Clinical Study Protocol

NCT Number: NCT02747927

Title: Phase III, Double-Blind, Randomized, Placebo-Controlled Trial to Investigate the Efficacy, Safety and Immunogenicity of a Tetravalent Dengue Vaccine (TDV) Administered Subcutaneously in Healthy Children Aged 4 - 16 Years Old

Study Number: DEN-301

Document Version and Date: Version 8.0, 14 September 2021

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL

Phase III, Double-Blind, Randomized, Placebo-Controlled Trial to Investigate the Efficacy, Safety and Immunogenicity of a Tetravalent Dengue Vaccine (TDV) Administered Subcutaneously in Healthy Children Aged 4 – 16 Years Old

Efficacy, Safety and Immunogenicity of Takeda's TDV in Healthy Children

Sponsor:	Takeda Vaccines, Inc. 40 Landsdowne Street Cambridge MA 02139 USA
Trial Identifier:	DEN-301
IND Number:	014292 **EudraCT Number:** 2018-003979-34
Vaccine Name:	Takeda's Tetravalent Dengue Vaccine Candidate (TDV)
Date:	14 September 2021
Amendment:	6
Version:	Version 8.0 (supersedes Version 7.0)

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

Table 1.a Contact Information

Issue	Contact
Serious adverse event and pregnancy reporting	IQVIA Integrated Safety Management Lifecycle Safety E-mail: TakedaDensafety@Quintiles.com Fax and telephone numbers for serious adverse event and pregnancy reporting will be provided to the site.
Medical Monitor (medical advice on conduct of protocol or compound)	Emergency medical contact information will be provided to the site.
Responsible Medical Officer (carries overall responsibility for the conduct of the trial)	Emergency medical contact information will be provided to the site.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This trial will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical trial protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of technical requirements for pharmaceuticals for human use, E6(R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

See appended signature page

[redacted], MD Date
[redacted], [redacted] Clinical
Development and Operations
Takeda Pharmaceuticals International AG

See appended signature page

[redacted], PhD Date
Global Clinical Project [redacted]
Takeda Pharmaceuticals International AG

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[redacted], PharmD, MSc Date
Vaccine Pharmacovigilance Benefit-Risk
[redacted]
Takeda Pharmaceuticals International AG

See appended signature page

[redacted], MSc Date
[redacted]
Vaccine Statistics
Global Statistics
Takeda Pharmaceuticals International AG

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the Sponsor. I agree to conduct this trial in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of trial subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation of technical requirements for pharmaceuticals for human use, E6(R2) Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.4 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix A – Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix B of this protocol.

_____ _____
Signature of Investigator Date

_____
Investigator Name (print or type)

_____
Investigator's Title

_____
Location of Facility (City, State)

_____
Location of Facility (Country)

1.3 Protocol Amendment Summary of Changes

This document describes the changes in reference to the Protocol incorporating Amendment No. 6.

1.3.1 Amendment History

Date	Amendment Number	Amendment Type	Region
17 December 2014	Initial Protocol	Not applicable	Global
17 November 2015	1	Substantial	Global
27 August 2018	2	Non-substantial	Global
28 January 2019	3	Non-substantial	Global
18 May 2020	4	Substantial	Global
20 April 2021	5	Substantial	Global
14 September 2021	6	Non-substantial	Global

1.3.2 Summary of Changes

Amendment to Protocol Version 7.0 dated 20 April 2021

Rationale for the amendment:

This protocol amendment has been made to correct minor errors to avoid any misunderstanding. These changes do not impact any protocol directed procedures.

Other modifications

Administrative trial information and document references have been updated as necessary.

Full details of the changes that have been made as part of this amendment are outlined below. In this section only, all new text is shown in bold italics and any redundant text is marked using strikethrough.

Section	Description of change
1.2	**REPRESENTATIVES OF TAKEDA** [redacted]~~, MD, PhD~~[redacted]***, MD*** [redacted]~~ Clinical Development Vaccines,~~ [redacted] ***Clinical Development and Operations*** Takeda Pharmaceuticals International AG
2.0	**Criteria for Exclusion:** **Trial entry** 7. Females of childbearing potential[1] who are sexually active, and who have not used any of the acceptable contraceptive method***s***[2] for at least 2 months prior to Day 1 (Month 0).
2.0	**Criteria for Exclusion:** **Booster Phase (Parts 4 and 5)** 7. Females of childbearing potential who are sexually active, and who have not used any of the acceptable contraceptive methods as specified under the criteria for entry into the trial, for at least 2 months prior to Day 1b (Month 0b) (see also trial entry ~~inclusion~~***exclusion*** criteria #~~5~~***7***).
7.2.2	7. Females of childbearing potential who are sexually active, and who have not used any of the acceptable contraceptive methods as specified under the criteria for entry into the trial, for at least 2 months prior to Day 1b (Month 0b) (see also trial entry ~~inclusion~~***exclusion*** criteria #~~5~~***7***).
16.0	4. World Health Organization~~.~~. Dengue and severe dengue. World Health Organization, Geneva, Switzerland~~, 2018~~***; 2021***. (Available at: http://www.who.int/mediacentre/factsheets/fs117/en/) (accessed ~~20 April~~ ***30 August*** 2021). 5. World Health Organization. Dengue hemorrhagic fever: diagnosis, treatment, prevention and control, 2nd Edn. ~~Geneva:~~ World Health Organization***, Geneva, Switzerland;*** ~~.~~ 1997. (Available at: ***https://apps.who.int/iris/handle/10665/41988***~~http://www.who.int/csr/resources/publications/dengue/Denguepublication/en/~~) (accessed ~~20 April~~ ***30 August*** 2021). 6. ***World Health Organization.*** Dengue - Guidelines for Diagnosis, Treatment, Prevention and Control. World Health Organization~~,~~***, Geneva, Switzerland;*** 2009. ***(Available at: https://www.who.int/publications/i/item/9789241547871) (accessed 30 August 2021)***~~(ISBN: 978 92 4 154787 1)~~. 11. ***The SAGE Working Group on Dengue Vaccines and WHO Secretariat. Background Paper on Dengue Vaccines;*** ~~Revised SAGE recommendation on use of dengue vaccine.~~ ***18*** April 2018. **(**Available at ~~https://www.who.int/immunization/diseases/dengue/revised_SAGE_recommendations_dengue_vaccines_apr2018/en/~~ ***https://www.who.int/immunization/sage/meetings/2018/april/2_DengueBackgrPaper_SAGE_Apr2018.pdf?ua=1)*** ~~[Accessed 20 April 2021]~~***(accessed 30 August 2021)***.

