Official Protocol Title:	A Phase 2, Randomized, Double-Blind, Multicenter Study to Evaluate the Safety and Immunogenicity of Three Different Potency Levels of V181 (Dengue Quadrivalent Vaccine rDENVΔ30 [live, attenuated]) in Healthy Adults
NCT number:	NCT05507450
Document Date:	14-Jul-2022

Title Page

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Protocol Title: A Phase 2, Randomized, Double-Blind, Multicenter Study to Evaluate the Safety and Immunogenicity of Three Different Potency Levels of V181 (Dengue Quadrivalent Vaccine rDENVΔ30 [live, attenuated]) in Healthy Adults

Protocol Number: 003-01

Compound Number: V181

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	17780
EudraCT	2020-004501-30

Approval Date: 14 July 2022

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study 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 01	14-JUL-2022	The primary reason for the amendment was to provide the potency levels for V181 and to extend the contraception requirements from 4 weeks after administration of study intervention to 90 days after administration of study intervention.
Original Protocol	03-DEC-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendments:

The primary reason for the amendment was to provide the potency levels for V181 and to extend the contraception requirements from 4 weeks after administration of study intervention to 90 days after administration of study intervention.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Primary Reasons for Amendment		
1.1 Synopsis 6.1 Study Intervention(s) Administered – Table 1	Added potency levels for each serotype being administered for each of the 3 V181 potency level groups, and deleted footnote about potency levels being 'to be determined'. Added a footnote to indicate that the provided potency levels represent the final dose strength for the 0.5 mL dose of V181.	Potency levels being administered were previously to be determined. To clarify that the potency levels described represent the final dose strength in each 0.5 mL dose of V181.
5.1 Inclusion Criterion No. 3 5.1 Inclusion Criterion No. 4	Extended contraception requirements from 4 weeks to 90 days.	To reduce the risk of pregnancy in WOCBP who are study participants (in accordance to MSD specifications for other live virus vaccines, such as VARIVAX™) or partners of male study participants (a spermatogenesis cycle is approximately 90 days).

Section # and Name	Description of Change	Brief Rationale
Additional Changes Made in Amendment		
Title Page 10.1.1 Code of Conduct for Clinical Trials	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and updated to the address.
1.1 Synopsis 6.1 Study Intervention(s) Administered – Table 1	Changed the intervention name for the placebo group from 'Diluent' to 'Placebo'. In the 'Use' column for V181 groups, changed 'Experimental' to 'Test Product.'	To reduce confusion around the study intervention being administered in the Placebo Group. To align with EU CTR.
1.3 Schedule of Activities	Added a row for the collection of study-supplied eVRC devices.	To clarify when eVRC devices will be collected.
2.1 Study Rationale 4.2 Scientific Rationale for Study Design 4.3 Justification for Dose 6.2.1 Dose Preparation	Removed placeholder text for the potency levels and/or added a cross-reference to the study interventions table.	To reflect that potency levels are now known and to ensure the ease of finding vaccine potency level information.
2.2.1 Dengue Disease and V181 Development	Added a description of the risk of ADE for dengue vaccines.	To clarify what ADE is and how it may affect the study.
4.1 Overall Design	Added a statement about eVRC devices.	To clarify that participants may be provided with an eVRC device or may have their personal device configured for eVRC.

Section # and Name	Description of Change	Brief Rationale
4.2.2 Rationale for the Use of Comparator/Placebo 6 Study Intervention 6.1 Study Intervention(s) Administered – Table 1 6.2.1 Dose Preparation	Removed references to 'diluent,' including removing the footnote in Table 1.	For consistency when referring to placebo and to reduce confusion around placebo and diluent.
5 Study Population	Added a statement about the confidentiality of collected information.	To align with EU CTR.
5.1 Exclusion Criterion No. 16	Changed donation requirements from 6 weeks to 90 days postvaccination.	To reduce the risk of viremic participants donating blood, eggs, or sperm.
6.1 Study Intervention(s) Administered – Table 1	Deleted footnote about dilution procedures for V181. Revised the column heading and footnote for investigational product from 'IMP/NIMP' to 'IMP or NIMP/AxMP'.	To avoid redundancy in the protocol with the detailed information that will be provided in the Pharmacy Manual. To align with EU CTR.
8.1.11.1 Withdrawal From Future Biomedical Research 10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research	Updated Sponsor email address for clinical specimen management.	To align with current email address.

Section # and Name	Description of Change	Brief Rationale
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events	Added a statement about investigators needing to indicate if an event was associated with a medication error, misuse, or abuse.	To align with EU CTR.
10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Added a subsection to define medication error, misuse, and abuse.	To align with EU CTR.
10.3.5 Recording AE and SAE – Assessment of Intensity	Added 2 rows to the AE Intensity Grading table to identify which assessments are performed for injection site AEs occurring on Days 1 through 5 and those occurring on Day 6 or later after vaccination. Added a row for 'Other' injection-site AEs occurring on Days 1 through 5, reformatted presentation of grading criteria, and updated footnotes to align with information presented in the table. Removed induration from list of injection-site reactions	To align with current reactogenicity guidance for vaccine studies. Induration is not being evaluated as an injection-site reaction in this study.

Section # and Name	Description of Change	Brief Rationale
Throughout	Minor administrative formatting, grammatical, and 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 Study to Evaluate the Safety and Immunogenicity of Three Different Potency Levels of V181 (Dengue Quadrivalent Vaccine rDENVΔ30 [live, attenuated]) in Healthy Adults

Short Title: Safety and Immunogenicity of Three V181 Dengue Vaccine Potencies in Adults

Acronym: V181-003

Hypotheses, Objectives, and Endpoints:

The following objectives and endpoints will be evaluated in healthy male and female participants, 18 to 50 years of age (inclusive).

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 the V181 Low Potency Level versus V181 Mid Potency Level Hypothesis: V181 Low Potency Level is non-inferior to V181 Mid Potency Level 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 Low Potency Level versus V181 Mid Potency Level] 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 evaluate the safety and tolerability of 3 different V181 potency levels with respect to the proportion of participants experiencing SAEs	- Vaccine-related serious adverse events from Day 1 through Day 28 postvaccination

Secondary Objectives	Secondary Endpoints
- To evaluate the safety and tolerability of 3 different V181 potency levels with respect to the proportion of participants experiencing solicited AEs	- Solicited injection-site adverse events from Day 1 through Day 5 postvaccination - Solicited systemic adverse events 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	Placebo
Study Blinding	Double-blind with in-house blinding
Blinding Roles	Sponsor Investigator Participants or Subjects
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 20 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 the Sponsor receives the last laboratory result or at the time of final contact with the last participant, whichever comes last.

Number of Participants:

Approximately 1265 participants will be randomized in this study.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Arm Name</th><th>Intervention Name</th><th>Unit Dose Strength[a] (PFU)</th><th>Route of Admin.</th><th>Vaccine Regimen</th><th>Use</th></tr>
<tr><td>V181 High Potency Level Group</td><td>V181 High Potency Level</td><td rowspan="3">CCI</td><td>SC</td><td>Single dose at Visit 1 (Day 1)</td><td>Test Product</td></tr>
<tr><td>V181 Mid Potency Level Group</td><td>V181 Mid Potency Level</td><td>SC</td><td>Single dose at Visit 1 (Day 1)</td><td>Test Product</td></tr>
<tr><td>V181 Low Potency Level Group</td><td>V181 Low Potency Level</td><td>SC</td><td>Single dose at Visit 1 (Day 1)</td><td>Test Product</td></tr>
<tr><td>Placebo Group</td><td>Placebo</td><td>0</td><td>SC</td><td>Single dose at Visit 1 (Day 1)</td><td>Placebo</td></tr>
<tr><td colspan="6">Admin.=administration; NA=not applicable; PFU = plaque forming unit; SC=subcutaneous
[a] This represents the final dose strength of each serotype for a 0.5 mL dose of V181 after field preparation, as per the pharmacy manual.</td></tr>
</table>
</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>4 intervention groups</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 12 months from the time the participant provides documented informed consent through the final contact.</td></tr>
</table>

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.	

