaccination, participants must be seronegative to all 4 dengue serotypes at baseline. Because the DENVs share common epitopes, having a prior exposure to 1 serotype influences the response to the other serotypes, which may confound the primary immunogenicity hypotheses.

The 2 vaccines originate from the same viral lineage (the same NIH live-attenuated viruses), thus contain the same antigenic composition and are produced by similar manufacturing processes utilizing adherent Vero cell cultures. However, V181 and Butantan-DV products were developed independently from each other, are produced from independently derived viral seeds, and while the processes are similar, there are some minor differences in the process itself, in the facilities/equipment used to manufacture the products, and in the composition and concentration of the excipients in the drug product formulation. Despite these minor differences, the safety and immunogenicity profiles of V181 are expected to be similar to those of Butantan-DV.

2.2 Background

Refer to the IB for detailed background information on V181, NIH dengue LATV, and Butantan-DV.

2.2.1 Dengue Disease and V181 Development

Dengue is among the most important arthropod-borne viral diseases in terms of human morbidity and mortality in the world [World Health Organization 2009] [Guzman, M. G., et al 2002] [Anderson, K. B., et al 2007] [Torres, J. R. and Castro, J. 2007] [Guzman, M. G., et al 2010] [Whitehorn, J. and Farrar, J. 2010] [Halstead, S. B. 2007] [Tapia-Conyer, R., et al 2009] [Suaya, J. A., et al 2009]. Dengue is endemic in many tropical and subtropical countries in Africa, the Americas, the Eastern Mediterranean, Asia, and the Pacific islands. Approximately 3 to 4 billion people live in these countries and are therefore at risk for dengue infection [Gubler, D. J. 2002] [Brady, O. J., et al 2012]. Furthermore, approximately 120 million people travel to dengue-endemic regions annually [Suaya, J. A., et al 2009].

Dengue disease is caused by any one of 4 virus serotypes (DENV1, DENV2, DENV3, and DENV4). Each serotype is widely distributed and capable of causing the full spectrum of dengue disease ranging from an inapparent or mild febrile illness, to classic DF characterized by high fever, headache, joint and muscle pain, rash, lymphadenopathy, and leukopenia, to life-threatening DHF and DSS. Primary dengue infection results in the induction of virus-neutralizing antibodies that are broadly cross-reactive early after infection and become more type-specific over time. Primary dengue infection confers long-lasting immunity against the infecting serotype, but only short-term protection against the other dengue serotypes. There is a strong association between a later second infection with a different viral serotype and the more severe disease forms (ie, DHF and DSS). It has been hypothesized that the increase in severity with secondary infection may be immune mediated through a mechanism termed antibody-dependent enhancement [Halstead, S. B. 2007] [Halstead, S. B. 2014] [Guzman, M. G., et al 2013]. According to this theory, non-neutralizing, cross-reactive, heterotypic antibodies bind to a heterologous infecting serotype and facilitate uptake of the virus into Fc receptor-bearing target cells (such as monocytes and macrophages), leading to increased viral replication, higher viral and viral antigen NS1 loads and cytokine release, which cumulatively manifests in the plasma leakage syndrome observed in DHF. Therefore, the major approach for developing an effective dengue vaccine and mitigating the risk of vaccine-induced sensitivity for more severe disease is a quadrivalent vaccine that will simultaneously and durably protect against disease caused by all 4 dengue serotypes [Halstead, S. B. and Deen, J. 2002].

Each year, approximately 390 million people are infected with dengue globally, causing an estimated 96 million symptomatic cases, with 2.1 million of those cases being classified as severe, resulting in approximately 21,000 deaths [Bhatt, S., et al 2013] [Thomas, S. J. and Endy, T. P. 2011]. Brazil is considered hyper-endemic for dengue with more than 12 million cases reported between 1990 and 2017 (with approximately 9 million reported between 2008 and 2017) [Andrioli, D. C., et al 2020]. Dengue disease in Brazil affects primarily adolescents and adults, with adults (18 to 59 years of age) contributing 60% to 70% of reported dengue cases. While the majority of dengue illness in Brazil is currently concentrated among adolescents and adults, data from the countrywide surveillance systems observed that, between 1998 and 2006, most cases of DHF were among adults 20 to 40 years of age, while in 2007, more than 53% of DHF cases occurred in children less than 15 years of age, with more than 40% of dengue hospitalizations among children less than 10 years of age indicating a possible increase in disease burden in children [Teixeira, M. G., et al 2013].

V181 is comprised of the attenuated viral strains rDENV1Δ30, rDENV2/4Δ30(ME), rDENV3Δ30/31, and rDENV4Δ30 and is intended to prevent disease caused by each of the 4 dengue serotypes (DENV1, DENV2, DENV3, and DENV4). The parental viruses for V181 were initially developed by the US NIH.

Attenuation of all 4 viral components in NIH dengue LATV was achieved by genetic modification, eg, deletion of 30 nucleotides in the 3' non-coding region (Δ30) of the dengue genome. DENV2 is the only serotype that is not a full-length homotypic genome, but is instead a chimeric virus with the prM and E protein from DENV2 inserted into an attenuated DENV4 backbone. In addition, DENV3 also has an additional 31-nucleotide deletion in the 3 non-coding region (Δ30/31). The vaccine viral strains are referred to as rDENV1Δ30, rDENV2/4Δ30(ME), rDENV3Δ30/31, and rDENV4Δ30 for DENV1, 2, 3, and 4 respectively.

All of the final vaccine strains have been fully characterized and their attenuation confirmed through in vitro and in vivo testing.

The overall goal of the V181 program is to demonstrate that a single SC dose of V181 is effective in preventing disease from all 4 dengue serotypes in both dengue-naïve and dengue-experienced individuals.

2.2.2 Preclinical and Clinical Studies

2.2.2.1 Preclinical Studies

Nonclinical studies have been performed on the components of the NIH dengue LATV formulation, which supports the V181 clinical program given that the vaccines are similar in design. Preclinical data for V181 and the NIH dengue LATV are provided in the V181 IB.

2.2.2.2 Clinical Studies

A brief summary of completed clinical studies is provided below, and details are provided in the V181 and Butantan-DV IBs.

2.2.2.2.1 MSD V181 Completed Clinical Studies

Results from the V181-001 Phase 1 study indicated V181 is highly immunogenic through 6 months Postdose 1, with a second dose in 6 months resulting in minimal or no additional boosting. The vaccine was generally safe and well tolerated in flavivirus-naïve and flavivirus-experienced participants though 1 year Postdose 2. AEs were generally assessed as mild to moderate in intensity by the participants.

2.2.2.2.2 NIH Dengue LATV Clinical Studies

The NIH has administered the dengue LATV monovalent components or tetravalent formulations comprising the same parental strains as V181 to more than 1000 participants to date, with studies in the US, Bangladesh, and Thailand. The NIH monovalent and tetravalent

vaccines were generally well tolerated in both nonclinical and clinical studies conducted by the NIH.

2.2.2.2.3 Butantan-DV Clinical Studies

Butantan-DV was administered in a Phase 2 study of 300 participants (of which 210 received Butantan-DV) in Brazil and was found to be immunogenic and generally safe and well tolerated in both dengue-naïve and dengue-experienced participants [Kallas, E. G., et al 2020]. It is currently being investigated in a Phase 3 safety and efficacy study with about 17,000 participants 2 to 59 years of age in Brazil. The Butantan-DV that will be used in this study will be manufactured in the same facility and with the same manufacturing process that produced the Butantan-DV used in the Phase 3 efficacy study.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants will directly benefit from study vaccination during participation, since this clinical study is being conducted to evaluate the safety and immunogenicity of an investigational dengue vaccine.

Data generated to date in V181, NIH dengue LATV, and Butantan-DV clinical studies demonstrate that these vaccines are generally safe, well tolerated, and highly immunogenic. The frequency, severity, and magnitude of the AEs identified in these studies support a favorable benefit-risk analysis for the dengue vaccine in the study population.

Additional details regarding specific benefits and risks for the participants in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

The following objectives and endpoints will be evaluated in healthy participants 18 to 50 years of age (inclusive) in low dengue-endemic areas in Brazil.

Objectives	Endpoints
Primary	
• To compare the dengue virus-neutralizing antibody geometric mean titers (GMTs) for each of the 4 dengue serotypes at Day 28 postvaccination for participants administered V181 versus Butantan-DV **Hypothesis (H1):** V181 is non-inferior to Butantan-DV for each of the 4 dengue serotypes based on GMTs at Day 28 postvaccination. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI of the GMT ratio [V181 versus Butantan-DV] to be greater than 0.67 for each dengue serotype).	• Dengue virus-neutralizing antibody titers for each of the 4 dengue serotypes as measured by virus reduction neutralization test (VRNT)
• To compare the dengue virus-neutralizing antibody seroconversion rates for each of the 4 dengue serotypes at Day 28 postvaccination for participants administered V181 versus Butantan-DV **Hypothesis (H2):** V181 is non-inferior to Butantan-DV for each of the 4 dengue serotypes based on seroconversion rates at Day 28 postvaccination. (The statistical criterion for non-inferiority requires the lower bound of the 2-sided 95% CI of the difference in the seroconversion rates [V181 minus Butantan-DV] to be greater than -0.1 for each dengue serotype).	• Dengue virus-neutralizing antibody titers for each of the 4 dengue serotypes as measured by VRNT
• To evaluate the safety and tolerability of V181 and Butantan-DV with respect to the proportion of participants experiencing vaccine-related serious adverse events (SAEs)	• Vaccine-related SAEs from Day 1 through Day 28 postvaccination

Objectives	Endpoints
Secondary	
• To evaluate the safety and tolerability of V181 and Butantan-DV with respect to the proportion of participants experiencing solicited AEs	• Solicited injection-site AEs from Day 1 through Day 5 postvaccination • Solicited systemic AEs from Day 1 through Day 28 postvaccination
Tertiary/Exploratory	
CCI [redacted]	

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, double-blind, active comparator-controlled, parallel-group, multisite, study to evaluate the safety and immunogenicity of V181 compared with Butantan-DV in healthy adults 18 to 50 years of age in Brazil.

Approximately 1240 participants will be randomized in a 1:1 ratio to receive a single dose of V181 or Butantan-DV. The duration of the study for each participant will be approximately

12 months from the time the participant provides documented informed consent through the final contact.