12. World Health Organization. Weekly Epidemiological Record. 2018. 93***(23)***:329-44. **(**Available at***:*** http://www.who.int/wer***)*** ~~[Accessed 20 April 2021]~~***(accessed 30 August 2021)***.

16. Lopez-Medina E, Biswal S, Saez-Llorens X, Borja-Tabora C, Bravo L, Sirivichayakul C, et al. Efficacy of a dengue vaccine candidate (TAK-003) in healthy children and adolescents two years after vaccination. J Infect Dis***.*** 2020***. doi: 10.1093/infdis/jiaa761*** [Epub ahead of print].

17. Tetravalent Dengue Vaccine Candidate (TDV) Global Investigator's Brochure***,*** ***Current*** Edition ~~11, 26 June 2020~~.

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2.0 TRIAL SUMMARY

Name of Sponsor: Takeda Vaccines, Inc. 40 Landsdowne Street, Cambridge MA 02139, USA		**Product Name:** Takeda's Tetravalent Dengue Vaccine Candidate (TDV)
Trial Title: Phase III, Double-Blind, Randomized, Placebo-Controlled Trial to Investigate the Efficacy, Safety and Immunogenicity of a Tetravalent Dengue Vaccine (TDV) Administered Subcutaneously in Healthy Children Aged 4 - 16 Years Old.		
IND No.: 014292		**EudraCT No.:** 2018-003979-34
Trial Identifier: DEN-301	**Phase:** III	**Trial Blinding Scheme:** Double-blind

Background:

Dengue fever is caused by infection with the dengue virus (DENV), a ribonucleic acid (RNA) virus that occurs as 4 recognized serotypes, DENV-1, DENV-2, DENV-3 or DENV-4. These dengue viruses are transmitted from human to human by mosquitoes (primarily *Aedes aegypti*). The 4 dengue viruses have spread worldwide and are endemic in Asia, Central and South America, the Caribbean, the Pacific Islands, parts of Australia, and parts of Africa. An estimated 50 - 100 million cases of dengue fever occur annually, which results in around 500,000 cases of dengue hemorrhagic fever (DHF) and an estimated 22,000 deaths, primarily in children. It is estimated that 2.5 billion people (40% of the world's population) live in areas at risk of dengue virus transmission.

Dengue fever is clinically defined as an acute febrile illness with 2 or more manifestations (headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, or leucopenia) and occurrence at the same location and time as other confirmed cases of dengue fever. The most severe forms of dengue infection – DHF and dengue shock syndrome (DSS) – are life threatening. Primary infection with any 1 of the 4 dengue serotypes is thought to result in life-long protection from re-infection by the same serotype, but does not protect against a secondary infection by 1 of the other 3 dengue serotypes and may lead to an increased risk of severe disease (DHF/DSS).

Treatment of dengue fever is based solely on symptoms and signs, with fluid replacement required for hemorrhagic or shock cases. No antiviral therapy for dengue virus infection is available. Preventive measures that rely on mosquito control and individual protection, are of limited efficacy, complex to implement and questionable in terms of cost-effectiveness. There is a great unmet global public health need for a safe and effective vaccine that will protect against all serotypes of dengue infection, and thereby reduce the morbidity and mortality associated with dengue disease. A first recombinant dengue vaccine (chimeric yellow fever virus-dengue virus tetravalent dengue vaccine [CYD-TDV]) has been approved since 2015 in several Asian and Latin American countries as well as in the United States and in the European Union. Clinical data indicate an unfavorable risk-benefit profile for children aged <9 years with this first approved vaccine. Additionally, vaccine efficacy was different between serotypes and depended on dengue pre-exposure status. More recent analyses found that people who had not been infected by dengue virus before vaccination had a higher risk of getting severe disease when they were infected with dengue virus after vaccination with CYD-TDV. In a revised Strategic Advisory Group of Experts on Immunization (SAGE) recommendation in April 2018, the SAGE concluded that for countries considering CYD-TDV vaccination as part of their dengue control program, a "pre-vaccination screening strategy" would be the preferred option, in which only dengue-seropositive persons are vaccinated. Hence, there is a continued unmet public health need for safer and more efficacious dengue vaccines.

Takeda's Tetravalent Dengue Vaccine Candidate (TDV) Background:

TDV consists of a mixture of 4 live, attenuated recombinant dengue virus strains expressing surface antigens corresponding to the 4 recognized dengue serotypes 1-4. The serotype 2 strain is based upon the attenuated laboratory-derived virus, DEN-2 Primary Dog Kidney (PDK)-53, originally isolated at Mahidol University, Bangkok, Thailand. The chimeric, attenuated vaccine strains for dengue serotypes 1, 3 and 4 were engineered by replacing the DEN-2 structural genes, pre-membrane (prM) and envelope (E), with the prM and E genes of the

wild type (WT) virus strains, DENV-1 16007, DENV-3 16562 or DENV-4 1036 virus, respectively. TDV is thus comprised of 4 recombinant, live attenuated dengue strains: a molecularly characterized, attenuated DEN-2 strain (TDV-2), a DEN-2/1 chimera (TDV-1), a DEN-2/3 chimera (TDV-3) and a DEN-2/4 chimera (TDV-4).

Nonclinical studies carried out in mice and nonhuman primates demonstrated an acceptable safety, immunogenicity, and efficacy profile of Takeda's TDV.

Data from 3 phase I trials and a phase II trial have shown satisfactory reactogenicity, safety and immunogenicity of Takeda's TDV in adults in non-endemic areas as well as in adults and children in endemic areas in Asia and Latin America. At the time of the current protocol amendment, the phase II trial that has enabled the selection of a final TDV dose formulation for use in the pivotal program has been finalized.