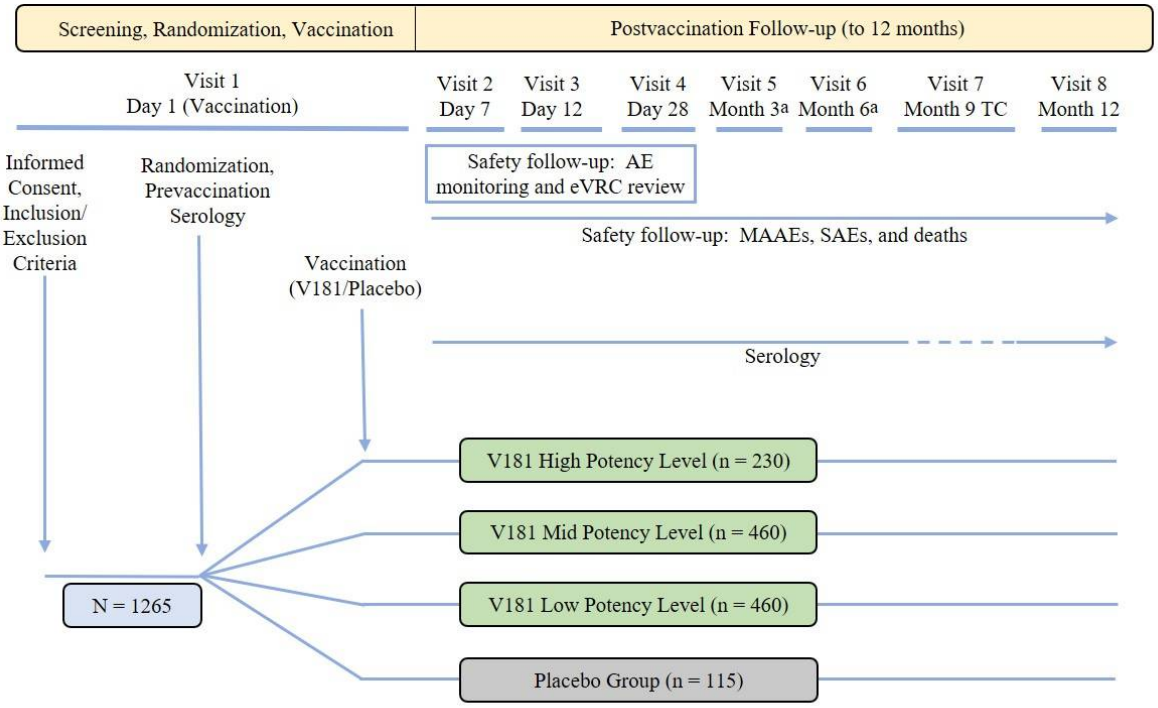
Study Accepts Healthy Volunteers: Yes

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 V181-003 Study Design



Abbreviations: eVRC = electronic vaccine report card; MAAE = medically attended adverse event; N = total number of participants; n = number of participants in dose group; SAE = serious adverse event; TC = telephone contact

a Antibody responses will be evaluated for half of the participants in each group at the Month 3 timepoint and the other half at the Month 6 timepoint in order to assess the durability of immune response.

1.3 Schedule of Activities

Study Period:	Screening/ Randomization/ Intervention			Follow-up (through Month 12 postvaccination)							Notes
Visit Number/Title:	1			2	3	4	5	6	7	8	
Scheduled Day or Month:	Day 1			Day 7	Day 12	Day 28	Month 3	Month 6	Month 9 TC	Month 12	For Visit 5, half of participants in each group will have TC and for Visit 6, other half will have TC.
Visit Window Permitted:	Pre-Dose	Dose	Post-Dose	±2 days (Days 5 to 9)	±2 days (Days 10 to 14)	+14 days (Days 28 to 42)	±14 days (Days 76 to 104)	±14 days (Days 166 to 194)	±14 days (Days 256 to 284)	±14 days (Days 346 to 374)	
Administrative Procedures											
Informed Consent	X										Consent must be obtained BEFORE any study procedures, including screening.
Informed Consent for FBR	X										Participation in FBR is optional. Consent must be obtained before collection of FBR samples.
Assignment of Screening Number	X										
Participant Identification Card	X										
Inclusion/Exclusion Criteria	X										
Medical History	X										Includes medical history for 5 years before screening.
Prior/Concomitant Medication/Vaccines Review	X			X	X	X	X	X	X	X	After Visit 4, report only concomitant medications associated with SAEs and/or receipt of investigational or approved dengue vaccine. Sections 5.2 and 6.6.

Study Period:	Screening/ Randomization/ Intervention			Follow-up (through Month 12 postvaccination)							Notes
Visit Number/Title:	1			2	3	4	5	6	7	8	
Scheduled Day or Month:	Day 1			Day 7	Day 12	Day 28	Month 3	Month 6	Month 9 TC	Month 12	For Visit 5, half of participants in each group will have TC and for Visit 6, other half will have TC.
Visit Window Permitted:	Pre-Dose	Dose	Post-Dose	±2 days (Days 5 to 9)	±2 days (Days 10 to 14)	+14 days (Days 28 to 42)	±14 days (Days 76 to 104)	±14 days (Days 166 to 194)	±14 days (Days 256 to 284)	±14 days (Days 346 to 374)	
Urine Pregnancy Test (WOCBP only)	X										Performed by site. WOCBP must have negative result before vaccination.
Serum hCG (WOCBP only)	X										Serum hCG is tested only if the urine pregnancy test is inconclusive. WOCBP must have negative result before vaccination.
Randomization/Vaccination											
Assignment of Randomization Number	X										
V181/Placebo Administration		X									Only blinded study personnel administer study vaccine/placebo. See Section 8.1.9.
Distribute eVRC			X								Study-site personnel will train participant on use of eVRC.
Immunogenicity Procedures											
Serum samples for Dengue Antibody Titers (VRNT)	X					X	X	X		X	• Day 1 blood sample must be collected before vaccination. See Section 8.2. • For half of participants in each of the 4 groups at Visits 5 and 6. See Section 4.

Study Period:	Screening/ Randomization/ Intervention			Follow-up (through Month 12 postvaccination)							Notes
Visit Number/Title:	1			2	3	4	5	6	7	8	
Scheduled Day or Month:	Day 1			Day 7	Day 12	Day 28	Month 3	Month 6	Month 9 TC	Month 12	For Visit 5, half of participants in each group will have TC and for Visit 6, other half will have TC.
Visit Window Permitted:	Pre-Dose	Dose	Post-Dose	±2 days (Days 5 to 9)	±2 days (Days 10 to 14)	+14 days (Days 28 to 42)	±14 days (Days 76 to 104)	±14 days (Days 166 to 194)	±14 days (Days 256 to 284)	±14 days (Days 346 to 374)	
Safety Procedures											
Full Physical Examination Including Height and Weight	X										Full physical examination is required to determine study eligibility. See Section 8.3.1.
Vital Signs	X										See Section 8.3.2.
Postvaccination Safety Observation			X								Blinded study personnel monitor participant at the study site for at least 30 min for any immediate reactions following vaccination. See Section 8.3.3.
AE/SAE Review	X			X	X	X	X	X	X	X	• After Visit 4, only MAAEs, SAEs, and deaths are reported. • Rashes with onset D1 to D28 postvaccination should be evaluated by the investigator within 72 hrs of onset (Section 8.3.5).
Review of eVRC				X	X	X					Review the eVRC with the participant at Visits 2, 3, and 4.
Collect Electronic Device for eVRC						X					For participants who received a study-supplied device.