Butantan has extensive experience evaluating Butantan-DV in Brazil and has active regulatory activities in Brazil including an ongoing Phase 3 efficacy trial. Therefore, in order to leverage that experience, this study will be conducted at investigator sites within Brazil. Given the high rate of dengue transmission across many regions in Brazil, a two-stage strategy will be implemented to maximize recruitment of dengue-seronegative individuals. First, data generated previously from the dengue surveillance system in Brazil (SINAN) as well as seroepidemiologic data collected from Brazilian populations will be reviewed to identify study sites with historically lower rates of dengue illness. Second, a POC serologic screening assay will be conducted at screening to determine a participant's eligibility based on dengue serostatus.

An unblinded pharmacist or unblinded qualified study-site personnel will be required at each site to manage clinical supplies and prepare the study vaccines in order to maintain the blinding of the clinical material and the study. The unblinded pharmacist or unblinded qualified study-site personnel will mask each syringe to conceal the contents before dispensing a vaccine dose to a blinded member of the study team for administration to the participant. The participant, investigator, and study-site personnel directly involved in the clinical evaluation of the participants, as well as MSD field personnel or delegate(s) and Sponsor and MSD Headquarters personnel involved with the conduct of this study will be blinded to the participant-level intervention assignments.

Prior to randomization and administration of study vaccine, participants will be screened to document general good health on Day 1. All participants will be provided an electronic device or have their own electronic device configured, if compatible, to complete the eVRC on a daily basis from the day of vaccination (Day 1) through Day 28 postvaccination in order to collect the following data:

- Solicited injection-site AEs of injection-site pain, injection-site erythema, and injection-site swelling from Day 1 through Day 5 postvaccination
- Solicited systemic AEs of rash, headache, fatigue (tiredness), myalgia (muscle pain), and arthralgia (joint pain) from Day 1 through Day 28 postvaccination
- Unsolicited AEs from Day 1 through Day 28 postvaccination
- Axillary temperatures from Day 1 through Day 28 postvaccination
- Concomitant medications and nonstudy vaccines from Day 1 through Day 28 postvaccination.

Following Day 28 postvaccination, MAAEs and SAEs (regardless of causality), deaths (due to any cause), and dengue-related events (regardless of seriousness) defined as laboratory-confirmed DF, DHF, and/or DSS will be reported through Month 12 postvaccination.

Participants who report protocol-specified fever, defined as axillary temperature ≥37.8°C, for at least 2 consecutive days postvaccination at any time during the study, will be instructed to schedule an acute visit for clinical evaluation and serum collection to test for dengue disease. The acute visit should occur as soon as possible and no later than 8 days after the second consecutive day of protocol-specified fever. Alternately, a participant may have an acute visit on the first day of protocol-specified fever if they choose, but if the fever persists on the second consecutive day, the participant must return for collection of a second serum sample within the aforementioned time period (see Figure 2 in Section 8.3.6). Investigators will conduct the clinical evaluation using the 2009 WHO Dengue Guidelines [World Health Organization 2009] (Section 10.3.6) to assess for dengue disease symptoms and clinical severity.

Virologically confirmed dengue is defined as 2 or more consecutive days of axillary temperature ≥37.8°C with positive results for quantitative serotype-specific RT-PCR assay and/or NS1 ELISA.

Participant safety will be monitored by an eDMC that will perform periodic reviews of safety data throughout the study (Appendix 1). Details will be provided in the eDMC charter.

Details on the safety endpoints evaluated in this study, including the endpoints reported on the eVRC, are provided in Section 8.3 and Section 9.4.2. Details on AEs, including definitions and reporting requirements, are provided in Appendix 3.

Blood samples for the assessment of immune responses will be collected from all participants prior to vaccination on Day 1 and at the Day 28, Month 3, and Month 12 postvaccination time points. As this study will be conducted in low dengue-endemic areas of Brazil and screening POC dengue serologic testing will be performed, it is expected that the baseline serostatus for the majority of randomized participants will be dengue seronegative. The final determination of baseline serostatus for the purposes of the primary analysis will be determined by VRNT. All participants with a prevaccination VRNT result that is seropositive for any 1 of the 4 dengue serotypes by VRNT will be excluded from the primary PP immunogenicity analysis population, as described in Section 9.5.1. Seropositivity is defined as having a serotype-specific VRNT titer at or above the LLOQ of the assay.

In addition to safety and immunogenicity assessments, blood samples for viremia testing will be obtained at the Day 7 and Day 12 postvaccination time points.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

The purpose of this study is to demonstrate that V181 is safe and well tolerated and elicits an immune response that is non-inferior to that of Butantan-DV at Day 28 postvaccination in adults 18 to 50 years of age in Brazil.

For the primary safety endpoint, the incidence of vaccine-related SAEs reported from Day 1 through Day 28 postvaccination will be evaluated to demonstrate that V181 and Butantan-DV have a similar safety profile. For the primary immunogenicity endpoints, geometric mean antibody titers and seroconversion rates at Day 28 postvaccination will be assessed to determine that the elicited immune response is comparable between V181 and Butantan-DV. The primary safety and immunogenicity analyses will be conducted at the Day 28 postvaccination time point to support clinical bridging between V181 and Butantan-DV. A CSR will be produced to present the study results from Day 1 through Day 28 postvaccination. Safety and immunogenicity results from Day 28 through Month 12 postvaccination will be summarized in a final, separate study report.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

The ability of V181 and Butantan-DV to induce neutralizing antibodies to the 4 vaccine virus serotypes through Day 28 postvaccination will be compared in this study using GMTs and seroconversion rates measured with the validated VRNT assay. GMTs and seroconversion rates are complementary ways of assessing vaccine immunogenicity. Seroconversion is defined as achieving a serotype-specific VRNT titer ≥LLOQ at Day 28 postvaccination in participants who are seronegative at baseline. The LLOQ is a measurable level of seroconversion in this baseline seronegative population.

The time point of Day 28 was chosen as the primary endpoint based on the immunogenicity results observed in the V181-001 Phase 1 study. Among flavivirus-naïve participants, the observed seropositivity rates ranged from 70.6% to 97.1% for each of the 4 dengue serotypes. The percentage of these flavivirus-naïve participants who achieved quadrivalent or trivalent responses was 86.5%. Additionally, antibody responses will be evaluated as presented below:

1. Visit 1 (baseline), Day 1, prevaccination
2. Visit 4, Day 28 postvaccination
3. Visit 5, Month 3 postvaccination
4. Visit 8, Month 12 postvaccination

The VRNT is a high-throughput virus-neutralization assay, specific for each of the 4 dengue serotypes (Section 8.2.1). While no correlate of protection has been established for dengue, the measurement of virus-neutralizing antibody responses provides a mechanism to assess the immunogenicity of the vaccine using a functional assay that may predict the potential for protection.

4.2.1.2 Safety Endpoints

The primary safety evaluation period for this study will be Day 1 through Day 28 postvaccination. The 28-day primary safety follow-up period was chosen based on safety

data from the V181-001 Phase 1 clinical study and the clinical studies for the NIH LATV. During this time period, active safety surveillance will be conducted using a validated eVRC, as was previously done in the V181-001 study.

Following Day 28 postvaccination, SAEs will be collected through Month 12 postvaccination for a comprehensive evaluation of safety for the duration of the trial.

4.2.1.3 Other Exploratory Endpoints

CCI

4.2.1.4 Pharmacokinetic Endpoints

Not applicable.

4.2.1.5 Pharmacodynamic Endpoints

Not applicable.

4.2.2 Rationale for the Use of Comparator

This study will compare the safety and immunogenicity of V181 to Butantan-DV, which serves as an active comparator. There is no placebo control group because the purpose of the study is to compare the safety and immunogenicity of V181 and Butantan-DV.

4.3 Justification for Dose

Results of the V181 Phase 1 study (V181-001) confirmed the acceptable safety, tolerability, and immunogenicity profiles of V181 at the proposed dose. Also, Butantan-DV was shown to be safe and induced robust balanced neutralizing antibody responses against the 4 DENV serotypes at the proposed dose in a Phase 2 trial and the same dose is being used in the ongoing Butantan-DV Phase 3 efficacy trial.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when MSD receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1) this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Healthy male and female participants between the ages of 18 and 50 years (inclusive) will be enrolled in this study.

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

5.1 Inclusion Criteria

A participant is eligible for inclusion in the study if the participant meets all of the following criteria:

Type of Participant and Disease Characteristics

1. Is healthy based on medical history and physical examination, according to the clinical judgment of the investigator.

Demographics

2. Is male or female, from 18 years to 50 years of age inclusive, at the time of signing the informed consent.

Male Participants

3. Male participants are eligible to participate if they agree to the following for at least 90 days after administration of study intervention:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Female Participants

4. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a WOCBP

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Appendix 5 for at least 90 days after administration of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum, as required by local regulations) before administration of study intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

5. The participant (or legally acceptable representative) has provided documented informed consent for the study.

Additional Categories

6. Is dengue seronegative based on a prevaccination POC dengue test.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

(If a participant meets any of the exclusion criteria marked with an asterisk [*], the Day 1 visit may be rescheduled for a time when these criteria are no longer met as long as the study is still open to enrollment.)

Medical Conditions

1. Has a known history of dengue or Zika natural infection.

2. * Has an acute febrile illness (axillary temperature ≥37.8°C) occurring within 72 hours prior to receipt of study vaccine.

3. Has a known hypersensitivity or history of severe allergic reaction (eg, swelling of the mouth and throat, difficulty breathing, hypotension or shock) to any component of the dengue vaccine, that required medical intervention.

4. Has a serious or progressive disease according to the investigator, including, but not limited to cancer, uncontrolled diabetes, severe cardiac, renal or hepatic insufficiency, systemic autoimmune, or neurologic disorder.

5. Has known or suspected impairment of immunological function, including, but not limited to congenital or acquired immunodeficiency, HIV infection, hematologic malignancy, or treatment for autoimmune diseases.

6. Has a condition in which repeated venipuncture or injections pose more than minimal risk for the participant, such as hemophilia, thrombocytopenia, other severe coagulation disorders, or significantly impaired venous access.

Prior/Concomitant Therapy

7. Has received a dose of any dengue vaccine (investigational or approved) prior to study entry, or plans to receive any dengue vaccine (investigational or approved) for the duration of the trial.

8. * Has received a licensed non-live vaccine within 14 days before receipt of study vaccine or is scheduled to receive any licensed non-live vaccine within 28 days following receipt of study vaccine. **Exception**: Inactivated influenza vaccine may be administered, but must be given at least 7 days before receipt of study vaccine or at least 28 days after receipt of study vaccine.

9. * Has received a licensed live vaccine within 28 days prior to receipt of study vaccine or is scheduled to receive any live vaccine within 28 days following receipt of study vaccine.