In Part 1 of the present ongoing Phase III trial, the primary endpoint was achieved with an overall vaccine efficacy (VE) of 80.2% (95% CI: 73.3 to 85.3). In Part 2, the analysis of secondary endpoints showed efficacies of 76.1% (95%CI: 68.5 to 81.9) in subjects who were seropositive at baseline, 66.2% (95% CI: 49.1 to 77.5) in subjects who were seronegative at baseline, 90.4% (95% CI: 82.6 to 94.7) against hospitalized dengue, and 85.9% (95% CI: 31.9 to 97.1) against dengue hemorrhagic fever. Vaccine efficacy varied by individual serotypes. Cumulative rates of serious adverse events (SAEs) were similar in TDV (4.0%) and placebo (4.8%) recipients, and were consistent with expected medical disorders in the trial population.

In Part 3 (yearly exploratory analysis), the overall VE for Year 2 (ie., during 12 months after the end of Part 1) compared to Year 1 (ie., 30 days post-second dose up to end of Part 1) was 56.2% (95% CI: 42.3 to 66.8) versus 80.2% (95% CI: 73.3 to 85.3). The Year 2 versus Year 1 analysis also showed efficacies of 60.3% (95% CI: 44.7 to 71.5) versus 82.2% (95% CI: 74.5 to 87.6) in subjects who were seropositive at baseline, and 45.3% (95% CI: 9.9 to 66.8) versus 74.9% (95% CI: 57.0 to 85.4) in subjects who were seronegative at baseline. The efficacy against hospitalized dengue for Year 2 was 76.1% (95% CI: 50.8 to 88.4%) versus 95.4% (95% CI: 88.4-98.2) for Year 1.

The current Investigator Brochure of Takeda's TDV contains additional product information and a more detailed review of pre-clinical and clinical trials.

Rationale for the Proposed Phase III Efficacy Trial:

Given the accelerating spread of dengue in the world, there is an urgent need for an effective dengue vaccine, not only for those who live in dengue endemic areas, but also for those who travel to those areas. In the absence of a correlate of protection, the World Health Organization (WHO) recommends that phase III dengue trials are performed in dengue endemic areas, where vaccinated and control individuals are at equal risk of acquiring the disease, allowing assessment of VE.

Although the ultimate goal of a dengue vaccine is to protect against all 4 serotypes, it is unlikely that a single trial will be sufficiently powered to demonstrate VE against each dengue serotype. Therefore, the WHO recommends a primary objective of VE measured against laboratory-confirmed dengue illness caused by any of the 4 serotypes.

The trial will be conducted in accordance with the protocol, the International Council for Harmonisation of technical requirements for pharmaceuticals for human use - Good Clinical Practice (ICH-GCP) Guidelines and any applicable regulatory requirements.

Parts 1, 2, and 3

This phase III trial is comprised of at least 3 parts for all subjects. Part 1 will assess VE against symptomatic dengue illness due to any serotype, and will provide data to support licensure based on WHO recommendations outlined above. An extended follow-up is planned in Part 2, aimed at providing additional data to allow a more precise assessment of VE against each serotype. Part 3 fulfils the WHO recommendation of long-term follow-up to evaluate safety.

In order to maintain the double-blind design, a placebo (Normal Saline) was used in this trial. A placebo had been chosen to avoid the use of a number of active vaccine comparators that would be required due to the wide age range of subjects (4 to 16 years of age) and the diverse countries participating. As no active comparator was possible as part of the trial design, a licensed vaccine will be offered to all subjects, irrespective of their full

participation in this trial and at least 6 months after any protocol defined vaccination. The choice of this vaccine was discussed between the Sponsor and the Investigator, and was approved by the appropriate ethics committee. This vaccine will be used according to the labeling approved in the country.

Booster Phase (Parts 4 and 5)

The booster phase of this phase III trial is comprised of 2 parts (Parts 4 and 5). Parts 4 and 5 will assess VE of a booster dose of TDV against symptomatic dengue illness due to any serotype, and will provide data on the effect of a booster dose on VE after a 2-dose vaccination regimen with TDV (2 single doses 3 months apart). Subjects will receive a single dose of TDV or placebo, depending on the assignment at the time of randomization in the trial (Day 1 [Month 0]). The trial blind will be maintained.

No new randomization will be performed for the booster phase of the trial. Only subjects from the Per-Protocol Set (PPS) who were 4 to 11 years of age at the time of randomization in the trial (Day 1 [Month 0]) will receive the booster vaccination between 4 years and approximately 4.5 years post-dose 2.

As no active comparator was possible as part of the trial design, a licensed vaccine will be offered to all subjects at least 6 months after any protocol defined vaccination. A similar offer will be given to subjects participating in the booster phase. A licensed vaccine will be offered according to local regulations to all subjects irrespective of their full participation in the booster phase and at least 6 months after booster vaccination. The choice of this vaccine will be discussed between the Sponsor and the Investigator, and will be approved by the appropriate ethics committee. This vaccine will be used according to the labeling approved in the country.

Trial Design:

This is a phase III, double-blind, randomized, placebo-controlled trial with 2 parallel groups. The trial includes for all subjects at least 3 time periods (Parts 1, 2 and 3) for surveillance of febrile illness with potential dengue etiology. The trial includes 2 additional time periods (Parts 4 and 5) for surveillance of febrile illness with potential dengue etiology for subjects participating in the booster phase of the trial.

The trial design and subject population for Parts 1, 2, and 3 of the trial and the booster phase (Parts 4 and 5) are below.

Parts 1, 2, and 3

Part 1 constitutes the primary analysis period, including primary efficacy analysis. Part 2 constitutes a period of additional active surveillance for secondary efficacy analyses. Part 3 constitutes modified active surveillance for the assessment of long-term safety.

- Part 1: Active surveillance for the primary assessment of efficacy in all subjects. During this time subjects will be contacted at least weekly to ensure identification of febrile illness that could potentially be due to dengue. This part will commence on the day of vaccination and finish once both of the following 2 criteria are fulfilled:
    1. 120 cases of dengue fever are confirmed.
    2. Minimum duration of subject follow-up of 12 months post-second vaccination.

  The end of Part 1 will be defined for each subject so that the duration of follow up after the second vaccination will be approximately the same for all subjects. Virologically confirmed cases in Part 1 count towards the primary efficacy objective if occurring at least 30 days post-second vaccination.
- Part 2: Active surveillance for an additional 6 months for each subject following the completion of Part 1. During this time subjects will be contacted at least weekly to ensure identification of febrile illness that could potentially be due to dengue.