Study Period:	Screening/ Randomization/ Intervention			Follow-up (through Month 12 postvaccination)							Notes
Visit Number/Title:	1			2	3	4	5	6	7	8	
Scheduled Day or Month:	Day 1			Day 7	Day 12	Day 28	Month 3	Month 6	Month 9 TC	Month 12	For Visit 5, half of participants in each group will have TC and for Visit 6, other half will have TC.
Visit Window Permitted:	Pre-Dose	Dose	Post-Dose	±2 days (Days 5 to 9)	±2 days (Days 10 to 14)	+14 days (Days 28 to 42)	±14 days (Days 76 to 104)	±14 days (Days 166 to 194)	±14 days (Days 256 to 284)	±14 days (Days 346 to 374)	
Biomarkers											
Blood (DNA) for FBR	X										Collect before vaccination from randomized and FBR-consented participants only.
Blood for [redacted] Testing				X	X						There must be at least 2 days between Visit 2 and Visit 3.
AE=adverse event; hCG=human chorionic gonadotropin; DNA= deoxyribonucleic acid; eVRC=electronic vaccination report card; FBR=future biomedical research; MAAE = medically attended adverse event; SAE=serious adverse event; TC=telephone contact; VRNT=virus reduction neutralization test; WOCBP=women of child-bearing potential											

2 INTRODUCTION

MSD is developing a dengue quadrivalent vaccine rDENVΔ30 (live, attenuated), hereafter referred to as V181, in collaboration with Instituto 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 LATV in preclinical and Phase 1 studies.

2.1 Study Rationale

V181-003 study is designed to assess the safety and immunogenicity of 3 potency levels of V181. Both clinical safety and immunogenicity data from this study will provide a better understanding of the clinical performance of the vaccine across a wide range of potencies and support the establishment of potency release specifications for the vaccine. The V181 study vaccine potency levels in this study are detailed in Table 1. The target potency of CCI [redacted]/serotype has been established in nonclinical studies conducted by the NIH and clinical studies conducted by MSD, the NIH, and Instituto Butantan. Participants will be randomized in a 2:4:4:1 ratio to the V181 High Potency Level Group, V181 Mid Potency Level Group, V181 Low Potency Level Group, and placebo.

The primary endpoint of the study is based on immunogenicity, which will be evaluated in the "purest" fashion in participants who are dengue-seronegative at baseline, so a pre-existing immunity to a dengue serotype/s does not augment the immune response to other serotypes and influence the results. The participant 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 a hypothesis-driven primary immunogenicity objective. Differences are not expected in immunogenicity by age subgroup within this study population.

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 disease 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]. Approximately 3 to 4 billion people living in tropical and subtropical countries are at-risk for infection. Each year, approximately 390 million people are infected with dengue viruses, causing an estimated 96 million symptomatic cases [Bhatt, S., et al 2013]. Of these, 2.1 million cases are severe, resulting in approximately 21,000 deaths [Thomas, S. J. and Endy, T. P. 2011]. Furthermore, approximately 120 million people travel to dengue-endemic regions annually [Suaya, J. A., et al 2009]. Therefore, there is a large, unmet medical need for dengue vaccines.

Dengue disease is caused by 4 virus serotypes: DENV1, DENV2, DENV3, and DENV4. Infection by any of the 4 serotypes is believed to result in life-long immunity against that serotype. Infection with one serotype may provide short-term protection (ie, 6 to 24 months) against other serotypes, but does not provide long-term protection. Secondary infections with a different viral serotype increase the risk for development of severe disease forms (ie, DHF and DSS) and death. It has been hypothesized that the increase in severity with secondary infection may be immune-mediated through a mechanism termed ADE [Halstead, S. B. 2007] [Halstead, S. B. 2014] [Guzman, M. G., et al 2013]. According to this hypothesis, nonneutralizing, 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 and higher viral and viral-antigen NS1 loads that trigger cytokine release that ultimately mediates the plasma leakage syndrome observed in DHF. Given this natural history, ADE represents a theoretical risk for any dengue vaccine. This risk is considered to be inversely related to efficacy (eg, risks in participants where vaccine is not effective or efficacy wanes) [Cassetti, M. C. 2014]. Study participants will be informed in the ICF of the potential risk of ADE after vaccination with V181 and ways to protect themselves from exposure to mosquitos if they travel to dengue endemic areas.

Based on the above ADE hypothesis, the foremost approach for developing an effective dengue vaccine and mitigating the risk of vaccine-induced sensitivity for more severe disease is a 4-valent vaccine that will simultaneously and durably protect against disease caused by all 4 dengue virus serotypes [Halstead, S. B. and Deen, J. 2002].

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 NIH and in-licensed by the Sponsor. 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 Studies

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

2.2.3 Completed Clinical Studies

A brief summary of completed clinical studies are provided below, and details are provided in the IB.

2.2.3.1 MSD V181 Completed Studies

Results from the V181-001 Phase 1 study indicated V181 is highly immunogenic through 6 months postdose 1 and generally safe and well tolerated in flavivirus-naïve and flavivirus-experienced participants. AEs were generally assessed as mild to moderate in intensity by the participants.

2.2.3.2 NIH Dengue LATV Completed Studies

To date, the NIH has administered the dengue LATV monovalent components or tetravalent formulations comprising the same parental strains as V181 to more than 1000 participants with studies ongoing in the US and Thailand. The NIH monovalent and tetravalent vaccines were generally well-tolerated in both nonclinical and human studies conducted by the NIH.

2.2.3.3 Butantan-DV Clinical Studies

V181 and Butantan-DV are derived from the same parental strains originally developed by the NIH, are produced using similar methods, have the same antigenic composition and are therefore fundamentally the same. Therefore, data from Butantan clinical trials are relevant for V181.

Butantan-DV was evaluated in a Phase 2 study of 300 participants (of which 210 received Butantan-DV) in Brazil. The vaccine was found to be immunogenic and generally safe and well-tolerated in both dengue-naïve and dengue-exposed participants [Kallas, E. G., et al 2020]. The vaccine is currently being investigated in a large Phase 3 safety and efficacy study with approximately 17,000 participants enrolled in Brazil.

2.2.4 Information on Other Study-related Therapy

Not applicable.

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 demonstrated 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

The following objectives and endpoints will be evaluated in healthy male and female participants, 18 to 50 years of age (inclusive).

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 the V181 Low Potency Level versus V181 Mid Potency Level **Hypothesis:** V181 Low Potency Level is non-inferior to V181 Mid Potency Level 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 Low Potency Level versus V181 Mid Potency Level] 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 evaluate the safety and tolerability of 3 different V181 potency levels with respect to the proportion of participants experiencing SAEs	• Vaccine-related serious adverse events from Day 1 through Day 28 postvaccination

Objectives	Endpoints
Secondary	
• To evaluate the safety and tolerability of 3 different V181 potency levels with respect to the proportion of participants experiencing solicited AEs	• Solicited injection-site adverse events from Day 1 through Day 5 postvaccination • Solicited systemic adverse events from Day 1 through Day 28 postvaccination
Tertiary/Exploratory	
CCI [redacted]	

4 STUDY DESIGN

4.1 Overall Design

This is a double-blind with in-house blinding, randomized, placebo-controlled, multicenter, study to evaluate the safety and immunogenicity of 3 different potency levels of V181, compared with placebo, in healthy adults 18 to 50 years of age. The study will be conducted in dengue non-endemic regions. Approximately 1265 participants will be randomized 2:4:4:1 to receive a single dose of 1 of 3 potency levels (high, mid, or low) of V181 or placebo. The duration of the study for each participant will be approximately 12 months from the time the participant signs the ICF through the final contact.

An unblinded pharmacist or unblinded qualified study site personnel at each site will be required to manage clinical supplies and prepare the study vaccine/placebo in order to maintain the blinding of the clinical material and the study. Once the study vaccine/placebo has been prepared, it will be provided to a blinded member of the study team for administration to the participant. The participant, the investigator, and Sponsor personnel or delegate(s) involved in the study intervention administration or clinical evaluation of the participants will be blinded to the intervention assignments.