10. Has received systemic corticosteroids (equivalent of ≥2 mg/kg/day of prednisone or ≥20 mg/day for persons weighing >10 kg) for ≥14 consecutive days and has not completed treatment at least 30 days before study entry or is expected to receive systemic corticosteroids at aforementioned dose and duration within 28 days following receipt of study vaccine. (Note: topical and inhaled/nebulized steroids are permitted.)

11. Has received systemic corticosteroids exceeding physiologic replacement doses (approximately 5 mg/day prednisone equivalent) within 14 days before vaccination.

12. Has received immunosuppressive therapies, including chemotherapeutic agents used to treat cancer or other conditions, treatments associated with organ or bone marrow transplantation, or autoimmune disease, within 6 months prior to receipt of study vaccine, or plans to receive immunosuppressive therapies within 28 days following receipt of study vaccine.

13. Has received a blood transfusion or blood products (including immunoglobulins) within 6 months prior to receipt of study vaccine or plans to receive a blood transfusion or blood products (including immunoglobulins) within 28 days following receipt of study vaccine.

Prior/Concurrent Clinical Study Experience

14. Has participated in another interventional clinical study within 6 months prior to signing the informed consent, or plans to participate in another interventional clinical study at any time during the duration of the current clinical study. Participants enrolled in observational studies may be included; these will be reviewed on a case-by-case basis for approval by MSD.

Diagnostic Assessments

Not applicable.

Other Exclusions

15. Has any other reason that, in the opinion of the investigator, may interfere with the evaluations required by the study. Reasons may include, but are not limited to, being unable to complete the eVRC, being unable to complete visits including non-office visit contacts (eg, telephone), or being unable to comply with study procedures.

16. Has planned donation of blood, eggs, or sperm at any time from signing the informed consent through 90 days postvaccination.

17. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site, Sponsor, or MSD staff directly involved with this study.

5.3 Lifestyle Considerations

No special restrictions on diet apply.

Since the study will evaluate immunogenicity of the vaccines at Day 28 postvaccination, it is suggested that participants who enroll in the study actively limit their exposure to mosquitoes to the extent possible until the Day 28 immunogenicity assessment, so as to avoid WT dengue infection.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who withdraws from the study will not be replaced.

6 STUDY INTERVENTION

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

Clinical supplies provided by the Sponsor and MSD will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Open-label, single-dose vials (V181) or multi-dose vials (Butantan-DV) will be supplied to the unblinded individual(s) at the clinical site. An unblinded pharmacist or unblinded qualified study-site personnel will prepare the study vaccines and will mask each syringe to conceal the contents prior to dispensing a vaccine dose to a blinded member of the study team for administration to the participant. Preparation and administration of the vaccine will occur as per the instructions in the Pharmacy Manual supplied by MSD.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 1.

Table 1 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use	IMP or NIMP/AxMP	Sourcing
V181 Group	Experi-mental	V181	Biological/ Vaccine	Sterile Suspension	10^2.8 – 10^3.8 PFU of each vaccine virus	0.5 mL	SC	Single dose at Visit 1	Test Product	IMP	Provided centrally by MSD
Butantan-DV Group	Experi-mental	Butantan-DV	Biological/ Vaccine	Sterile Suspension	10^3.4 – 10^4.1 PFU of each vaccine virus	0.5 mL	SC	Single dose at Visit 1	Test Product	IMP	Provided by Sponsor through local depot

DV=dengue vaccine; EEA=European Economic Area; IMP=investigational medicinal product; MSD=Merck Sharp & Dohme LLC; NIMP/AxMP=noninvestigational/auxiliary medicinal product; PFU=plaque forming unit; SC=subcutaneous.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

The Sponsor of this study is Instituto Butantan. MSD is executing the study.

The instructions for preparation of V181 and Butantan-DV are provided in the Pharmacy Manual supplied by MSD.

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc.).

Refer to Section 8.1.10 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

The study vaccine will be reconstituted by the unblinded pharmacist or unblinded qualified study-site personnel, as described in Section 6.3.3 and in the Pharmacy Manual.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country MSD personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by MSD.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to V181 or Butantan-DV.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. Both V181 and Butantan-DV will be provided open-label. Therefore, an unblinded pharmacist or unblinded qualified study-site personnel will be responsible for receiving, maintaining, preparing, and dispensing the study vaccines in accordance with a Pharmacy Manual provided by MSD. An unblinded Clinical Research Associate will monitor vaccine accountability at the study site.

A formal study of the visual appearances of the V181 and Butantan-DV cannot be performed prior to the study. Therefore, the unblinded pharmacist or unblinded study-site personnel will mask each syringe to conceal the contents prior to dispensing a vaccine dose to a blinded member of the study team for administration to the participant.

The participant, investigator, and study-site personnel directly involved in the clinical evaluation of the participants, as well as MSD field personnel or delegate(s) and Sponsor and MSD Headquarters personnel involved with the conduct of this study will be blinded to the participant-level intervention assignments.

To avoid bias, contact between the unblinded study-site personnel and participants is strictly prohibited throughout the study. Additionally, blinded study-site personnel will not be present when the study vaccine is prepared. Blinded study-site personnel will be responsible for all safety follow-up and immunogenicity specimen collection after study vaccine administration. Laboratory personnel responsible for conducting the assays will remain blinded to vaccination group assignments throughout the duration of the study.

An external unblinded statistician and statistical programmer not directly involved in the conduct of the study will be responsible for providing unblinded report deliverables to the eDMC. Details will be provided in the eDMC charter.

The primary safety and immunogenicity analyses will be performed, and a CSR will be prepared to present the results from Day 1 through the Day 28 postvaccination time point. After the database lock for the primary analysis, Sponsor and MSD Headquarters personnel involved in the conduct of the trial will be unblinded to vaccination group assignments. A blinded MSD Headquarters medical monitoring team will monitor the study after Day 28 through Month 12 postvaccination. Participants, investigators, study-site personnel, and MSD field personnel or delegates (eg, blinded Clinical Research Associate) will remain

blinded to the individual vaccination group assignments until the final study analyses are completed following the Month 12 (final) database lock.

See Section 8.1.13 for a description of the method of unblinding a participant during the study should such action be warranted.

6.4 Study Intervention Compliance

Participant study intervention compliance is defined in this study as a participant who receives the protocol-specified single dose of V181 or Butantan-DV. Any changes in the protocol-specified vaccination plan require consultation between the investigator and MSD Clinical Director and written documentation of the collaborative decision on participant management.

6.5 Management of GMO

V181 and Butantan-DV are GMOs. Standard precautions should be followed for vaccine preparation and administration. Needles and syringes that have been in contact with the study vaccines, as well as all other potentially contaminated materials, will be collected in dedicated containers and will be destroyed in a safe manner. This study will be conducted under local country regulations for use of a GMO.

6.6 Concomitant Therapy

Medications or vaccinations specifically prohibited within 28 days following receipt of study vaccine are described in Section 5.2. Receipt of any investigational or approved dengue vaccine (other than study vaccines) is prohibited during the duration of the study. If there is a clinical indication for any medications or vaccinations specifically prohibited, the investigator should discuss this with the MSD Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician.

Any medication or nonstudy vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives from the time of vaccination through Day 28 postvaccination must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

After Day 28 postvaccination, report only concomitant medications related to SAEs or dengue events, or receipt of any dengue vaccine (investigational or approved) other than study vaccines. The MSD Clinical Director should be contacted if there are any questions regarding concomitant or prior therapy.

6.6.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.7 Dose Modification (Escalation/Titration/Other)

No dose modification is specified to be used in this study.

6.7.1 Stopping Rules

There are no prespecified stopping rules for this study.

6.8 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.9 Clinical Supplies Disclosure

This study is blinded but supplies are provided as open label; therefore, an unblinded pharmacist or qualified study-site personnel will be used to blind supplies. Study intervention identity (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity. The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.13). If the emergency unblinding call center is not available for a given site in this study, the central electronic intervention randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. MSD will not provide random code/disclosure envelopes or lists with the clinical supplies.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

In clinical studies with a single intervention, discontinuation of study intervention can only occur prior to the intervention and generally represents withdrawal from the study.

Participants who receive a single-dose intervention cannot discontinue study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 8.1.12. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes

provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by MSD, as well as the investigator or the Sponsor, for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The total maximum amount of blood volume drawn from each participant over the duration of the study is approximately 50 mL, as detailed in the Laboratory Manual.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated ICF should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study ICF.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.2 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial screening. Specific details on the screening/rescreening visit requirements are in Section 8.8.1.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Inclusion/Exclusion Criteria

Prior to randomization, all inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.5 Medical History

A medical history will be obtained by the investigator or qualified designee prior to vaccination at Visit 1 (Day 1). The participant's relevant medical history for the 5 years prior to Visit 1 (Day 1) will be obtained to ensure that the participant satisfies the inclusion and exclusion criteria of the study. In addition, the investigator will inquire about the participant's history of dengue or Zika natural infection at any time prior to Visit 1 (Day 1).

For those participants remaining in the study at the time of Amendment 04, the investigator will also inquire about the participant's history of any other flavivirus infection(s) (west nile, yellow fever, etc) at any time prior to Visit 1 (Day 1).

8.1.6 Prior and Concomitant Medications Review

8.1.6.1 Prior Medications

The investigator or qualified designee will review prior medication/vaccination use and record prior medications/vaccines taken by the participant within 30 days before enrolling in the study in order to assess the study inclusion and exclusion criteria, including time windows for medication/vaccination use. In addition, the investigator will inquire about the receipt of any investigational or approved dengue vaccine at any time prior to Visit 1 (Day 1).

For those participants remaining in the study at the time of Amendment 04, the investigator will also inquire about the receipt of any other investigational or approved flavivirus vaccine (west nile, yellow fever, etc) at any time prior to Vist 1 (Day 1).

8.1.6.2 Concomitant Medications

At Visit 1 (Day 1) and at Visits 2, 3, and 4 postvaccination, the investigator or qualified designee will record medications and nonstudy vaccines, if any, taken by the participant through Day 28 postvaccination.

In addition, the participant will use the eVRC (Section 8.1.11) to record new and/or concomitant medications and nonstudy vaccines received from Day 1 through Day 28 postvaccination.

After Day 28 postvaccination, report only concomitant medications related to SAEs or dengue events, or receipt of any dengue vaccine (investigational or approved) other than study vaccines.

8.1.7 Pregnancy Testing

Pregnancy testing requirements for study inclusion are described in Section 5.1.

A pregnancy test consistent with local requirements (which must be sensitive to detect hCG at concentrations of 25 IU/L) must be performed in WOCBP at screening as shown in Section 1.3 or within 24 hours before study vaccine is administered. Urine or serum tests may be used, and results must be negative prior to vaccination. If a urine pregnancy test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. A detailed definition of WOCBP is provided in Appendix 5.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, at any time during the study.