  Virologically confirmed cases in Parts 1 and 2 contribute towards the secondary efficacy objectives.
- Part 3: Modified active surveillance for the assessment of safety in all subjects following the completion of Part 2 and lasting approximately 3 years for each subject. The modified active surveillance during Part 3 will maintain at least weekly contacts through Part 3 of the trial, but the intensity of investigation will be modified based on the need for hospitalization. Surveillance will identify febrile illness of any severity that could potentially be due to dengue.

Subjects may be enrolled into a dry-run to commence and test febrile surveillance methodology. This dry-run

will involve pre-vaccination surveillance for dengue and may be conducted for up to 10 months prior to vaccination on Day 1. It may not be required in all sites and may not be applicable to all subjects at the trial sites where it is conducted. The need for and duration of the dry-run at an individual site will depend on the experience of the site in conducting similar trials. For ease of terminology, trial time points will use the date of first vaccination (Day 1) as the reference point, so activities occurring prior to the day of first vaccination (Day 1) will be referred to as Day –x to Day -1 (the day before first vaccination).

The target sample of 20,100 healthy children and adolescents aged between 4 and 16 years will be randomized to receive either TDV or placebo in a 2:1 ratio. Randomization by using an interactive system (Interactive Web Response System [IWRS] or Interactive Voice Response System [IVRS]) will be stratified by region and age range (children aged 4-5 years, 6-11 years, and 12-16 years) to ensure each age range has the appropriate ratio of TDV to placebo in each region. In addition, recruitment will follow an enrollment plan to ensure representative enrollment across the age ranges and regions. This is considered necessary to mitigate the relative difficulty of recruitment of subjects at the extremes of the age-ranges in this trial. Each subject will receive TDV or placebo by a subcutaneous (SC) injection into the upper arm. A subset of the same subjects (number [N]=4,000) will be included in specific safety and immunogenicity evaluations (safety/immunogenicity subset, hereafter referred to as 'subset'). This subset will also be selected randomly using IWRS or IVRS and stratified by region and age range (children aged 4-5 years, 6-11 years, and 12-16 years).

Aspects of active surveillance (dry-run, Parts 1 and 2):

Definition of active surveillance

During active surveillance (dry-run, Parts 1 and 2), any subject with febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) will be asked to return to the site for dengue fever evaluation by the Investigator. Subjects/ guardians will be contacted at least weekly to ensure robust identification of febrile illness by reminding subjects/guardians of their obligation to return to the site in case of febrile illness. This contact will be implemented through appropriate methods that may differ in each trial site (eg, phone calls, text messaging, home visits, school-based surveillance). The text messaging system, if used, will be identified and evaluated by the Sponsor before use. Each trial site will have locally-developed Standard Procedures (ie, Internal Operating Procedures) that details the local healthcare map relevant to the trial (as assessed by the trial site), methodology of febrile illness surveillance and case handling.

Duration of active surveillance

Active surveillance for febrile illness will commence at the dry-run or on Day 1 (Part 1) and will continue until the end of Part 2.

Part 1 is designed to support the primary objective of assessment of efficacy of the vaccine candidate in preventing virologically confirmed dengue fever induced by any dengue serotype, and will include active surveillance until the 2 conditions described above are fulfilled.

Part 2 is designed to provide additional data regarding the secondary efficacy objectives detailed below. These analyses involve subsets of dengue cases, such as dengue due to a single serotype, and will therefore be less precise than the primary efficacy endpoint which considers dengue cases regardless of severity or serotype. A longer surveillance period enables the identification of additional dengue cases, thereby improving the precision of the secondary efficacy objectives. For this reason, all subjects will continue active surveillance for 6 months following the completion of Part 1.

Aspects of modified active surveillance (Part 3):

Modified active surveillance will start after the completion of Part 2 and will last for approximately 3 years. Modified active surveillance will be implemented to detect dengue cases of any severity in a tiered approach based on the need for hospitalization. Any subject with febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) will be asked to return to the site for evaluation by the Investigator. Subjects presenting with febrile illness not requiring hospitalization will be screened for dengue disease (by reverse transcriptase polymerase chain reaction [RT-PCR]) unless there is alternate laboratory confirmed etiology. They will undergo local laboratory evaluations as per standard medical practice. Subjects with febrile illness requiring hospitalization will be evaluated as during active surveillance (ie, dry-run, Parts 1 and 2). During Part 3, there

will be a minimum frequency of 1 contact every week through appropriate methods that may differ in each trial site (see above). Modified active surveillance will be performed according to locally-developed Standard Procedures as described above.

The trial design (Parts 1, 2, and 3) is presented in Figure 2.a. Differences between active surveillance (dry-run, Parts 1 and 2) and modified active surveillance (Part 3) are summarized in Table 2.a.

Figure 2.a Schematic Showing Parts 1, 2, 3

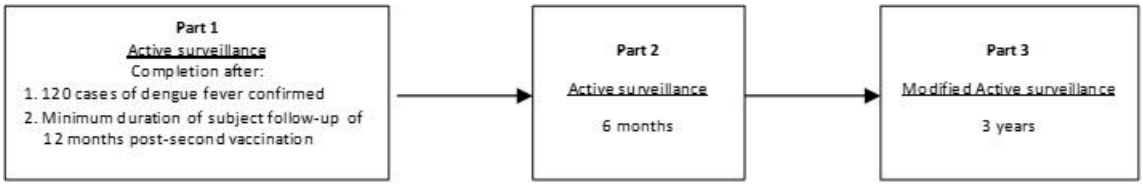


Table 2.a Differences between Active Surveillance (Dry-Run, Parts 1 and 2) and Modified Active Surveillance (Part 3)

	Active Surveillance (dry-run, Parts 1 and 2)	Modified Active Surveillance (Part 3)	
Contact frequency	At least weekly	At least weekly	
Threshold for evaluation	All febrile illness (irrespective of need for hospitalization)	Febrile illness requiring hospitalization	Febrile illness not requiring hospitalization (unless the febrile illness has an alternate laboratory confirmed etiology).
Laboratory evaluations	- Within 5 days: RT-PCR, NS1 antigen, IgM, IgG ELISA (central laboratory); and platelet count, hematocrit, ALT, and AST (locally) - 7-14 days after the acute sample: IgM and IgG ELISA (central laboratory); and platelet count, hematocrit, ALT, and AST (locally) - Other laboratory evaluations as per standard of care (locally)	- Within 5 days: RT-PCR (central laboratory) - Other laboratory evaluations as per standard of care (locally)	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ELISA = enzyme-linked immunosorbent assay; IgG/IgM = Immunoglobulin G/M; NS1 = nonstructural protein 1; RT-PCR = reverse transcriptase polymerase chain reaction

Case definition for efficacy objectives:

A virologically confirmed dengue case is defined as febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) or illness clinically suspected to be dengue by the Investigator with a positive serotype-specific RT-PCR. The presence of a febrile illness or clinically suspected dengue will be recorded in the electronic Case Report Form (eCRF) by the Investigator.