Participants will be screened to document general good health on Day 1. When deemed eligible for study participation, participants will be randomized and vaccinated with 1 of 3 different potency levels of V181 or placebo on the same day (Day 1).

A standardized eVRC will be distributed to all participants for the collection of the following data on a daily basis beginning with the day of vaccination (Day 1) through Day 28 postvaccination:

- 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
- Oral temperatures from Day 1 through Day 28 postvaccination
- Concomitant medications and nonstudy vaccines from Day 1 through Day 28 postvaccination

All participants will be provided with an electronic device or will have their own electronic device configured, if compatible, to complete the eVRC. Study-supplied devices will be collected on Day 28.

Solicited AEs listed above and unsolicited AEs (including MAAEs and SAEs) will be collected Day 1 through Day 28. Following Day 28 postvaccination, MAAEs, SAEs (regardless of causality), and deaths (due to any cause) will be collected through Month 12 postvaccination.

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.

Blood samples for the assessment of immune responses will be collected from all participants before vaccination on Day 1 and at the Day 28 and Month 12 postvaccination time points. Participants in each treatment group will be randomized in a centralized process so that half of the participants in each group have blood samples collected at Month 3 and the other half at Month 6. Participants who are not scheduled to have blood draws as per their assigned schedules, will have telephone visits. As this study will be conducted in non-endemic countries, it is expected that the baseline serostatus for the majority of participants will be dengue-seronegative. Therefore, screening for dengue serostatus will not be conducted. The final determination of baseline serostatus for the purpose of the primary analysis will be by the VRNT.

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

Serum samples from both, the immunogenicity and CCI blood draws, will each be aliquoted in 2 tubes. One tube will be shipped to a prespecified central laboratory and 1 tube will remain at the site as a back-up sample in case the main sample is destroyed in any way. The Sponsor will notify the site when the back-up samples can be shipped to the laboratory. Refer to the Investigator Study File Binder for guidance regarding sample blood volumes and other laboratory procedures.

The primary safety and immunogenicity analyses will be conducted at the Day 28 postvaccination time point to support the establishment of the potency release specifications for V181. A CSR will be written to present the study results from this time period. Immunogenicity and safety results from the Day 28 through Month 12 postvaccination time period will be summarized in a final, separate study report (see Section 9.2).

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

This study is designed to assess the immune responses for participants 18 to 50 years of age following vaccination with a single dose of 1 of 3 potency levels of V181. The High, Mid (target), and Low Potency Levels that will be administered are detailed in Table 1. Both clinical safety and immunogenicity data from this study will support the establishment of potency release specifications for V181. For the primary immunogenicity objective,

postvaccination immune responses will be assessed for participants to confirm that the immune response for the V181 Low Potency Level falls within a predetermined ratio in comparison to the V181 Mid (target) Potency Level. The V181 High Potency Level will provide an assessment of the safety of V181 at a potency level that is higher than the Mid (target) Potency Level.

4.2.1 Rationale for Endpoints

4.2.1.1 Immunogenicity Endpoints

A single dose of 1 of 3 potency levels of V181 will be assessed for postvaccination neutralizing antibody responses to the 4 vaccine virus serotypes at Day 28 postvaccination using the validated VRNT assay. Specimens for the primary endpoints for immunogenicity testing will be obtained from the entire study population (N=1265) at Day 28.

The time point of Day 28 was chosen as the primary endpoint based on the immunogenicity results observed in the V181-001 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 85.3%. In addition to the evaluation for all participants at Day 28, antibody responses will be evaluated for half of the participants in each group at Month 3 and the other half at Month 6, and for all participants at Month 12 postvaccination time points in order to assess the durability of immune responses.

The above immunogenicity schedule was designed to evaluate the phenomenon of a 3-phase immune response in seronegative participants to natural infection or live vaccines. Specifically, this refers to (1) a rapid increase in titer (over about 1 month); (2) a rapid decay after that peak (over another month); and then (3) a slower decay to a new equilibrium [Alter, G. 2020]. Based on these immune kinetics, an alternating immunogenicity visit design is planned in order to evaluate immunogenicity at multiple timepoints while minimizing the number of blood draws per participant [Food and Drug Administration 2019]. At each of the Month 3 and Month 6 visits, half of the participants will have blood draws for immunogenicity. Those participants who are assigned for blood draws at Month 3 will have telephone calls at Month 6; likewise participants who are assigned to have telephone calls at their Month 3 visit will have blood draws at their Month 6 visit. The resulting schema will provide immunogenicity data at 4 separate postvaccination time points (Day 28, Month 3, Month 6, and Month 12), while only requiring 3 postvaccination blood draws per participant.

As noted above, because the primary endpoint of the study is based on immunogenicity, the study will be conducted in participants who are dengue-seronegative at baseline, so a pre-existing immunity to a dengue serotype/s does not augment the immune response to other serotypes and influence the results. A participant is classified as dengue-seronegative if VRNT is negative for all four dengue serotypes.

The VRNT is a high-throughput virus neutralization assay, specific for each of the 4 dengue serotypes. Serum samples are first diluted and incubated with virus to allow for antibody

binding and virus neutralization. The serum and virus mixture is then added and incubated with Vero cells to allow for infection by non-neutralized virus. The number of individual infected cells is detected and counted by virus immunostaining, before plaque formation. Results are expressed as Neutralizing Titer. 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 is Day 1 through Day 28 postvaccination. The 28-day primary safety follow-up period was selected based on the safety data from the V181-001 Phase 1 clinical study and the clinical studies for the NIH LATV.

An eVRC will be distributed to all participants in order to collect participant-reported events on a daily basis from the day of vaccination (Day 1) through Day 28 postvaccination. The eVRC is a validated tool routinely used for safety surveillance in vaccine clinical studies conducted by the Sponsor and was previously used in the V181-001 clinical 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.

Details on the safety endpoints evaluated in this study are provided in Section 8.3 and Section 9.4.2. Details on AEs, including definitions and reporting requirements, are provided in Section 10.3 (Appendix 3).

4.2.1.3 Other Exploratory Endpoints

CCI

[redacted]

4.2.1.4 Future Biomedical Research

The Sponsor will conduct future biomedical research on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the

measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

Placebo (used to prepare dilutions of the V181 High Potency Level and V181 Mid Potency Level to the V181 Low Potency Level) will be administered as 1 arm of this study (n=115 participants) in order to preserve the blinding and provide a control for the safety assessment of the active study vaccine arms. Additionally, the study is being conducted in non-endemic countries where there is low risk of dengue infection and vaccination with licensed dengue vaccine(s) is not routinely conducted.

4.3 Justification for Dose

A single dose of 1 of 3 potency levels of V181, or placebo, will be administered subcutaneously on Day 1 in this study. Results from the V181 Phase 1 study (V181-001) demonstrated that V181 has an acceptable safety profile and is immunogenic at the potency level of CCI [redacted] for each vaccine component (ie, the "mid" potency level under evaluation in this study). Two other V181 potencies (ie, "high" and "low" level potencies) will be evaluated in this study in order to better understand the clinical performance of the vaccine across a wide range of potencies and to support the establishment of potency release specifications for V181 (see Table 1). While the safety and immunogenicity of V181 will be evaluated across all of the 3 potency levels, the primary immunogenicity endpoint focuses on immunogenicity of V181 at a lower potency compared with that induced at the target potency level as the key criteria to be assessed.

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 the Sponsor 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), 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, 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:

Type of Participant and Disease Characteristics

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

Participants Assigned Male Sex at Birth

3. Male participants are eligible to participate if they agree to the following for at least 90 days after administration of study intervention (a spermatogenesis cycle is approximately 90 days):

    - Abstains 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 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 the first dose 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. The participant may also provide consent for Future Biomedical Research. However, the participant may participate in the main study without participating in Future Biomedical Research.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

(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 known history of dengue or zika natural infection.