8.1.8 Baseline Dengue Serostatus POC Screening Assay

A point of care (POC) serologic assay will be conducted at screening to determine a participant’s eligibility based on dengue serostatus as the participant must be dengue

seronegative to proceed with randomization. The POC assay must be conducted within 24 hours prior to vaccination.

The dengue POC assay is a lateral flow immunoassay for the simultaneous detection and differentiation of IgG and IgM anti-DENV (DENV1, 2, 3, and 4) in human serum, plasma, or whole blood. It is intended to be used by clinicians as a screening test and provides a preliminary test result to aid in the diagnosis of infection or prior infection with DENVs.

8.1.9 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment randomization. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.10 Study Intervention Administration

Study vaccines should be prepared and administered by appropriately qualified members of the study-site personnel (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local/state, country, and institutional guidance.

Study intervention is given on the day of treatment allocation/randomization or as close as possible to the date on which the participant is allocated/assigned.

Once the study vaccine has been prepared by the unblinded pharmacist or unblinded qualified study-site personnel, the study vaccine will be provided to a blinded member of the study team for administration to the participant. A blinded study-site person should administer the study vaccine subcutaneously using the syringe that was prepared and masked by the unblinded pharmacist or unblinded qualified study-site personnel.

Details of the vaccination should be documented on the appropriate eCRF as specified in the data entry guidelines.

Procedures for handling, preparing, dispensing, disposing, and returning the unblinded vaccines are provided in the Investigator Trial File Binder, which includes the Pharmacy Manual.

8.1.10.1 Timing of Dose Administration

In this study, V181 or Butantan-DV will be administered as a 0.5-mL SC injection at Visit 1 (Day 1). The day of the study vaccination is considered Day 1 of the study. Study participants will be observed by blinded study-site personnel for at least 30 minutes following vaccination for any immediate AEs; the time period may be extended if clinically indicated.

8.1.11 Electronic Vaccination Report Card (eVRC)

The eVRC was developed to be administered electronically via a hand-held device and is used to record AEs during the postvaccination period, as defined in Section 8.4.7. The eVRC is structured as recommended in the final US FDA Patient-Reported Outcome Guidance [U.S. Department of Health and Human Services 2009].

Participants will be provided an electronic device or have their own electronic device configured, if compatible, to complete the eVRC. The participant will be trained by the investigator or delegate in the use of the eVRC as indicated in Section 1.3.1. Noncompliance with the eVRC will require retraining by the site as soon as possible to ensure accurate and complete data capture.

Daily body temperatures, injection-site reactions, other complaints or illnesses, and concomitant medications/nonstudy vaccines will be recorded on the eVRC from Day 1 through Day 28 postvaccination (see Section 4.1). Participants will be required to measure their temperature using a digital thermometer provided by MSD and the size of injection-site reactions of swelling and redness using a ruler provided by MSD. Refer to Section 8.4.7 for safety assessments using the eVRC.

For the specific AEs collected via the eVRC, the investigator or delegate will discuss information entered into the eVRC with the participant at Day 7, Day 12, and Day 28 postvaccination (V2, V3, and V4) and apply the appropriate assessment of overall intensity grade as described in Appendix 3.

Any differences between eVRC data and the clinical database must be documented in the participant's source record.

8.1.12 Discontinuation and Withdrawal

Participants in this study will receive a single dose of study vaccine on Day 1 and cannot discontinue study intervention.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.13 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically

qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to MSD. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity grade of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the medical record prior to the unblinding, the unblinding should not be delayed.

If unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the MSD Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and MSD personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician should continue to be monitored in the study.

Additionally, the investigator or medically qualified designee must go into the IRT system and perform the unblind in the IRT system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this study, the IRT system should be used for emergency unblinding in the event that this is required for participant safety.

8.1.14 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Immunogenicity and Other Laboratory Assessments

All serum samples for immunogenicity and other laboratory assessments will be exported from Brazil to the US for testing.

8.2.1 DENV-Reduction Neutralization Test (VRNT)

The VRNT will be conducted to assess neutralizing antibodies for each of the 4 dengue vaccine serotypes (DENV1, DENV2, DENV3, DENV4) in specimens collected from vaccinated participants prior to vaccination on Day 1 (baseline) and at the Day 28, Month 3, and Month 12 postvaccination time points.

The VRNT for all 4 dengue serotypes was validated at Q2 Solutions contract research organization (US). The VRNT is performed by a two-fold serial dilution of serum samples and positive controls, and addition of an equal volume of diluted DENV (DENV1, DENV2, DENV3, or DENV4) containing a consistent target amount of virus for each given serotype. Virus control containing diluted virus without serum is also tested. After an incubation period to allow for virus-neutralization, each serum/virus mixture and virus control is transferred to a tissue culture plate containing confluent Vero cells and incubated to allow for non-neutralized virus adsorption. Following adsorption, the infected cells are incubated for a specified period of time to allow for replication of the virus. Plates are fixed, and infection is detected by immunostaining using a specific anti-dengue rabbit antibody and a secondary antibody labeled with Alexa Fluor 488. The titer of a sample is determined by counting and comparing the number of infected cells in the presence of the test serum to the virus control. The results are reported as a neutralization titer, which is the reciprocal of the dilution that reduced the number of infected cells by a defined percentage compared to the virus control. Calculations are performed using a 4-parameter nonlinear logistic equation. Dengue serostatus will be determined based on the $VRNT_{60}$ LLOQ (titer results <LLOQ are considered negative), corresponding to each dengue serotype and established during assay validation.

8.2.2 Dengue Viremia RT-PCR Assay (Dengue Vaccine and/or Dengue Wild Type)

CCI

[redacted]

8.2.3 Dengue NS1 ELISA

The FDA-approved InBios DENV Detect™ NS1 Antigen ELISA in Human Serum assay is being validated at Q2 Solutions contract research organization (US). The DENV Detect™ NS1 antigen ELISA is an enzymatically amplified "two-step" sandwich-type immunoassay to detect low levels of NS1 in serum. In this assay, controls and unknown serum samples are

diluted in sample dilution buffer, containing secondary antibody, and incubated in microtitration wells. These wells have been coated with a highly effective NS1 antibody and then blocked. NS1 antigens present in the samples are then "sandwiched" between the capture and secondary antibodies. The presence of NS1 antigen is confirmed by the colorimetric response obtained using an antibody-HRP conjugate and liquid 3, 3', 5, 5'-tetramethylbenzidine (TMB) substrate. Once the reaction is stopped, using an acidic solution, the enzymatic turnover of the substrate is determined by absorbance measurement at 450 nanometers.

8.2.4 Exploratory Immunogenicity Testing

CCI

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The maximum amount of blood collected per participant can be found in Section 8.

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

8.3.1 Physical Examinations Including Height and Weight

As part of the screening procedures, a complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard at Visit (Day 1).

A complete physical examination includes, but is not limited to, the assessment of vital signs (heart rate, respiratory rate, seated BP, and body temperature); assessment of head, eyes, ears, nose and throat (HEENT); auscultation of the heart and lung; and examination of the abdomen, skin, lymph nodes, neurological system, and musculoskeletal system. Height and

weight will also be measured and recorded. Investigators should pay special attention to clinical signs related to previous serious illnesses.

For participants with suspected dengue (participants who experience protocol-specified fever [axillary temperature of ≥37.8°C] for at least 2 consecutive days postvaccination at any time during the study), a brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard during the acute and convalescent follow-up visits.

In the source documents, investigators should document physical examination data and the status of all active medical conditions. Any clinically significant abnormality should be recorded on the appropriate eCRF.

8.3.2 Vital Signs

Vital signs are part of the physical examination at Visit 1 (Day 1) and include axillary body temperature, heart rate, respiratory rate, and seated BP.

BP and heart rate measurements will be assessed after the participant has at least 5 minutes of rest in a quiet setting without distractions, and from a sitting position, with a completely automated device. Manual techniques will be used only if an automated device is not available.

Abnormal vital signs must be confirmed by repeat testing after 15 minutes. Findings related to the vital signs should be documented in the participant source documentation. Any clinically significant abnormality will be recorded on the appropriate eCRF.

Axillary temperatures will be recorded by participants on the eVRC from Day 1 through Day 28 postvaccination. For this study, protocol-specified fever is defined as axillary temperature ≥37.8°C.

For participants with a febrile illness that is assessed as dengue or possible/probable dengue, vital signs will be collected during the acute and convalescent follow-up visits (Section 8.3.6).

8.3.3 Postvaccination Safety Observation Period

All participants will be observed, by blinded study-site personnel only, for at least 30 minutes postvaccination for any immediate reactions. If any immediate AEs are observed during this period, the time at which the event occurred within this timeframe, as well as the event itself, any concomitant medications that were administered, any medical intervention provided, and resolution of the event, must be recorded on the appropriate eCRFs.

8.3.4 Clinical Safety Laboratory Assessments

No clinical safety laboratory assessments are planned for this study.

8.3.5 Assessment of Rash

Rash is a solicited systemic AE, and participants who experience rash during the primary postvaccination safety period (Day 1 through Day 28 postvaccination) will be asked to record rash events on the eVRC. In addition, participants should be instructed to contact the site promptly to ensure that the rash is assessed by the investigator within 72 hours of onset, when reported Day 1 through Day 28 postvaccination. If rash assessment cannot occur at a planned visit (Visit 2, Visit 3, or Visit 4) within 72 hours of the participant's rash onset, then the rash should be assessed by the investigator at an unscheduled visit. Details of the rash assessment should be documented on the appropriate eCRF as specified in the data entry guidelines.

8.3.6 Assessment of Suspected Dengue Disease

The rationale for reporting all dengue-related events throughout the study is to collect data on dengue cases and severity because of previously reported increased dengue hospitalizations after vaccination with Dengvaxia® in baseline dengue-seronegative participants.

For the first 28 days after vaccination, participants should measure and record their temperature daily on the eVRC. After the 28-day period following vaccination through Month 12, participants should be advised to measure and record their temperature daily only when they feel febrile. Temperature should be documented on the appropriate eCRF as specified in the data entry guidelines.

Participants who experience protocol-specified fever (axillary temperature of ≥37.8°C) for ≥2 consecutive days postvaccination at any time during the study should schedule an acute visit as soon as possible and no later than 8 days after the second day of protocol-specified fever.

At the acute visit, the investigator will perform a clinical evaluation to assess the participant for dengue disease symptoms and severity using 2009 WHO Dengue Guidelines [World Health Organization 2009] (Section 10.3.6). Serum samples will be obtained from the participant at the acute visit to determine the presence of DENV for the purpose of confirming dengue infection in the context of the trial (Table 2); investigators will not receive the results of the tests performed during these visits and should evaluate and treat the participant according to their clinical judgment outside the scope of the trial.