Handling of febrile illness cases (suspected dengue cases):

Subjects presenting with febrile illness (defined as temperature ≥ 38°C on any 2 of 3 consecutive days) or clinically suspected dengue during the dry-run, Parts 1 and 2 or requiring hospitalization during Part 3 will have 2 blood samples taken to confirm dengue infection, in addition to those taken as part of the clinical care of the subject. The first or acute blood sample will be taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever). Testing will include dengue immunoglobulin (Ig) M (IgM) and IgG enzyme-linked immunosorbent assay (ELISA), dengue nonstructural protein 1 (NS1) antigen ELISA, dengue RT-PCR, hematocrit, platelet count and liver function tests (LFTs [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)]). The second or convalescent blood sample will be taken during the convalescent phase of the disease (ie, between 7 and 14 days after the acute sample) and will be tested for dengue IgM/IgG by ELISA, hematocrit, platelet count, and LFTs (as above).

Local standards of care may require additional tests, based on clinical presentation and at medical discretion. Additional dengue neutralizing antibody and other laboratory tests may be performed. In addition to blood tests,

clinical evaluation will be performed for signs of hemorrhage or plasma leakage as well as any other abnormal signs or symptoms.

In addition, during Part 3, subjects presenting with febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) or clinically suspected dengue and not requiring hospitalization will have 1 blood sample taken for dengue infection confirmation by RT-PCR unless there is an alternate laboratory confirmed etiology.

The blood sample will be taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever). Febrile illness cases within 30 days after vaccination will be investigated for the presence of WT or vaccine-derived dengue virus. The testing algorithm is described in the serology plan. Clinical evaluation will be performed for signs of hemorrhage or plasma leakage as well as any other abnormal signs or symptoms. Local standards of care may require additional tests, based on clinical presentation and at medical discretion.

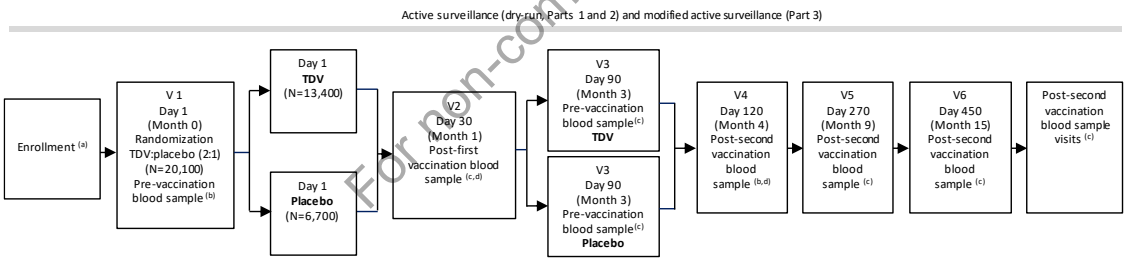
A febrile illness as described above will require an interval of at least 14 days from a previous febrile illness to avoid overlap of acute and convalescent visits from 1 episode with those from a second episode.

Procedures

After informed consent/assent has been obtained (which may be up to 10 months prior to vaccination on Day 1 [Month 0] as described above and as a result of the dry-run) each subject will be assessed for eligibility to participate in the trial. On Day 1 (Month 0) a pre-vaccination blood sample will be taken, randomization to TDV or placebo, and vaccination will occur. A second vaccination will be administered at Day 90 (Month 3). Subjects included in the subset (see above) will also be randomly selected using the IWRS or IVRS.

Any withdrawals from enrollment until Day 1 will be replaced so that 20,100 subjects are randomized and vaccinated; any withdrawals after randomization will not be replaced. The trial schedule (subject flow and visits) is presented in Figure 2.b.

Figure 2.b Schematic to Show Subject Flow Through the Trial (Parts 1, 2, and 3)



Note: (i) Any subjects who withdraw between enrollment and randomization will be replaced so that 20,100 subjects are randomized; subjects who withdraw after randomization will not be replaced.
(ii) Subjects presenting with febrile illness (defined as temperature ≥38°C on any two of three consecutive days) or clinically suspected dengue during the dry-run, Parts 1 and 2, or with febrile illness requiring hospitalization during Part 3 will have two blood samples taken to confirm dengue infection. The first or acute blood sample will be taken during the acute phase of the disease (i.e., as soon as possible and preferably within 5 days after the onset of fever); the second or convalescent blood sample will be taken during the convalescent phase of the disease (i.e., between 7 to 14 days after the acute sample).
(iii) During Part 3, subjects presenting with febrile illness (defined as temperature ≥38°C on any two of three consecutive days) or clinically suspected dengue and not requiring hospitalization will have one blood sample taken during the acute phase of the disease (i.e., as soon as possible and preferably within 5 days after the onset of fever) unless there is an alternate laboratory confirmed etiology.