2. *Has an acute febrile illness (temperature ≥38.0°C [≥100.4°F] oral or equivalent) occurring within 72 hours before receipt of study vaccine/placebo.

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

4. 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.

5. 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.

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

Prior/Concomitant Therapy

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

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

9. * Has received a licensed live vaccine within 28 days before receipt of study vaccine/placebo or is scheduled to receive any live vaccine within 28 days after receipt of study vaccine/placebo.

10. Has received systemic corticosteroids (equivalent of ≥2 mg/kg/day of prednisone or ≥20 mg/d 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 after receipt of study vaccine/placebo. (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 before receipt of study vaccine/placebo or plans to receive immunosuppressive therapies within 28 days after receipt of study vaccine/placebo.

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

Prior/Concurrent Clinical Study Experience

14. Has participated in another clinical study of an investigational product within 6 months before 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 the Sponsor.

Diagnostic Assessments

Not applicable.

Other Exclusions

15. Has any other reason that, in the opinion of the investigator, may interfere with the evaluation 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 or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

No lifestyle restrictions are required for this study.

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 will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

V181 study vaccine will be prepared by reconstitution before administration, as described in Section 6.2.1; therefore, clinical supplies will be open-label in this study. The open-label clinical supplies will be distributed to unblinded study personnel at the clinical site and prepared by an unblinded pharmacist or unblinded qualified study site personnel, as per the instructions in the Investigator Study File Binder, which includes the Pharmacy Manual, provided by the Sponsor. There is no visual difference between the V181 potency level study vaccine and placebo in the syringe. Once study vaccine/placebo has been prepared, it will be provided to a blinded member of the study team for administration to the participant.

6.1 Study Intervention(s) Administered

The study intervention(s) 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) (PFU)[a]	Dosage Level(s)	Route of Admin-istration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
V181 High Potency Level Group	Experimental	V181 High Potency Level	Biological/ Vaccine	Sterile Solution	CCI	0.5 mL	SC	Single dose at Visit 1	Test Product	IMP	Sponsor
V181 Mid Potency Level Group	Experimental	V181 Mid Potency Level	Biological/ Vaccine	Sterile Solution		0.5 mL	SC	Single dose at Visit 1	Test Product	IMP	Sponsor
V181 Low Potency Level Group	Experimental	V181 Low Potency Level	Biological/ Vaccine	Sterile Solution		0.5 mL	SC	Single dose at Visit 1	Test Product	IMP	Sponsor
Placebo Group	Placebo Comparator	Placebo	Biological/ Vaccine	Sterile Solution	0	0.5 mL	SC	Single dose at Visit 1	Placebo	IMP	Sponsor

AxMP=auxiliary medicinal product; DENV=dengue virus; EEA = European Economic Area; IMP = investigational medicinal product; NIMP = non-investigational medicinal product; PFU=plaque forming unit; SC = subcutaneous

The classification of IMP and NIMP/AxMP 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.

[a] This represents the final dose strength of each serotype for a 0.5 mL dose of V181 after field preparation, as per the pharmacy manual.

All supplies indicated in Table 1 will be provided per the "Sourcing" column depending on 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 8.1.9 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

The study vaccine/placebo will be prepared by the unblinded pharmacist or unblinded qualified study site personnel, as described in Section 6 and Table 1, according to the following procedures:

- The V181 High Potency Level study vaccine will be prepared by reconstituting the High Potency Level vaccine vial provided by the Sponsor with water for injection and then field mixing (diluting) with placebo to reach the appropriate potency level.
- The V181 Mid Potency Level study vaccine will be provided by the Sponsor at the intended potency of [redacted], and will only require reconstitution with water for injection before administration.
- The V181 Low Potency level study vaccine will be prepared by reconstituting the V181 Mid Potency Level study vaccine with water for injection and then field mixing (diluting) with placebo to reach the lower potency.
- The placebo is supplied in liquid form and does not require reconstitution.

Details for the preparation of the study vaccine/placebo are provided in the Pharmacy Manual provided by the Sponsor.

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 Sponsor 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 the Sponsor.

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 4 study intervention arms. Participants will be assigned randomly in a 2:4:4:1 ratio to the V181 High Potency Level Group, V181 Mid Potency Level Group, V181 Low Potency Level Group, and placebo.

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. V181 study vaccine (3 potency levels) and placebo will be provided open-label. Therefore, an unblinded pharmacist or unblinded qualified study site personnel will be responsible for receiving, maintaining, and preparing the study vaccine/placebo in accordance with a Pharmacy Manual provided by the Sponsor. An unblinded Clinical Research Associate will monitor vaccine accountability at the study site.

Once the study vaccine/placebo has been prepared by the unblinded pharmacist or unblinded qualified study site personnel, the study vaccine/placebo will be provided to a blinded member of the study team for administration to the participant. To avoid bias, contact between the unblinded study personnel and participants is strictly prohibited throughout the study. Additionally, blinded site personnel will not be present when the study vaccine/placebo is prepared. Blinded study-site personnel will be responsible for all safety follow-up, and blinded study-site personnel will be responsible for immunogenicity specimen collection before/after study vaccine/placebo administration. Laboratory personnel responsible for conducting the assays will remain blinded to vaccination group assignments throughout the duration of the study.

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

An 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.

Following Day 28 database lock, most Sponsor Headquarters personnel involved in the conduct of the trial will be unblinded to vaccination group assignments for the primary safety and immunogenicity analyses. The primary CSR will be authored to present the results from Day 1 through Day 28 to support the establishment of the potency release specifications for V181. A blinded medical monitoring team will monitor the study after Day 28 through Month 12 postvaccination.

Investigators, study site personnel, participants, and Sponsor field personnel or delegate(s) will remain blinded to treatment group assignments until the final study analyses are completed following the Month 12 (final) database lock.

See Section 8.1.12 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 placebo. Any changes in the protocol-specified vaccination plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Management of GMO

V181 is comprised of 4 genetically modified live viruses. Universal precautions should be followed for vaccine preparation and administration. Needles and syringes that have been in contact with the study vaccine, 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

The following medications/vaccinations are prohibited before and/or during the study:

- Any dengue vaccine (investigational or approved) before study entry, or plans to receive any dengue vaccine (investigational or approved) for the duration of the trial
- Any licensed non-live vaccine 14 days before receipt of study vaccine/placebo or is scheduled to receive any licensed non-live vaccine within 28 days after receipt of study

vaccine/placebo. Inactivated influenza vaccine may be administered but must be given at least 7 days before or 28 days after receipt of study vaccine/placebo.

- Any licensed live vaccine within 28 days before or after receipt of study vaccine/placebo.
- 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 doses and duration within 28 days after receipt of study vaccine/placebo (topical and inhaled/nebulized steroids are permitted).
- Has received systemic corticosteroids exceeding physiologic replacement doses (approximately 5 mg/day prednisone equivalent) within 14 days before vaccination.
- 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 before receipt of study vaccine/placebo or plans to receive immunosuppressive therapies within 28 days after receipt of study vaccine/placebo.
- Has received a blood transfusion or blood products (including immunoglobulins) within 6 months before receipt of a study vaccine/placebo or plans to receive a blood transfusion or blood products (including immunoglobulins) within 28 days after receipt of study vaccine/placebo.

The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant in the study requires the mutual agreement of the investigator, the Sponsor, and the participant.

Any medication or 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 (Visit 4), only concomitant medications associated with SAEs should be reported. The 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

No dose modification is allowed 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 following 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 8.1.12). 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. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 8.1.12 for a description of the method of unblinding a participant during the study, should such action be warranted.

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 before 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, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.11. 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 the investigator and 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 approximate total maximum amount of blood volume drawn from each participant is 50 mL, as detailed in the Investigator Study File Binder.