Details of the febrile event assessment should be documented on the appropriate eCRF as specified in the data entry guidelines. A rash associated with an acute visit for suspected dengue should be documented on the appropriate eCRF.

Alternatively, a participant may choose to have an acute visit on the first day of protocol-specified fever and the investigator will follow the process outlined above; however, if the fever persists on the second consecutive day, then the participant must return for collection of a second serum sample, no later than 8 days after the second consecutive day of protocol-specified fever. The clinical evaluation must be conducted at the first acute visit, but may be repeated during the second visit at the investigator's discretion.

Based on the duration of the participant-reported fever and the serum sample test results, there are 3 possible outcomes, as outlined in Table 2.

Table 2 Evaluation and Outcomes for Febrile Event Assessments

Participant-reported Protocol-specified Fever [a]	Laboratory Result	Outcome
≥2 consecutive days	Positive for RT-PCR and/or NS1 ELISA	Virologically confirmed dengue case, per the protocol-specified definition
1 day or multiple nonconsecutive days	Positive for RT-PCR and/or NS1 ELISA	Dengue case
≥1 day	Negative for RT-PCR and/or NS1 ELISA	Not a dengue case

ELISA=enzyme-linked immunosorbent assay; NS=non-structural protein; RT-PCR=reverse transcription polymerase chain reaction.

[a] Protocol-specified fever is defined as axillary temperature of ≥37.8°C.

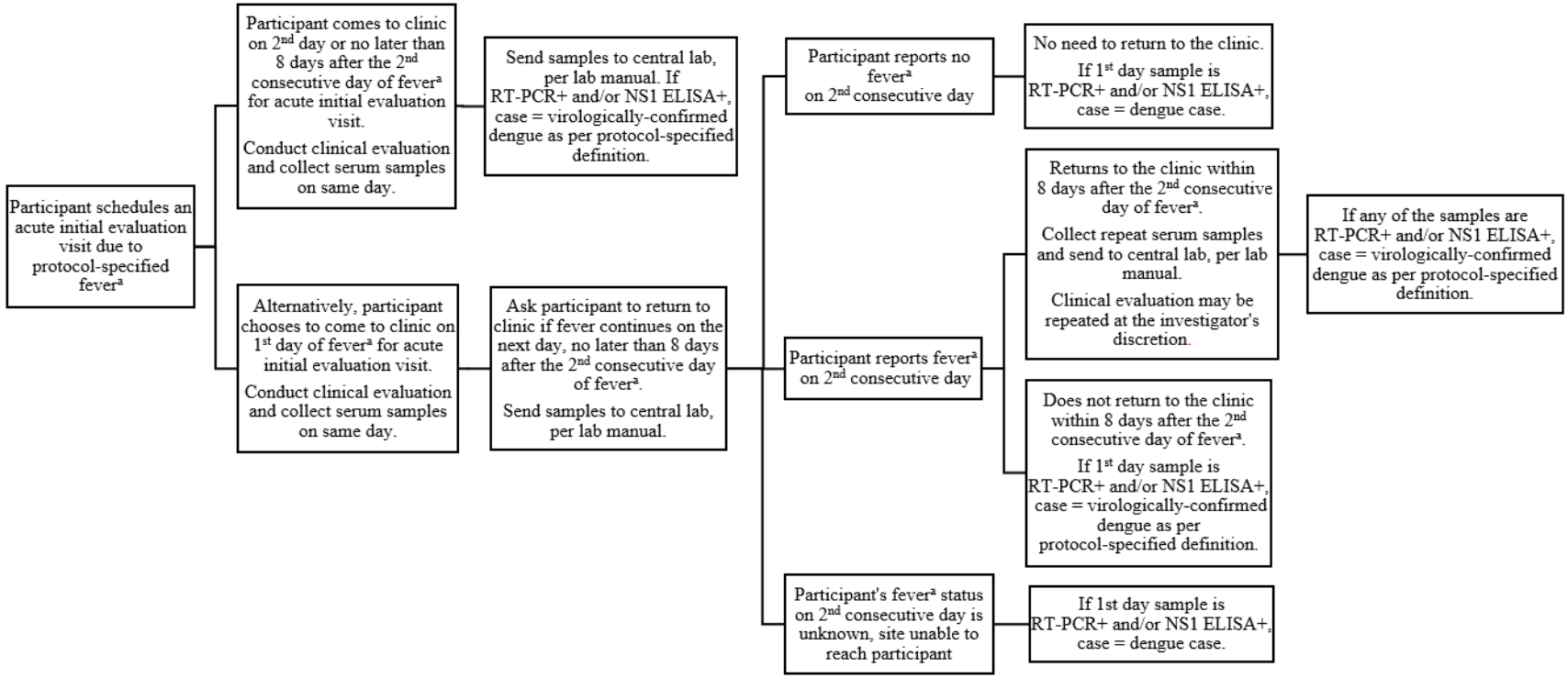
Figure 2 outlines possible scenarios for participants who experience protocol-specified fever (axillary temperature of ≥37.8°C) and present at the clinic for an acute visit.

If, based on clinical and/or local laboratory evaluation, the investigator assesses a case as dengue or possible/probable dengue, a convalescent follow-up visit to collect information about the severity and recovery from the febrile illness is to occur 14 to 28 days after the acute visit clinical evaluation. During the convalescent follow-up visit, the investigator will conduct a clinical evaluation. Guidelines for the investigator's clinical assessment of suspected dengue are in Section 10.3.6.

During extended follow-up visits (V5 and V8) and telephone contacts (V6 and V7), all participants will be reminded to schedule an acute visit in the event of at least 2 consecutive days of protocol-specified fever.

Febrile events evaluated by the investigator at an acute visit will be reported as MAAEs. Febrile events evaluated from Day 1 through Day 28 will also be reported as an NSAE. At any time during the study, report febrile events that meet serious criteria as an SAE.

Figure 2 V181-002 Assessment of Febrile Events for Suspected Dengue Disease



ELISA=enzyme-linked immunosorbent assay; MAAE=medically attended adverse event; NS=non-structural protein; RT-PCR=reverse transcription polymerase chain reaction

[a] Protocol-specified fever is defined as axillary temperature of ≥37.8°C. All febrile events evaluated at the site (acute visit) will be reported as MAAEs.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, overall intensity grade, and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before randomization, must be reported by the investigator if they cause the participant to be excluded from the study, or are the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

From the time of randomization through Day 28 postvaccination (primary safety follow-up period), all AEs, SAEs, and other reportable safety events must be reported by the investigator.

All MAAEs, SAEs, and deaths that occur from the time of randomization through Month 12 postvaccination must be reported by the investigator, regardless of whether the events are considered to be vaccine-related by the investigator.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify MSD.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to MSD or designee within the time frames as indicated in Table 3.

Table 3 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to MSD:**
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. - any death until participant completion of study (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to MSD of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor and MSD have a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor and MSD will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor and MSD policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor or MSD will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to MSD.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable for this study.

8.4.7 Adverse Events Reported on the eVRC

Participants will use an eVRC to report solicited and unsolicited AEs (Section 8.1.11).

The definitions of solicited and unsolicited AEs are provided in Appendix 3.

8.4.7.1 Solicited Adverse Events

Solicited AEs for this study are summarized in Table 4.

Table 4 Solicited Adverse Events for V181-002

Type of Solicited Adverse Event	Predefined Solicited Adverse Events	Solicited Time Period
Injection site	• Injection-site pain/tenderness • Injection-site erythema/redness • Injection-site swelling	Day 1 through Day 5 postvaccination
Systemic	• Rash • Headache • Fatigue (tiredness) • Myalgia (muscle pain) • Arthralgia (joint pain)	Day 1 through Day 28 postvaccination

All solicited injection-site AEs will be considered related to study intervention. The investigator will assess all solicited injection-site AEs for overall intensity grade, and all systemic AEs for both overall intensity grade and causality (Appendix 3).

In addition, the investigator will review all solicited AEs for the following:

- Is the event a symptom of another diagnosis?
- Is the event ongoing at the end of the solicited period?
- Does the event meet serious criteria?

Investigators are responsible for reviewing, assessing, and reporting data entered in the eVRC on the appropriate eCRF(s) as specified in the data entry guidelines. In addition, solicited injection-site AEs and solicited systemic AEs reported by the participant using the eVRC will be transferred directly to MSD's database.

8.4.7.2 Unsolicited Adverse Events

Unsolicited AEs for this study are events that are 1) not predefined in Table 4, or 2) predefined in Table 4, but reported at any time outside the solicited time period. Unsolicited AEs reported by the participant will be entered by study-site personnel on the appropriate eCRF.

As described in Section 8.4, the investigator will assess unsolicited events that meet the definition of an AE or SAE with respect to seriousness, overall intensity grade, and causality.

8.4.8 Events of Clinical Interest

No specific ECIs will be collected for this study.

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than 1 dose of the investigational V181 or Butantan-DV.

No specific information is available on the treatment of overdose.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.8.1 Screening

Prior to randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures will be conducted at Visit 1 (Day 1) and may be repeated after consultation with MSD.

8.8.2 Treatment Period/Vaccination Visit

Requirements during the treatment period are outlined in Section 1.3.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or the nonconfirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in an sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below; the comprehensive plan is provided in Sections 9.2 to 9.12.