[a] Prior to entry into the dry-run or Day 1 (Month 0)
[b] Blood sample for dengue neutralizing antibodies for all subjects
[c] Additional blood samples for dengue neutralizing antibodies will be taken in the subset on Day 30 (Month 1), Day 90 (Month 3), Day 270 (Month 9), Day 450 (Month 15), and then every 12 months until the end of Part 3.
[d] Day 30 (Month 1) and Day 120 (Month 4) blood samples should be taken at least 28 days after the first and second vaccination, respectively.
V= Visit

Between 4 years and approximately 4.5 years post-dose 2 in Part 3, the parent/guardian of subjects who are included in the PPS and who were 4 to 11 years of age at the time of randomization in the trial on Day 1 (Month 0) will be asked to allow their child/ward to receive the booster dose of trial vaccine (TDV or placebo). It is anticipated that some subjects eligible for the booster phase of the trial may have or may not have completed Part 3 of the trial by the time the protocol amendment is implemented and it is feasible to enroll them into the booster phase for ethical and scientific reasons. Those subjects may be enrolled into the booster phase provided the Institutional Review Board/Independent Ethics Committee approved the current protocol amendment, the subjects meet the entry criteria, and the global enrollment into the booster phase is ongoing. Details on data analysis for subjects who do not complete Part 3 of the trial will be provided in the Statistical Analysis Plan (SAP).

Immunogenicity evaluation (microneutralization test [MNT_{50}]):

All subjects:

- Blood samples will be collected pre-vaccination on Day 1 (Month 0) and post-second vaccination on Day 120 (Month 4).

Subset:

- Additional blood samples will be collected post-first vaccination on Day 30 (Month 1), pre-vaccination on Day 90 (Month 3), post-second vaccination on Day 270 (Month 9) and Day 450 (Month 15), and then every 12 months until the end of Part 3.

Safety evaluation:

All subjects:

- Identification of febrile episodes with potential dengue etiology for the trial duration.
- Blood samples will be collected in the event of febrile illness as described above.

Documentation of all SAEs during Parts 1 and 2. During Part 3, investigators will be required to report all deaths as well as SAEs assessed as related, or deemed relevant by the Investigator in the context of vaccine safety.

Subset:

- Subjects will be provided with a diary card for the recording of:
  - Solicited local adverse events (AEs) for 7 days following each vaccination (day of vaccination + 6 subsequent days). These will include:
    - Injection site pain, injection site erythema, and injection site swelling.
  - Solicited systemic AEs for 14 days following each vaccination (day of vaccination + 13 subsequent days). These will include:
    - Child <6 years: fever, irritability/fussiness, drowsiness and loss of appetite.
    - Child ≥6 years: asthenia, fever, headache, malaise and myalgia.
- Unsolicited AEs for 28 days following each vaccination (day of vaccination + 27 subsequent days) will be collected by interview (ie, at Day 30 [Month 1] and Day 120 [Month 4], as applicable).

Booster Phase (Parts 4 and 5)

Parts 4 and 5 constitute a period of modified active surveillance for exploratory efficacy, immunogenicity and safety analyses post-booster vaccination.

- Part 4: Modified active surveillance post-booster vaccination and lasting minimum 13 months for each subject.
- Part 5: Modified active surveillance following the completion of Part 4 and lasting 1 year for each subject.

The modified active surveillance during Parts 4 and 5 will maintain at least weekly contacts through Parts 4 and 5 of the trial, but the intensity of investigation will be modified based on the need for hospitalization. Surveillance will identify febrile illness of any severity that could potentially be due to dengue.

No new randomization will be performed for the booster phase of the trial. Only subjects from the PPS who were 4 to 11 years of age at the time of randomization in the trial on Day 1 (Month 0) can participate in the booster phase of this trial. Subjects assigned to participate in the booster phase of the trial will receive a single dose of TDV or placebo, depending on the assignment at the time of randomization in the trial (Day 1 [Month 0]). The target sample size for the booster phase is approximately 10,500 subjects (TDV: approximately 7,000 subjects, placebo: approximately 3500 subjects). The booster dose will be administered between 4 years and approximately 4.5 years post-dose 2. A subset of subjects who were 4 to 11 years of age at the time of randomization on Day 1 (Month 0) will be assigned to the booster immunogenicity subset for specific safety and immunogenicity evaluations. Assignment to the booster immunogenicity subset (approximately 2100 subjects) is also based on randomization performed in Part 1 on Day 1 (Month 0).

For ease of terminology, trial time points will use the date of booster vaccination (Day 1b) as the reference point,

so activities occurring prior to the day of booster vaccination (Day 1b) will be referred to as Day –x to Day -1b (the day before booster vaccination).

Aspects of modified active surveillance in the booster phase of the trial (Parts 4 and 5):

Modified active surveillance will continue after the completion of Part 3 and will last for approximately 25 months to detect dengue cases of any severity in a tiered approach based on the need for hospitalization post-booster vaccination. Any subject with febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) will be asked to return to the site for evaluation by the Investigator. Subjects presenting with febrile illness not requiring hospitalization will be screened for dengue disease (by RT-PCR) unless there is alternate laboratory confirmed etiology. They will undergo local laboratory evaluations as per standard medical practice. Subjects with febrile illness requiring hospitalization will be evaluated as during active surveillance (ie, dry-run, Parts 1 and 2). During Parts 4 and 5, there will be a minimum frequency of 1 contact every week through appropriate methods that may differ in each trial site (see above). Modified active surveillance will be performed according to locally-developed Standard Procedures as described above.

The trial design (Parts 4 and 5) is presented below in Figure 2.c. Modified active surveillance (Parts 4 and 5) is summarized in Table 2.b.

Figure 2.c Schematic to Showing Parts 4 and 5

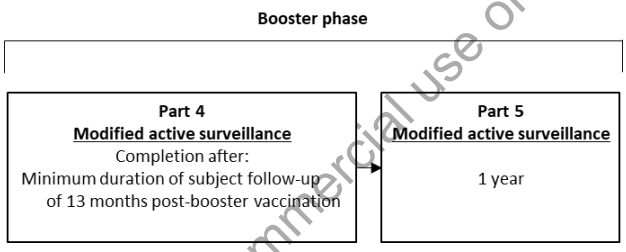


Table 2.b Modified Active Surveillance (Parts 4 and 5)

	Modified Active Surveillance (Parts 4 and 5)	
Contact frequency	At least weekly	
Threshold for evaluation	Febrile illness requiring hospitalization.	Febrile illness not requiring hospitalization (unless the febrile illness has an alternate laboratory confirmed etiology).
Laboratory evaluations	- Within 5 days: RT-PCR, NS1 antigen, IgM, IgG ELISA (central laboratory); and platelet count, hematocrit, ALT, and AST (locally) - 7-14 days after the acute sample: IgM and IgG ELISA (central laboratory); and platelet count, hematocrit, ALT, and AST (locally) - Other laboratory evaluations as per standard of care (locally)	- Within 5 days: RT-PCR (central laboratory) - Other laboratory evaluations as per standard of care (locally)

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ELISA: enzyme-linked immunosorbent assay, IgG/IgM: Immunoglobulin G/M, NS1: nonstructural protein 1, RT-PCR: reverse transcriptase polymerase chain reaction.