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) before participating in this clinical study or FBR. 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 informed consent form 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 informed consent form.

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

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 before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are provided in Section 8.10.1.

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 healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Inclusion/Exclusion Criteria

Before 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. The participant's relevant medical history for the 5 years before Visit 1 (Day 1) will be obtained to ensure that the participant satisfies the inclusion and exclusion criteria of the study.

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/vaccinations 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.

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 their eVRC (Section 8.1.10) to record new and/or concomitant medications and nonstudy vaccines received from Day 1 through Day 28 postvaccination.

After Day 28 postvaccination, only concomitant medications related to SAEs are reported. Receipt of any dengue vaccine (investigational or approved) other than study vaccine/placebo must also be reported.

8.1.7 Pregnancy Test

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 or within 24 hours before the first dose of study vaccine/placebo is administered as described in Section 1.3. Urine or serum tests may be used, and results must be negative before study vaccine/placebo is administered. If a urine pregnancy test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. A negative urine or serum β-hCG pregnancy test

must be documented on the day of vaccination before administration of study vaccine/placebo. A detailed definition of WOCBP is provided in Appendix 5. Additional pregnancy tests may be performed at the discretion of the investigator or as required by local regulation at any time during the study.

8.1.8 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.

8.1.9 Study Intervention Administration

Study vaccine/placebo should be prepared and administered by appropriately qualified members of the study 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.

Unblinded study personnel not otherwise involved in the conduct of the study will prepare study vaccine/placebo. Unblinded study personnel should not have contact with participants.

Once the study vaccine/placebo has been prepared by the unblinded pharmacist or unblinded qualified study site personnel, the study vaccine/placebo will be provided to a blinded member of the study team for administration to the participant. All safety and immunogenicity assessments will be conducted by blinded personnel, and the participant will be blinded to the study vaccine/placebo received.

Details of each vaccination should be documented on the appropriate eCRF as specified in the data entry guidelines. Procedures for handling, preparing, and administering, disposing of, and returning the unblinded vaccines are provided in the Investigator Study File Binder, which includes the Pharmacy Manual.

8.1.9.1 Timing of Dose Administration

In this study, V181 or placebo will be administered as a 0.5-mL subcutaneous 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 each vaccination for any immediate AEs; the time period can be extended if clinically indicated.

8.1.10 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 8.4.8. 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 before dispensing it to the participant at Visit 1 (Day 1). Noncompliance with the eVRC will require retraining by the site as soon as possible to ensure accurate and complete data capture.

Daily oral 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 temperature using a digital thermometer provided by the Sponsor and the size of injection-site reactions of swelling and redness using a ruler provided by the Sponsor. Refer to Section 8.4.8 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 (Visit 2, Visit 3, and Visit 4) 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.

8.1.11 Discontinuation and Withdrawal

Participants in this study will receive a single dose intervention 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.

8.1.11.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the

investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.12 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 the Sponsor. Before 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 before 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 Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the investigator, site personnel, and Sponsor 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.

8.1.13 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 Assessments

8.2.1 Dengue Virus 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 before vaccination on Day 1 (baseline) and at the Day 28, Month 3, Month 6 and Month 12 postvaccination time points.

The VRNT for all 4 dengue serotypes was validated at Q2 Solutions contract research organization (San Juan Capistrano, CA). The VRNT is performed by a two-fold serial dilution of serum samples and positive controls, and addition of an equal volume of diluted dengue virus (DENV1, DENV2, DENV3, or DENV4) containing a consistent target amount of virus for each given serotype. Virus control containing diluted virus without serum sample 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 labelled 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 60% compared to the virus control. Calculations are performed using a 4-parameter nonlinear logistic equation. Dengue serostatus will be determined based on the VRNT60 LLOQ (titer results < LLOQ are considered negative), corresponding to each dengue serotype and established during assay validation.

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8.3 Safety Assessments

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) as per institutional standard at Visit 1 (Day 1).

A complete physical examination includes, but is not limited to, the assessment of vital signs (heart rate, respiratory rate, seated blood pressure, and oral temperature), height, weight, heart and lungs, abdomen, as well as head, eyes, ears, nose, and throat (HEENT), skin, lymph nodes, neurological system, and musculoskeletal system. Investigators should pay special attention to clinical signs related to previous serious illnesses.

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 and Body Temperature Measurements

Vital signs and body temperature recordings are part of the physical examination at Visit 1 (Day 1) and include:

- Body temperature, heart rate, respiratory rate, and seated blood pressure.
- Blood pressure 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.

Oral temperatures will be recorded by participants using the eVRC from Day 1 through Day 28 postvaccination.

For this study, any temperature ≥100.4°F (≥38.0°C) oral or oral equivalent will be considered an AE of fever. All fevers must be reported Day 1 through Day 28 postvaccination unless the fever is a symptom of another reported AE.

8.3.3 Postvaccination Safety Observation Period

All participants will be observed, by blinded study-site personnel only, for at least 30 minutes following vaccination 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 to Day 28 postvaccination) will be asked to record rash events on the eVRC. Additionally, 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 from Day 1 to 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.

8.4 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, intensity/toxicity 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 28 days following vaccination, 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 (extended safety follow-up period) 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 the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 2.

Table 2 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 Sponsor:
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)	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, ECIs, 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 the Sponsor 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 has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements 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 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 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 (spontaneously reported to the investigator or their designee) that occurs in a participant during the study are reportable to the Sponsor.

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 Events of Clinical Interest

There are no specific events of clinical interest for this study.

8.4.8 Adverse Events Reported on the Electronic Vaccination Report Card

Each participant will be provided an eVRC to report solicited and unsolicited AEs (Section 8.1.10).

8.4.8.1 Solicited Adverse Events

Solicited AEs for this study are summarized in Table 3.

Table 3 Solicited Adverse Events for V181-003

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	• Fatigue (tiredness) • Headache • Myalgia (muscle pain) • Rash • 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 solicited 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 the Sponsor's database.

8.4.8.2 Unsolicited Adverse Events

Unsolicited AEs for this study are events that are either not predefined in Table 3 or predefined in Table 3 but reported at any time outside of the solicited time period. Unsolicited AEs reported by the participant will be entered by the study site personnel on the appropriate eCRF.

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

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than one dose of the investigational V181 vaccine/placebo.

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 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for future biomedical research, the following specimens will be obtained as part of future biomedical research:

- DNA for future research
- Leftover main study serum samples from dengue antibody titers (VRNT assays)
- Leftover main study serum from CCI samples CCI

8.9 Health Economics Medical Resource Utilization and Health Economics

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

8.10 Visit Requirements

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

8.10.1 Screening

Screening procedures will be conducted at Visit 1 (Day 1) as outlined in Section 1.3.

Screening procedures may be repeated after consultation with the Sponsor.

8.10.2 Treatment Period/Vaccination Visit

Requirements during the treatment period are outlined in Section 1.3.

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

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

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 other non-confirmatory 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 statistical analysis plan are summarized below; the comprehensive plan is provided in Section 9.2 through Section 9.12.

Study Design Overview	A Phase 2, Randomized, Double-Blind, Multicenter Study to Evaluate the Safety and Immunogenicity of Three Different Potency Levels of V181 (Dengue Quadrivalent Vaccine rDENVΔ30 [live, attenuated]) in Healthy Adults
Treatment Assignment	There are 4 vaccination arms. Participants will be assigned randomly in a 2:4:4:1 ratio to the V181 High Potency Level Group, V181 Mid Potency Level Group, V181 Low Potency Level Group, or Placebo using an IRT. A double-blind/masking technique will be used.
Analysis Populations	Immunogenicity: Per-Protocol Population Safety: All Participants as Treated (ApaT)
Primary Endpoint(s)	Immunogenicity (Primary): Dengue virus-neutralizing antibody GMTs for each of the 4 dengue serotypes at Day 28 postvaccination as measured by the VRNT Safety (Primary): Vaccine-related serious adverse events (SAEs) from Day 1 through Day 28 postvaccination
Key Secondary Endpoints	Safety (Secondary): • Solicited injection-site adverse events (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, the comparison between groups will be made based on serotype-specific 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.

Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as SOC terms) are either prespecified as "Tier1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed. There are no Tier 1 events for this protocol. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events (Miettinen and Nurminen [M&N] method [1985] [Miettinen, O. and Nurminen, M. 1985]). Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by vaccination group are provided for Tier 3 safety parameters.
Interim Analyses	There are no planned interim analyses for this study.
Multiplicity	No multiplicity adjustment is needed for this study as success is required on all 4 dengue serotypes.
Sample Size and Power	The overall sample size will be approximately 1265 with 230 participants in the high potency group, 460 participants in each of the mid and low potency groups, and 115 participants in the placebo group. The study has an overall power of >95% to establish that the V181 Low Potency Level is non-inferior to the V181 Mid Potency Level for all four serotypes at an overall one-sided, 2.5% alpha-level.

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 the Sponsor. 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 treatment 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 in order to inform potency specifications for the V181 vaccine. 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 (SAEs and deaths only) and immunogenicity through Month 12 postvaccination. Results from the Day 28 through Month 12 postvaccination time period will be presented in a final, separate study report.

After database lock for the primary analysis, most Sponsor Headquarters personnel involved in the conduct of the trial will be unblinded to vaccination group assignments. A blinded

medical monitoring team will monitor the study after Day 28 through Month 12 postvaccination. Investigators, study site personnel, participants, and Sponsor field personnel or delegate(s) (eg, Clinical Research Associate) will remain blinded to treatment 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 3.0.

9.4 Analysis Endpoints

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

9.4.1 Immunogenicity and CCI Endpoints

Primary Immunogenicity Endpoint

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

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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 paint) from Day 1 through Day 28 postvaccination

Additional Safety Endpoints

- Unsolicited AEs from Day 1 through Day 28 postvaccination
- Elevated temperature (≥100.4°F [38.0°C] oral equivalent) from Day 1 through Day 28 postvaccination
- All MAAEs, SAEs, and deaths through completion of study participation

9.5 Analysis Populations

9.5.1 Immunogenicity Analysis Populations

The Per-Protocol population will serve as the primary population for the analysis of the immunogenicity data in this study. The Per-Protocol population excludes participants due to deviations from the protocol that may substantially affect the results of the primary immunogenicity endpoints. 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 will be defined as having VRNT 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 before study vaccination or though Day 28 postvaccination.
- Collection of blood sample at the timepoint for the analysis outside of the pre-specified window, as described in Section 1.3

The final determination on protocol deviations, and thereby the composition of the PP population, will be made before the unblinding of the database and will be documented in a separate memo. The key immunogenicity analyses will also be performed using the Full Analysis Set (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 that they are randomized for the analysis of immunogenicity data using the FAS population. No adjustment will be made for missing data.

9.5.2 Safety Analysis Populations

The All Participants as Treated (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/placebo. Participants will be included in the vaccination group corresponding to the study vaccine/placebo 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 4 (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

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

H0: $GMT_x/GMT_y \leq 0.67$

Versus

H1: $GMT_x/GMT_y > 0.67$

where GMT_x represents the GMT at 28 days postvaccination in the V181 Low Potency Level group and GMT_y represents the GMT at Day 28 postvaccination in the V181 Mid Potency Level 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 titers 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 two-sided 95% confidence interval of GMT ratio (V181 Low Potency Level vs. V181 Mid Potency Level) being greater than 0.67.

CCI [redacted]

CCI [redacted] [Clopper, C. J. 1934].

Table 4 Analysis Strategy for Immunogenicity Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach[a]	Statistical Method[b]	Analysis Population	Missing Data Approach
Primary Endpoint				
Dengue virus-neutralizing antibody GMTs 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

CI = confidence interval; FAS = Full Analysis Set; GMT = Geometric Mean Titer; PP = Per-Protocol

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

[b] Estimation of the dengue virus-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 titers 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 all relevant parameters.

The analysis of safety will be performed for each of the V181 Potency Level groups (V181 High Potency Level, V181 Mid Potency Level, V181 Low Potency Level) versus placebo following a tiered approach (Table 5). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as SOC terms) are either pre-specified as "Tier1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on the number of events observed. A separate safety analysis will be performed with comparisons between the V181 High Potency Level vs the V181 Mid Potency Level as well as the V181 Low Potency Level vs the V181 Mid Potency Level. This analysis will include comparisons with the following tables: overall AE summary, solicited injection site AEs, solicited systemic AEs, and distribution of maximum temperatures.

Tier 1 Events

Safety parameters or adverse events of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. There are no Tier 1 events for this protocol as there is no formal safety hypothesis.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events (Miettinen and Nurminen [M&N] method [1985] [Miettinen, O. and Nurminen, M. 1985]).

Membership in Tier 2 requires that at least 4 participants in any treatment group exhibit the event. The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs for Tier 2 events may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs.

In addition to individual events that occur in 4 or more participants in any treatment group, the broad AE categories consisting of the proportion of participants with any AE, a vaccine-related AE, an MAAE, a vaccine-related MAAE, an SAE, a vaccine-related SAE, discontinuation due to an AE, and death will be considered Tier 2 endpoints. Solicited injection-site AEs (pain, erythema, and swelling) from Day 1 through Day 5 postvaccination, solicited systemic AEs (rash, headache, fatigue [tiredness], myalgia [muscle pain], and arthralgia [joint pain]) from Day 1 through Day 28 postvaccination, and vaccine-related SAEs from Day 1 through Day 28 postvaccination will also be considered a Tier 2 endpoint.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Table 5 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint[a]	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE[a]	X	X
	Any vaccine-related AE[a]	X	X
	Any MAAE[a]	X	X
	Any vaccine-related MAAE[a]	X	X
	Any SAE[a]	X	X
	Any vaccine-related SAE[a]	X	X
	Discontinuation due to AE[a]	X	X
	Death[a]	X	X
	Solicited injection-site AEs: pain, erythema, and swelling	X	X
	Solicited systemic AEs: rash, headache, fatigue (tiredness), myalgia (muscle pain), and arthralgia (joint pain)	X	X
	Elevated temperature (≥100.4°F [38.0°C] oral equivalent)	X	X
	Specific AEs by SOC and PT[b] (incidence ≥4 participants in one of the vaccination groups)	X	X
Tier 3	Specific AEs by SOCs and PT[b] (incidence <4 participants in all of the vaccination groups)		X

AE = adverse event; CI = confidence interval; MAAE – medically attended adverse event; PT = preferred term; SAE = serious adverse event; SOC=system organ class; X = results will be provided

[a] These endpoints are broad AE categories. For example, descriptive statistics for the safety endpoint of "Any AE" will provide the number and percentage of participants with at least one AE.

[b] Includes only those endpoints not already pre-specified as Tier 2 endpoints.

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

No interim analyses are planned 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 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

No multiplicity adjustment is needed for this study as success is required on all 4 dengue serotypes.

9.9 Sample Size and Power Calculations

9.9.1 Sample Size and Power for Immunogenicity Analyses

This study will randomize participants in a 2:4:4:1 ratio into the 4 vaccination groups (V181 High Potency Level Group, V181 Mid Potency Level Group, V181 Low Potency Level Group, and Placebo). The overall sample size will be approximately 1265 with 230 participants in the High Potency Level Group, 460 participants in each of the Mid and Low Potency Level Groups, and 115 participants in the placebo group. The study has an overall power of >95% to establish that the V181 Low Potency Level is non-inferior to the V181 Mid Potency Level for all four serotypes at an overall one-sided, 2.5% alpha-level. The power and sample size are based on the following assumptions: 1) an approximately 15% non-evaluable rate, 2) the non-inferiority margin of 0.67, 3) the true GMT ratio is assumed to be 1, and 4) the standard deviation of the natural-log titers is estimated to be 1.25 for each dengue serotype based on previous clinical and assay data. Given these assumptions, using the most conservative standard deviation, the lowest estimated GMT ratio that would meet a lower bound criterion of 0.67 is approximately 0.78.