Study Design Overview	A Phase 2, Randomized, Double-Blind, Multicenter, Safety and Immunogenicity Clinical Bridging Study to Compare V181 (Dengue Quadrivalent Vaccine rDENVΔ30 [live, attenuated]) to Butantan Dengue Vaccine (Butantan-DV) in Healthy Adults 18 to 50 Years of Age in Brazil
Treatment Assignment	There are 2 vaccination arms. Participants will be assigned randomly in a 1:1 ratio to receive V181 or Butantan-DV using an IRT. A double-blind/masking technique will be used.
Analysis Populations	Immunogenicity: PP Population Safety: APaT
Primary Endpoint(s)	Immunogenicity (Primary): DENV-neutralizing antibody GMTs for each of the 4 dengue serotypes at Day 28 postvaccination as measured by VRNT DENV-neutralizing antibody seroconversion rates for each of the 4 dengue serotypes at Day 28 postvaccination as measured by the VRNT. Seroconversion is defined as achieving a serotype-specific VRNT titer ≥LLOQ at Day 28 postvaccination in participants who are seronegative at baseline. Safety (Primary): Vaccine-related SAEs from Day 1 through Day 28 postvaccination

Key Secondary Endpoints	Safety (Secondary): Solicited injection-site AEs of pain, erythema, and swelling from Day 1 through Day 5 postvaccination Solicited systemic AEs of rash, headache, fatigue (tiredness), myalgia (muscle pain) and arthralgia (joint pain), from Day 1 through Day 28 postvaccination
Statistical Methods for Key Immunogenicity Analyses	To address the primary immunogenicity non-inferiority objective in terms of GMTs (H1), the comparison between groups will be made based on serotype-specific antibody GMTs for the 4 dengue serotypes at Day 28 postvaccination. The estimation of the GMT ratios and the corresponding 95% CIs will be calculated using a linear model with the log-transformed antibody titer as the response and a single term for vaccination group. To address the primary immunogenicity non-inferiority objective in terms of seroconversion rates (H2), the comparison between groups will be made based on serotype-specific antibody seroconversion rates for the 4 dengue serotypes at Day 28 postvaccination. The between-treatment difference (V181 minus Butantan-DV) and its 95% CI will be calculated using M&N method [Miettinen, O. and Nurminen, M. 1985].
Statistical Methods for Key Safety Analyses	For overall safety endpoints and specific AEs point estimates and 95% CIs for the differences between treatment groups in the percentages of participants with events will be provided using the M&N method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	There are no planned interim analyses for this study.
Multiplicity	The study will be considered to have met its primary objectives for immunogenicity if, at Day 28 postvaccination, V181 is demonstrated non-inferior to Butantan-DV for the 4 dengue serotypes for both primary endpoints (virus-neutralizing antibody GMTs and virus-neutralizing antibody seroconversion rates). All hypotheses will be tested individually for each serotype at a 1-sided 0.025 alpha level. This approach controls the 1 sided type-I error rate at 0.025, thus no multiplicity adjustment is required.
Sample Size and Power	Immunogenicity: This study will randomize participants in a 1:1 ratio into the 2 vaccination groups (V181 vs Butantan-DV). The overall sample size will be approximately 1240 with 620 participants in each vaccination group. This sample size ensures sufficient power (approximately 90%) to assess the endpoints for both primary hypotheses. All statistical tests will be conducted at a 1-sided 2.5% alpha level. Details are provided in Section 9.9.1 Safety: If no vaccine-related SAEs are observed among the 620 participants in each vaccination group, this study will provide 97.5% confidence that the underlying percentage of participants with vaccine-related SAEs is <0.6% in each vaccination group.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of MSD. This study will be conducted as a double-blind study under in-house blinding procedures.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study vaccination assignment. Randomization will be implemented in an IRT.

The primary safety and immunogenicity evaluation period for this study is defined as the period from Day 1 through Day 28 postvaccination. A CSR will be produced to present the results for this time period. The official, final database for the Day 28 analysis will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. After the Day 28 postvaccination visit, participants will be followed for safety (MAAEs, SAEs, deaths, and dengue-related events only) and immunogenicity through Month 12 postvaccination. Results for the Month 3 immunogenicity endpoints may be analyzed separately after Month 3 VRNT results become available and protocol deviations have been identified. Results for the remainder of the study through Month 12 postvaccination time period will be presented in a final, separate study report.

After the database lock for the primary analysis, most Sponsor and MSD Headquarters personnel involved in the conduct of the trial will be unblinded to vaccination group assignments. A blinded MSD Headquarters medical monitoring team will monitor the study after Day 28 through Month 12 postvaccination. Participants, investigators, study-site personnel, and MSD field personnel or delegates (eg, blinded Clinical Research Associate) will remain blinded to vaccination group assignments until the final study analyses are completed following the Month 12 (final) database lock.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

Immunogenicity and safety endpoints that will be evaluated are listed below.

9.4.1 Immunogenicity and Viremia Endpoints

Primary Immunogenicity Endpoints

- DENV-neutralizing antibody GMTs for each of the 4 dengue serotypes at Day 28 postvaccination as measured by VRNT.

- DENV-neutralizing antibody seroconversion rates for each of the 4 dengue serotypes at Day 28 postvaccination as measured by VRNT. Seroconversion is defined as achieving a serotype-specific VRNT titer ≥LLOQ at Day 28 postvaccination in participants who are seronegative at baseline. For participants who are seropositive at baseline (included in the FAS population) seroconversion is defined as achieving a 4-fold rise in serotype-specific VRNT titer at Day 28 postvaccination. Further information on the LLOQ will be documented in the sSAP.

Additional Immunogenicity and Viremia Endpoints

9.4.2 Safety Endpoints

An initial description of safety measures is provided in Section 4.2.1.2. The overall safety and tolerability profile for each vaccine will be assessed by clinical review of all safety data collected. Solicited and unsolicited injection-site and systemic AEs will be summarized overall, and by maximum reported intensity. The primary safety evaluation period for this study will be Day 1 through Day 28 postvaccination.

Primary Safety Endpoints

- Vaccine-related SAEs from Day 1 through Day 28 postvaccination

Secondary Safety Endpoints

- Solicited injection-site AEs of injection-site pain, injection-site erythema, and injection-site swelling from Day 1 through Day 5 postvaccination
- Solicited systemic AEs of rash, headache, fatigue (tiredness), myalgia (muscle pain), and arthralgia (joint pain) from Day 1 through Day 28 postvaccination

Additional Safety Endpoints

- Unsolicited AEs from Day 1 through Day 28 postvaccination
- Elevated temperature (≥37.8°C axillary) from Day 1 through Day 28 postvaccination
- MAAEs, SAEs, deaths, and dengue-related events from Day 1 through Month 12 postvaccination

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Populations

The PP population will serve as the primary population for the analysis of the immunogenicity data in this study. The PP population excludes participants due to deviations from the protocol that may substantially affect the results of the primary immunogenicity endpoint. Potential deviations that may result in the exclusion of a participant from the PP population for all immunogenicity analyses include:

- Prevaccination baseline blood sample test result is seropositive for any of the 4 dengue serotypes by VRNT. Seropositivity is defined as having a serotype-specific VRNT titer at or above the LLOQ of the assay.
- Failure to receive correct clinical material as per randomization schedule.
- Receipt of prohibited medication or prohibited vaccine prior to study vaccination or through Day 28 postvaccination.
- Collection of a blood sample at the time point for the analysis outside the prespecified window (as described in Section 1.3.1).
- Any virologically confirmed dengue case that occurs prior to the immunogenicity time point (Day 28, Month 3, Month 12 postvaccination) being evaluated.

The final determination on protocol violations, and thereby the composition of the PP population, will be made prior to the unblinding of the database and will be documented in a separate memo. The key immunogenicity analyses will also be performed using the FAS population, which consists of all randomized participants who receive study vaccination and have at least 1 valid serology result. Participants will be included in the vaccination group to which they are randomized for the analysis of immunogenicity data using the FAS population. No adjustment will be made for missing data.

If more than 10% of the participants have seropositive results at baseline, immunogenicity summaries of seropositive participants will also be generated.

9.5.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who received at least 1 dose of study vaccine. Participants will be included in the vaccination group corresponding to the study vaccine they actually received for the analysis of safety data using the APaT population. For most participants this will be the vaccination group to which they are randomized.

9.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Statistical methods related to exploratory objectives will be further described in

the sSAP. The key immunogenicity analyses to be performed are summarized in Table 5 (Section 9.6.1). The safety analyses are summarized in Section 9.6.2. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

9.6.1 Statistical Methods for Immunogenicity Analyses

Primary Endpoints/Hypothesis (H1)

The primary hypothesis of non-inferiority of antibody GMTs for each dengue serotype (DENV1, DENV2, DENV3, and DENV4) will be addressed by 4 one-sided tests of non-inferiority (1 corresponding to each dengue serotype) conducted at α=0.025 level (1-sided). For each dengue serotype, the hypotheses to be tested are:

H0: $GMT_1/GMT_2 \leq 0.67$

Versus

H1: $GMT_1/GMT_2 > 0.67$

where GMT_1 represents the GMT at Day 28 postvaccination in the V181 group and GMT_2 represents the GMT at Day 28 postvaccination in the Butantan-DV group. Estimation of the GMT ratios and computation of the corresponding 95% CIs will be calculated using t-distribution with the variance estimate from a linear model utilizing the log-transformed antibody titer as the response and a single term for vaccination group. The point estimates will be calculated by exponentiating the estimates of the mean of the natural log values and the CIs will be derived by exponentiating the CIs of the mean of the natural log values based on the model. The statistical criterion for non-inferiority requires that the lower bound of 2-sided 95% CI of GMT ratio (V181 vs Butantan-DV) being greater than 0.67.

Primary Endpoints/Hypothesis (H2)

The primary hypothesis of non-inferiority of seroconversion rates for each dengue serotype (DENV1, DENV2, DENV3, and DENV4) will be addressed by 4 one-sided tests of non-inferiority (1 corresponding to each dengue serotype) conducted at α=0.025 level (1-sided). For each dengue serotype, the hypotheses to be tested are:

H0: $p_1-p_2 \leq -0.1$

Versus

H1: $p_1-p_2 > -0.1$

where p_1 represents the seroconversion rate at Day 28 postvaccination in the V181 group and p_2 represents the seroconversion rate at Day 28 postvaccination in the Butantan-DV group. For each dengue serotypes, V181 is non-inferior to Butantan-DV if the lower bound of the 2-sided 95% CI for the between-treatment differences (V181 minus Butantan-DV) is greater than -0.1. The M&N method an unconditional, asymptotic method, will be used for this analysis [Miettinen, O. and Nurminen, M. 1985].

CCI

[redacted]

Table 5 Analysis Strategy for Primary Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[a]	Statistical Method	Analysis Population	Missing Data Approach
DENV-neutralizing antibody GMTs (H1) for each of the 4 dengue serotypes at Day 28 postvaccination as measured by VRNT	P S	t-distribution with the variance estimate from a linear model[b] (estimate, 95% CI, p-value)	PP FAS	Missing data will not be imputed
DENV-neutralizing antibody seroconversion rates (H2) for each of the 4 dengue serotypes at Day 28 postvaccination as measured by VRNT	P S	Miettinen and Nurminen (estimate, 95% CI, p-value)	PP FAS	Missing data will not be imputed

CI=confidence interval; DENV=dengue virus; FAS=Full Analysis Set; GMT=geometric mean titer; PP=Per-Protocol; VRNT=virus reduction neutralization test

[a] P=Primary approach; S=Supportive approach.

[b] Estimation of the DENV-neutralizing antibody GMTs and computation of the corresponding 95% CIs will be calculated using t-distribution with the variance estimate from a linear model utilizing the log-transformed antibody titer as the response and a single term for vaccination group.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters.