Handling of febrile illness cases (suspected dengue cases):

Subjects presenting with febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) requiring hospitalization during Parts 4 and 5 will have 2 blood samples taken to confirm dengue infection, in addition to those taken as part of the clinical care of the subject. The first or acute blood sample will be taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever). Testing

will include dengue IgM and IgG ELISA, dengue NS1 antigen ELISA, dengue RT-PCR, hematocrit, platelet count and LFTs (AST and ALT). The second or convalescent blood sample will be taken during the convalescent phase of the disease (ie, between 7 and 14 days after the acute sample) and will be tested for dengue IgM/IgG by ELISA, hematocrit, platelet count, and LFTs (as above). In some circumstances, additional investigations (including additional PCR and viral genome sequencing) will be performed to further characterize the detected infectious dengue virus.

Local standards of care may require additional tests, based on clinical presentation and at medical discretion. Additional dengue neutralizing antibody and other laboratory tests may be performed. In addition to blood tests, clinical evaluation will be performed for signs of hemorrhage or plasma leakage as well as any other abnormal signs or symptoms.

Subjects presenting with febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) or clinically suspected dengue and not requiring hospitalization during Parts 4 and 5 will have 1 blood sample taken for dengue infection confirmation by RT-PCR unless there is an alternate laboratory confirmed etiology. The blood sample will be taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever). Febrile illness cases within 30 days after vaccination will be investigated for the presence of WT or vaccine-derived dengue virus. The testing algorithm is described in the serology plan. Clinical evaluation will be performed for signs of hemorrhage or plasma leakage as well as any other abnormal signs or symptoms. Local standards of care may require additional tests, based on clinical presentation and at medical discretion.

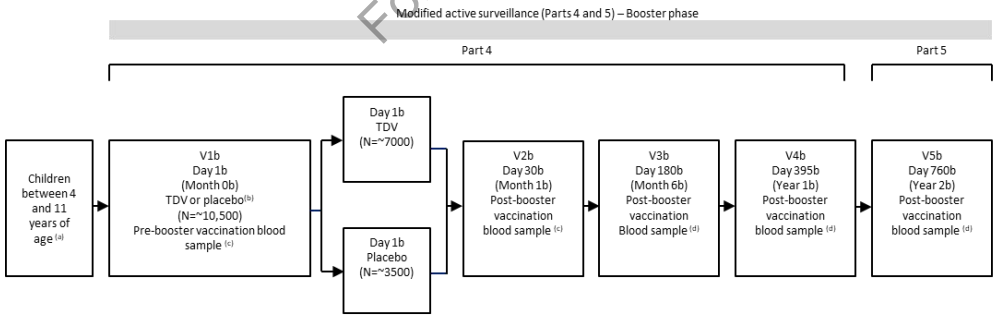
A febrile illness as described above will require an interval of at least 14 days from a previous febrile illness to avoid overlap of acute and convalescent visits from 1 episode with those from a second episode.

Procedures

After informed consent/assent has been obtained for the booster phase of the trial, each subject will be assessed for eligibility to participate in the booster phase. On Day 1 booster (b) (Month 0b) a pre-booster vaccination blood sample will be taken and booster vaccination will occur.

The trial schedule (subject flow and visits) for the booster phase of the trial (Parts 4 and 5) is presented below in Figure 2.d.

Figure 2.d Schematic to Show Subject Flow Through the Booster Phase of the Trial (Parts 4 and 5)



Note: (i) The blood sampling will be re-set based on the day of booster vaccination ('b' will be used to denote booster visits – e.g., V1b, Day 1b, Month 0b)
(ii) Subjects presenting with febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) requiring hospitalization will have two blood samples taken to confirm dengue infection. The first blood sample will be taken during the acute phase (ie, as soon as possible and preferably within 5 days after the onset of fever); the second sample will be taken during the convalescent phase (ie., between 7 to 14 days after the first blood sample). Subjects presenting with febrile illness (defined as temperature ≥38 °C on any 2 of 3 consecutive days) or clinically suspected dengue and not requiring hospitalization during Parts 4 and 5 will have 1 blood sample taken for dengue infection confirmation by RT-PCR unless there is an alternate laboratory confirmed etiology. The blood sample will be taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever).

a. Subjects who are included in the Per-Protocol Set and were 4 to 11 years of age at the time of randomization in the trial (see Figure 6.b) .
b. Subjects will receive a booster dose of TDV or placebo, depending on the assignment at the time of randomization in the trial (see Figure 6.b).
c. Blood sample for dengue neutralizing antibodies for all subjects.
d. Additional blood sample for dengue neutralizing antibodies in the booster immunogenicity subset.

Booster immunogenicity evaluation (MNT_{50}):

Note: 'b' will be used to denote trial visits of the booster phase.

All subjects in the booster phase:

- Blood samples will be collected pre-booster vaccination on Day 1b (Month 0b) and post-booster vaccination on Day 30b (Month 1b).

Booster immunogenicity subset:

- Additional blood samples will be collected post-booster vaccination on Day 180b (Month 6b), Day 395b (Month 13b), and Day 760b (Month 25b).

Safety evaluation:

All subjects in the booster phase:

- Identification of febrile episodes with potential dengue etiology for the trial duration.
- Blood samples will be collected in the event of febrile illness as described above.
- Documentation of all SAEs during Parts 4 and 5.

Booster immunogenicity subset:

- Subjects will be provided with a diary card for the recording of:
  - Solicited local AEs for 7 days following booster vaccination (day of booster vaccination + 6 subsequent days). These will include:
    - Injection site pain, injection site erythema, and injection site swelling
  - Solicited systemic AEs for 14 days following booster vaccination (day of booster vaccination + 13 subsequent days). These will include:
    - Asthenia, fever, headache, malaise and myalgia.
- Unsolicited AEs for 28 days following booster vaccination (day of booster vaccination + 27 subsequent days) will be collected by interview (ie, at Day 30b [Month 1b]).