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 0.30% (1 of every 333 participants receiving the vaccine), there is a 50% chance of observing at least 1 vaccine-related SAE among 230 participants in the V181 High Potency Level vaccination group. If the incidence rate is 1 of every 144 recipients (0.69%), there is an 80% chance of observing at least 1 vaccine-related SAE. If no vaccine-related SAEs are observed among the 230 participants in the V181 High Potency Level vaccination group, this study will provide 97.5% confidence that the underlying percentage of participants with vaccine-related SAE is <1.6% in the V181 High Potency Level vaccination group.

Table 6 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 230 participants in the V181 High Potency Level group and 115 participants in the Placebo group, and are based on a 2-sided 5% alpha level. The calculations are based on an asymptotic method proposed by Farrington and Manning[Farrington, C. P. and Manning, G. 1990]; no multiplicity adjustments were made.

Table 6 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 230 Participants in the V181 High Potency Level Group and 115 Participants in the Placebo Group)

Incidence of an Adverse Event		**Risk Difference**
V181 High Potency Level Group (%)	**Placebo (%)**	**Percentage Points**
5.7	0.1	5.6
9.8	2.0	7.8
14.7	5.0	9.7
21.9	10.0	11.9
28.3	15.0	13.3
34.3	20.0	14.3
45.5	30.0	15.5
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) [Farrington, C. P. 1990]		

If the underlying incidence of a vaccine-related SAE is 0.15% (1 of every 665 participants receiving the vaccine), there is a 50% chance of observing at least 1 vaccine-related SAE among 460 participants in the V181 Mid Potency Level and V181 Low Potency Level Groups. If the incidence rate is 1 of every 287 recipients (0.35%), there is an 80% chance of observing at least 1 vaccine-related SAE. If no vaccine-related SAEs are observed among the 460 participants in each of the V181 Mid Potency Level and V181 Low Potency Level Groups, this study will provide 97.5% confidence that the underlying percentage of participants with vaccine-related SAE is <0.9% in each of the V181 Mid Potency Level and V181 Low Potency Level Groups.

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 460 participants in the V181 Mid Potency Level or V181 Low Potency Level Group and 115 participants in the Placebo 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 were 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 460 Participants in the V181 Mid Potency Level or V181 Low Potency Level Group and 115 Participants in the Placebo Group)

Incidence of an Adverse Event		**Risk Difference**
V181 Mid/Low Potency Level Group (%)	**Placebo (%)**	**Percentage Points**
5.0	0.1	4.9
9.0	2.0	7.0
13.8	5.0	8.8
20.8	10.0	10.8
27.1	15.0	12.1
33.0	20.0	13.0
44.2	30.0	14.2
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) [Farrington, C. P. 1990]		

9.10 Subgroup Analyses

The subgroup analyses will be comprised of descriptive summary statistics for immunogenicity by gender and age. Further details of subgroup analyses will be documented in the sSAP.

9.11 Compliance (Medication Adherence)

Given that participants will receive only a single dose of 1 of 3 V181 potency levels or placebo, compliance will not be calculated. The number and proportion of randomized participants receiving each study vaccination 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 each of the 3 V181 potency levels and randomized participants administered placebo.

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. Before 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 before 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 the Sponsor'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 in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor 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 the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor 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 will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information 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 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, 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 that information furnished to the investigator by the Sponsor 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 (or Sponsor 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 before transmission to the Sponsor.

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

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. 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 Senior Management. The EOC will receive and decide upon any recommendations made by the DMC 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 interim data from this study. The voting members of the committee are external to the Sponsor. 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 interim 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 Sponsor 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 will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor 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, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor 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 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will

review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. 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, the EMA clinical trials directive, 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.

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 the Sponsor.

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

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor 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 this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor 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 the Sponsor 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 the Sponsor 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 the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor 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 the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

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

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 the Sponsor prematurely terminates a particular study site, the Sponsor 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

Clinical laboratory tests 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 poteintial 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 nontherapeutic 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'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 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."

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 before informed consent to treat a pre-existing condition that has not worsened.

- Refer to Section 8.4.6 for protocol-specific exceptions.

Definition of Unsolicited and Solicited AE

- An unsolicited AE is an AE that was not solicited using an eVRC and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.

- 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.

Definition of MAAE

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

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

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 before the use of an MSD 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 the Sponsor.

- 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 the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. 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 intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies definitely acting like something is wrong).

  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

- Injection site erythema/redness or swelling from the day of vaccination through Day 5 postvaccination will be evaluated by maximum size.

- 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 follow the "FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007."

Injection Site AE Overall Intensity Grading Scale

Injection-Site Reaction to Study Vaccine/Placebo[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/placebo				
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/placebo				
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

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 Preventative Vaccine Clinical Trials, September 2007" [Food and Drug Administration 2007].

[a] Based upon information provided by the participant on the eVRC and verbally during VRC 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. 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	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
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
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

ER=emergency room

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

ER=emergency room; eVRC=electronic Vaccination Report Card; SAE=serious adverse event
[a] Based upon information provided by the patient 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

[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's product cause the AE?

- The determination of the likelihood that the Sponsor'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'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's product caused the AE:

    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor'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'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'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'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'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR 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'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's product relationship).

    - Yes, there is a reasonable possibility of Sponsor's product relationship:

        - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

    - No, there is not a reasonable possibility of Sponsor's product relationship:

        - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor'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 the Sponsor. 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 the Sponsor.

- 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 Sponsor 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 the Sponsor within 24 hours of receipt of the information.

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

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

- The primary mechanism for reporting to the Sponsor 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 the Sponsor 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 the Sponsor.
- 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 Study File Binder (or equivalent).

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 nonhormonal 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,d] • IUS[c] • 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[a] *Failure rate of <1% per year when used consistently and correctly***.**
• Combined (estrogen- and progestogen- containing) hormonal contraception[b,c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[b,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

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in the future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	Adverse event
ADE	Antibody-dependent enhancement
ApaT	All-Participants-as-Treated
hCG	human chorionic gonadotropin
Butantan-DV	Butantan-Dengue Vaccine
CI	Confidence interval
CRF	Case report form
CSR	Clinical study report
CTFG	Clinical Trials Facilitation Group
DENV	Dengue virus
DHF	Dengue hemorrhagic fever
DNA	Deoxyribonucleic acid
DSS	Dengue shock syndrome
DMC	Data Monitoring Committee
ECI	Event of clinical interest
eCRF	Electronic case report form
EDC	Electronic data capture
eDMC	External Data Monitoring Committee
EEA	European Economic Area
EMA	European Medicines Agency
EOC	Executive Oversight Committee
eVRC	Electronic Vaccination Report Card
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GMO	genetically modified organism
GMT	Geometric mean titer
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 on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Intervention randomization system
IUD	Intrauterine device
IUS	Intrauterine system
LAM	Lactational amenorrhea method
LATV	Live-attenuated tetravalent vaccine
LLOQ	Lower limit of quantification
MAAE	Medically attended adverse event
NA	Not applicable
NIH	National Institute of Health

Abbreviation	Expanded Term
NIMP	Non-Investigational Medicinal Product
NSAE	Nonserious adverse event
PFU	Plaque-forming unit
PP	Per Protocol
PT	Preferred term
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SC	Subcutaneous
SoA	Schedule of activities
SOC	System organ class
sSAP	Supplemental statistical analysis plan
SUSAR	Serious unexpected serious adverse reaction
TBD	To-be determined
US	United States
VRNT	Virus Reduction Neutralization Test
WOCBP	Woman/women of childbearing potential
WT	Wild-type

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