9.6.2.1 Overall Safety Assessment

The overall safety evaluation will include a summary by vaccination group of the number and percentage of participants with at least one AE, vaccine-related AE, MAAEs, vaccine-related MAAEs, SAE, vaccine-related SAE, discontinuation due to AE, and deaths; solicited

injection-site AEs of injection-site pain, injection-site erythema, and injection-site swelling; solicited systemic AEs of rash, headache, fatigue (tiredness), myalgia (muscle pain), and arthralgia (joint pain); and elevated temperature. Point estimates and 95% CIs for the differences between vaccination groups in the percentage of participants with the event will be provided based on the criteria described below for specific AEs.

The number and percentage of participants with specific AEs will also be provided. Point estimates and 95% CIs for the differences between treatment groups in the percentages of participants with specific AEs will be provided for AEs that occur in at least 1% of participants in any vaccination group. Events reported less frequently than in 1% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful differences.

CIs for between vaccination group differences will be provided using the stratified M&N method [Miettinen, O. and Nurminen, M. 1985]. CIs that are not adjusted for multiplicity should only be regarded as helpful descriptive measures for the review of the safety profile and not as a formal method for assessing statistical significance of between-group differences. Rainfall plots with point estimates and 95% CIs will be displayed for AEs that occur in at least 1% of participants in any vaccination group. Point estimates and 95% CIs will be provided for the percentage of participants with safety parameters that meet predefined limits of change based on the same criteria used above for the specific AEs.

9.6.2.2 Assessment of Safety Topics of Special Interest

There is no safety topic of special interest in this study.

Table 6 summarizes analysis strategy for safety endpoints in this study.

Table 6 Analysis Strategy for Safety Parameters

Analysis Part	Safety Endpoint	Descriptive Statistics	95% Between-Group CI	Inferential Analysis	Graphical Display
Overall Safety Assessment	Any [serious] [vaccine-related] AE	X	X		
	Any [vaccine-related] MAAE	X	X		
	Discontinuation due to AE	X	X		
	Death	X			
	Solicited injection-site AEs: pain, erythema, and swelling (Day 1 through Day 5 postvaccination)	X	X		
	Solicited systemic AEs: rash, headache, fatigue (tiredness), myalgia (muscle pain), and arthralgia (joint pain) (Day 1 through Day 28 postvaccination)	X	X		
	Elevated temperature	X	X		
	Specific AEs by SOC and PT	X	X[a]		X[a]
Assessment of Safety Topics of Special Interest	None				

AE=adverse event; CI=confidence interval; MAAE=medically attended adverse event; SOC=System Organ Class; PT=Preferred Term; X=results will be provided.

[a] Threshold for incidence will be applied for CI and Graphical Display

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the vaccination groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (eg, age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by vaccination group either by descriptive statistics or categorical tables.

9.7 Interim Analyses

There are no planned interim analyses for this study. Participant safety will be monitored by an eDMC that will perform periodic reviews of safety data throughout the study (Appendix 1). An external unblinded statistician and statistical programmer not directly involved in the conduct of the study will be responsible for providing unblinded report deliverables to the eDMC. Details will be provided in the eDMC charter.

9.8 Multiplicity

The study will be considered to have met its primary objectives for immunogenicity if, at Day 28 postvaccination, V181 is demonstrated non-inferior to Butantan-DV for the 4 dengue serotypes for both primary endpoints (DENV-neutralizing antibody GMTs and DENV-neutralizing antibody seroconversion rates). All hypotheses will be tested individually for each serotype at a 1 sided 0.025 alpha level. This approach controls the 1-sided type-I error rate at 0.025, thus no multiplicity adjustment is required.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Immunogenicity Analyses

This study will randomize participants in a 1:1 ratio into the 2 vaccination groups (V181 vs Butantan-DV). The overall sample size will be approximately 1240 with 620 participants in each vaccination group. This sample size ensures sufficient power (approximately 90%) to assess the endpoints for both primary hypotheses. The power for each individual hypothesis is provided below.

Primary Endpoints/Hypothesis (H1)

With this study sample size and the assumptions listed below, the power for the primary hypothesis to establish that V181 is non-inferior to Butantan-DV for all 4 dengue serotypes at an overall 1-sided, 2.5% alpha level based on GMTs is >95%. The power and sample size are based on the following assumptions: 1) an approximately 20% non-evaluable rate (496 evaluable participants per vaccination group) which includes an assumption of 10% of the participants being excluded due to be seropositivity at baseline; 2) the non-inferiority margin of 0.67; 3) the true GMT ratio is assumed to be 1; and CCI [redacted]

Primary Endpoints/Hypothesis (H2)

With the assumptions listed below, the power for the primary hypothesis to establish that V181 is non-inferior to Butantan-DV for all 4 dengue serotypes at an overall 1-sided, 2.5% alpha level based on seroconversion rates is ~90%.The power is based on the following assumptions: 1) an approximately 20% non-evaluable rate (496 evaluable participants per vaccination group) which includes an assumption of 10% of the participants being excluded due to be seropositivity at baseline; 2) the non-inferiority margin of -0.1 for the difference (V181 – Butantan-DV); and CCI [redacted]

9.9.2 Sample Size and Power for Safety Analyses

The probability of observing at least 1 vaccine-related SAE in this study depends on the number of participants vaccinated and the underlying percentage of participants with a

vaccine-related SAE in the study population. If the underlying incidence of a vaccine-related SAE is 0.11% (1 of every 895 participants receiving the vaccine), there is a 50% chance of observing at least 1 vaccine-related SAE among 620 participants in each vaccination group. If the incidence rate is 1 of every 386 recipients (0.26%), there is an 80% chance of observing at least 1 vaccine-related SAE. If no vaccine-related SAEs are observed among the 620 participants in each vaccination group, this study will provide 97.5% confidence that the underlying percentage of participants with vaccine-related SAE is <0.6% in each vaccination group.

Table 7 summarizes the percentage point differences between the 2 vaccination groups that could be detected with 80% probability for a variety of hypothetical underlying incidences of an AE. These calculations assume 620 participants each in the V181 group and the Butantan-DV group, and are based on a 2-sided 5% alpha level. The calculations are based on an asymptotic method proposed by Farrington and Manning (1990) [Farrington, C. P. and Manning, G. 1990]; no multiplicity adjustments will be made.

Table 7 Differences in Incidence of Adverse Event Rates Between the 2 Vaccination Groups That Can be Detected With an ~80% Probability (Assuming a 2-Sided 5% Alpha Level With 620 Participants in the V181 Group and 620 Participants in the Butantan-DV Group)

Incidence of an Adverse Event		**Risk Difference**
V181 (%)	**Butantan-DV (%)**	**Percentage Points**
1.5	0.1	1.4
4.9	2.0	2.9
9.1	5.0	4.1
15.3	10.0	5.3
21.1	15.0	6.1
26.7	20.0	6.7
37.5	30.0	7.5
Incidences presented here are hypothetical and do not represent actual adverse experiences in either group. Based on an asymptotic method proposed by Farrington and Manning (1990).		

9.10 Subgroup Analyses

CCI [redacted]

9.11 Compliance (Medication Adherence)

The number and proportion of randomized participants receiving each vaccine will be summarized (see Section 9.12).

9.12 Extent of Exposure

The extent of exposure will be summarized by the number and proportion of randomized participants administered V181 or Butantan-DV.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus

source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is MSD's responsibility to determine, based on these regulations, whether a request for financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor or delegate in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor and MSD to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by MSD. The investigator/subinvestigator(s) also consent to the transmission of this information to MSD in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor and MSD will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by MSD. Any participant records or datasets that are transferred to MSD will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor and MSD in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor and MSD, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor and MSD that information furnished to the investigator by the Sponsor or MSD will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor, MSD (or Sponsor or MSD representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to MSD.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

MSD is required to record the name and address of each IRB/IEC that reviews and approves this study. MSD, on behalf of the Sponsor, is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

The EOC is comprised of members of Sponsor and MSD Senior Management. The EOC will receive and decide upon any recommendations made by the eDMC regarding the study.

10.1.4.2 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the periodic data from this study. The voting members of the committee are external to the Sponsor and MSD. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review periodic study results, consider the overall risk and benefit to study participants and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the MSD protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor and MSD will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor and MSD will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor and MSD, the investigator agrees to submit all manuscripts or abstracts to the Sponsor and MSD before submission. This allows the Sponsor and MSD to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007, the Sponsor of the study is solely responsible for registering the study and posting its results to http://www.clinicaltrials.gov or other local registries. Butantan, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue

participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

This study, sponsored by Butantan, will be conducted in a manner consistent with the MSD Code of Conduct for Clinical Trials (Section 10.1.1).

Section III.A. (Regulatory Authority and Ethics Committee Review) of the Code of Conduct is adapted for this study to clarify that it is the Sponsor's responsibility to submit the protocol and protocol amendments to the regulatory authorities, as follows:

> All protocols and protocol amendments will be submitted by the Sponsor for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.
>
> The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. The Sponsor will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

Section IV.B. (Clinical Research Funding) of the Code of Conduct is adapted for this study to accurately identify Butantan as the trial Sponsor, as follows:

> Informed consent forms will disclose that the trial is sponsored by Butantan, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from this trial will indicate MSD as a source of funding.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by MSD.

The investigator will promptly inform MSD of any regulatory authority inspection conducted for this study.

The investigator agrees to provide MSD with relevant information from inspection observations/findings to allow the Sponsor and/or MSD to assist in responding to any citations resulting from regulatory authority inspection and will provide MSD with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on MSD's studies. The investigator will immediately disclose in writing to MSD if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to MSD or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to MSD by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of MSD or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by MSD or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

MSD or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of MSD. No records may be transferred to another location or party without written notification to MSD.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

MSD in collaboration with the Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event MSD in collaboration with the Sponsor prematurely terminates a particular study site, MSD or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

Safety laboratory assessments (ie, blood chemistry, hematology, and urinalysis) are not planned for this study.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the participant.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired non-therapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor or MSD's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor or MSD for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

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

- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

- Refer to Section 8.4.6 for protocol-specific exceptions.

Definition of Solicited and Unsolicited AE

- Solicited AEs are predefined local (at the injection site) and systemic events for which the participant is specifically questioned, and which are noted by the participant in the eVRC.

- An unsolicited AE is an AE that was not solicited using an eVRC and that is communicated by a participant who has provided documented informed consent. Unsolicited AEs include serious and nonserious AEs and may be reported via the eVRC or via other methods.

Definition of MAAE

- AEs in which medical attention is received during an unscheduled, non-routine outpatient visit, such as an ER visit, office visit, or an urgent care visit with any medical personnel for any reason. Routine visits are not considered MAAEs. Examples of routine visits include: physical examination, wellness visits, or vaccinations.

- Determination of MAAEs is the responsibility of the investigator or a qualified designee. Once identified, MAAEs should be reported to MSD per the timeline for reporting AEs/SAEs.

NOTE: For this study a febrile event reported during an acute visit (see Section 8.3.6) is considered an MAAE.

10.3.3 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

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

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of Sponsor or MSD's product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

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

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to MSD.

- Is a cancer
- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to MSD in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by MSD. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to MSD.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of overall intensity grade for each AE and SAE (and other reportable event) reported during the study. An overall intensity grade will be assigned to injection-site AEs, specific systemic AEs, other systemic AEs, and vital sign (temperature) AEs as shown in the following tables. The overall intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007" [Food and Drug Administration 2007].

Injection-Site AE Overall Intensity Grading Scale

Injection-Site Reaction to Study Vaccine[a]	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life-Threatening (Grade 4)**
Injection-site AEs occurring Days 1 through 5 following receipt of study vaccine				
Pain/Tenderness	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Erythema/Redness	≤5 cm (size measured as A or B)	5.1 to 10 cm (size measured as C or D)	>10 cm (size measured as E→)	Necrosis or exfoliative dermatitis or results in ER visit or hospitalization
Swelling	≤5 cm (size measured as A or B)	5.1 to 10 cm (size measured as C or D)	>10 cm (size measured as E→)	Necrosis or ER visit or hospitalization
Other	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Any injection-site reaction that begins ≥6 days after receipt of study vaccine				
Pain/Tenderness Erythema/Redness Swelling Other	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization

Injection-Site Reaction to Study Vaccine[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Injection-site AEs occurring Days 1 through 5 following receipt of study vaccine				

AE=adverse event; ER=emergency room; eVRC=electronic Vaccination Report Card
The overall intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007" [Food and Drug Administration 2007].

[a] Based upon information provided by the participant on the eVRC and verbally during eVRC review. Erythema/Redness and Swelling are specific injection-site AEs with size designations of letters A (<2.5 cm), B (2.5 to 5 cm), C (5.1 to 7.4 cm), D (7.5 to 10 cm), and E (>10 cm), based upon a graphic in the eVRC user guide. If the participant has an ER visit or is hospitalized for any injection-site AE, that AE is to be assigned an intensity grade of 4, regardless of the size measured.

Specific Systemic AE Overall Intensity Grading Scale

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue/tiredness	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Muscle pain/myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Joint pain/arthralgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Rash	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

ER=emergency room
The overall intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007" [Food and Drug Administration 2007].

Other Systemic AE Overall Intensity Grading Scale

Systemic Illness[a]	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)[b]
Illness or clinical AE (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and required medical intervention	ER visit or hospitalization

AE=adverse event; ER=emergency room; eVRC=electronic Vaccination Report Card; SAE=serious adverse event
The overall intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007" [Food and Drug Administration 2007].

[a] Based upon information provided by the participant on the eVRC and verbally during the eVRC review during the primary safety follow-up period. For SAEs reported beyond the primary safety follow-up period, grading will be based upon the initial report and/or follow-up of the event.

[b] AEs resulting in death will be assessed as Grade 4.

Vital Sign (Temperature) Overall Intensity Grading Scale

Vital Signs[a]		Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life-Threatening (Grade 4)
Fever	(°C)[b]	38.0 to 38.4	38.5 to 38.9	39.0 to 40.0	>40.0
	(°F)[b]	100.4 to 101.1	101.2 to 102.0	102.1 to 104.0	>104.0

The overall intensity grading scales used in this study are adapted from the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007" [Food and Drug Administration 2007].

[a] Participant should be at rest for all vital sign requirements.

[b] Oral temperature; no recent hot or cold beverages or smoking.

Assessment of causality

- Did the Sponsor or MSD's product cause the AE?

- The determination of the likelihood that the Sponsor or MSD's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialled document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor or MSD's product and the AE**; the greater the correlation with the

components and their respective elements (in number and/or intensity), the more likely the Sponsor or MSD's product caused the AE:

- **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor or MSD's product such as: reliable history, acceptable compliance assessment (diary, etc.), seroconversion or identification of vaccine virus in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor or MSD's product? Is the time of onset of the AE compatible with a vaccine-induced effect?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?

- **Rechallenge:** Was the participant re-exposed to the Sponsor or MSD's product in the study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose vaccine study; or (3) Sponsor or MSD's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR OR MSD'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR OR MSD'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE MSD CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor or MSD's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor or MSD's product relationship).
    - Yes, there is a reasonable possibility of Sponsor or MSD's product relationship:
        - There is evidence of exposure to the Sponsor or MSD's product. The temporal sequence of the AE onset relative to the administration of the Sponsor or MSD's product is reasonable. The AE is more likely explained by the Sponsor or MSD's product than by another cause.
    - No, there is not a reasonable possibility of Sponsor or MSD's product relationship:
        - Participant did not receive the Sponsor or MSD's product OR temporal sequence of the AE onset relative to administration of the Sponsor or MSD's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor or MSD's product. (Also entered for a participant with overdose without an associated AE.)
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to MSD. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to MSD.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by MSD to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to MSD within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to MSD

AE, SAE, and other reportable safety event reporting to MSD via electronic data collection tool

- The primary mechanism for reporting to MSD will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

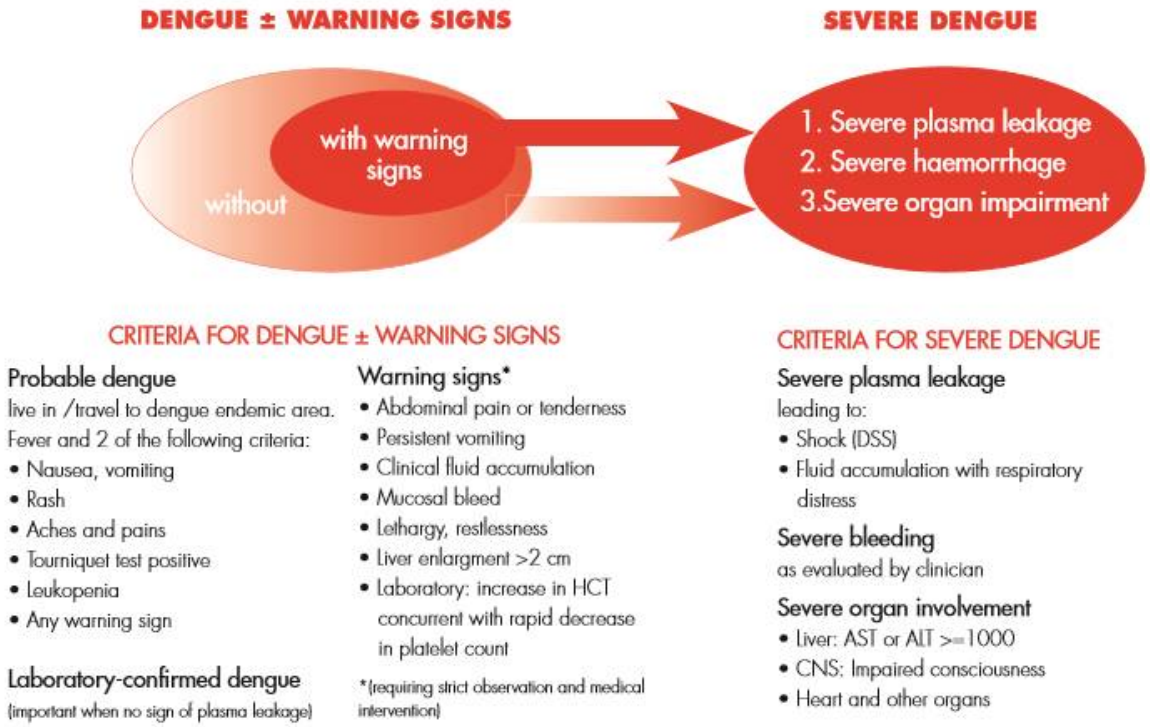
SAE reporting to MSD via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to MSD.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

10.3.7 2009 WHO Dengue Guidelines for Diagnosis, Treatment, Prevention and Control

Criteria for diagnosing dengue (with or without warning signs) and severe dengue from the 2009 WHO Dengue Guidelines [World Health Organization 2009] are presented in Figure 3.

Figure 3 Suggested Dengue Case Classification and Levels of Severity



ALT=alanine amino transferase; AST=aspartate amino transferase; CNS=central nervous system; DSS=dengue shock syndrome; HCT=hematocrit.

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

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

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

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

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c] • IUS[d] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly*.
• Combined (estrogen- and progestogen- containing) hormonal contraception[c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c] - Oral - Injectable
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [d] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not applicable.

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
ANVISA	Agência Nacional de Vigilância Sanitária (Brazilian Health Regulatory Agency)
APaT	All Participants as Treated
AxMP	auxiliary medicinal product
BP	blood pressure
Butantan-DV	Butantan Dengue Vaccine
CFR	Code of Federal Regulations
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CSR	clinical study report
CTFG	clinical trial facilitation group
DENV	dengue virus
DF	dengue fever
DHF	dengue hemorrhagic fever
DMC	Data Monitoring Committee
DSS	dengue shock syndrome
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data collection
eDMC	external DMC
EEA	European Economic Area
ELISA	enzyme-linked immunosorbent assay
EOC	Executive Oversight Committee
ER	emergency room
eVRC	electronic Vaccination Report Card
FAS	Full Analysis Set
FDA	Food and Drug Administration (US)
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMO	genetically modified organism
GMT	geometric mean titer
hCG	human chorionic gonadotropin
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device

Abbreviation	Expanded Term
IUS	intrauterine hormone-releasing system
LAM	lactational amenorrhea method
LATV	live-attenuated tetravalent vaccine
LLOQ	lower limit of quantitation
MAAE	medically attended adverse event
M&N	Miettinen and Nurminen
mFRNT	micro-focus reduction neutralization test
NIH	National Institute of Health
NIMP	Non-Investigational Medicinal Product
NS	nonstructural protein
NSAE	nonserious adverse event
PCR	polymerase chain reaction
PFU	plaque forming unit
POC	point of care
PP	Per-Protocol
PT	preferred term
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SINAN	Brazil Information System for Notifiable Diseases
SoA	schedule of activities
SOC	system organ class
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
US	United States
VRC	Vaccination Report Card
VRNT	virus reduction neutralization test
WHO	World Health Organization
WOCBP	woman/women of childbearing potential
WT	wild type

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