Primary Objective:

To evaluate the efficacy of 2 doses of TDV in preventing symptomatic dengue fever of any severity and due to any of the 4 dengue virus serotypes in 4-16 year old subjects.

Secondary Objectives:

To be assessed post-second vaccination:

Efficacy:

- To assess the efficacy of TDV in preventing symptomatic dengue fever of any severity induced by individual dengue serotypes.
- To assess the efficacy of TDV in preventing symptomatic dengue fever of any severity by dengue exposure status at baseline.
- To assess the efficacy of TDV in preventing hospitalization due to virologically confirmed dengue fever.
- To assess the efficacy of TDV in preventing severe dengue induced by any dengue serotype.

Safety:

- To describe the safety of TDV.
- To describe the reactogenicity of TDV in a subset of subjects.

Immunogenicity:

- To assess the immunogenicity of TDV in a subset of subjects.

Exploratory Objectives:

Parts 1, 2, and 3

Efficacy:

- To describe the efficacy of TDV in preventing virologically confirmed dengue fever between first and second vaccinations.
- To describe the efficacy of TDV in preventing virologically confirmed dengue fever from first vaccination until end of Part 2.
- To describe virologically confirmed and hospitalized dengue fever identified during Part 3.
- To describe virologically confirmed dengue fever identified during Part 3.
- For the correlate of protection, a threshold antibody titer value may be evaluated to predict VE using descriptive methodology.
- To describe the profiles of IgG, IgM, and NS1 antigen during episodes of febrile illness.

Booster phase (Parts 4 and 5)

Efficacy:

- To assess the efficacy of a TDV booster dose in preventing symptomatic dengue fever of any severity induced by any dengue serotype.
- To assess the efficacy of a TDV booster dose in preventing symptomatic dengue fever of any severity by dengue exposure status at baseline.
- To assess the efficacy of a TDV booster dose in preventing hospitalization due to virologically confirmed dengue fever induced by any dengue serotype.
- To assess the efficacy of a TDV booster dose in preventing severe dengue induced by any dengue serotype.

Safety:

- To describe the safety of a TDV booster dose.
- To describe the reactogenicity of a TDV booster dose in a subset of subjects.

Booster immunogenicity:

- To assess the immunogenicity of a TDV booster dose in a subset of subjects.

Subject Population:

Healthy subjects: Yes.

Parts 1, 2, and 3:

Planned Minimum/Maximum Age: 4 years/16 years.

Planned Number of Subjects: 20,100.

Planned Number of Arms: Two arms in a 2:1 ratio (13,400 TDV: 6700 placebo), 2-dose regimen (Day 1 [Month 0] and Day 90 [Month 3]), SC route

Booster Phase (Parts 4 and 5):

Planned Minimum/Maximum Age: 4 years/11 years at the time of randomization in the trial (Day 1 [Month 0]); the booster vaccination is scheduled between 4 years and approximately 4.5 years post-dose 2.

Planned Number of Subjects: approximately 10,500.

Planned Number of Arms: Two arms in a 2:1 ratio (approximately 7,000 TDV: approximately 3500 placebo), single dose regimen (Day 1b [Month 0b]), SC route

Criteria for Inclusion:

Trial entry

1. The subject is aged 4 to 16 years inclusive, at the time of randomization.
2. Individuals who are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the Investigator.
3. The subject and/or the subject's parent/guardian signs and dates an assent/written informed consent form where applicable, and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements.
4. Individuals who can comply with trial procedures and are available for the duration of follow-up.

Booster phase (Parts 4 and 5)

Subject eligibility for enrollment in the booster phase of the trial is determined according to the following criteria:

1. The subject is included in the PPS of the trial.
2. The subject was aged 4 to 11 years at the time of randomization in the trial (Day 1 [Month 0]).
3. The subject and/or the subject's parent/guardian signs and dates an assent/written informed consent form where applicable, and any required privacy authorization prior to the initiation of any trial procedures for the booster phase of the trial, after the nature of the booster phase of the trial has been explained according to local regulatory requirements.
4. Individuals who can comply with trial procedures for the booster phase and are available for the duration of follow-up post-booster vaccination.

Criteria for Exclusion:

Trial entry

1. Febrile illness (temperature ≥38°C) or moderate or severe acute illness or infection at the time of randomization.
2. History or any illness that, in the opinion of the Investigator, might interfere with the results of the trial or pose an additional risk to the subject due to participation in the trial, including but not limited to:
    a. Known hypersensitivity or allergy to any of the vaccine components.
    b. Female subjects (post-menarche) who are pregnant or breastfeeding.
    c. Individuals with any serious chronic or progressive disease according to judgment of the Investigator (eg, neoplasm, insulin-dependent diabetes, cardiac, renal or hepatic disease, neurologic or seizure disorder or Guillain-Barré syndrome).
    d. Known or suspected impairment/alteration of immune function, including:
        i. Chronic use of oral steroids (equivalent to 20 mg/day prednisone ≥12 weeks/ ≥2 mg/kg body weight/day prednisone ≥2 weeks) within 60 days prior to Day 1 (Month 0) (use of inhaled, intranasal, or topical corticosteroids is allowed).
        ii. Receipt of parenteral steroids (equivalent to 20 mg/day prednisone ≥12 weeks / ≥2 mg/kg body weight/day prednisone ≥2 weeks) within 60 days prior to Day 1 (Month 0).
        iii. Administration of immunoglobulins and/or any blood products within the 3 months prior to Day 1 (Month 0) or planned administration during the trial.
        iv. Receipt of immunostimulants within 60 days prior to Day 1 (Month 0).
        v. Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within 6 months prior to Day 1 (Month 0).
        vi. Human immunodeficiency virus (HIV) infection or HIV-related disease.
        vii. Genetic immunodeficiency.
3. Receipt of any other vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to Day 1 (Month 0) or planning to receive any vaccine within 28 days after Day 1 (Month 0).
4. Participation in any clinical trial with another investigational product 30 days prior to Day 1 (Month 0) or intent to participate in another clinical trial at any time during the conduct of this trial.

5. Previous participation in any clinical trial of a dengue candidate vaccine, or previous receipt of a dengue vaccine.
6. First degree relatives of individuals involved in trial conduct.
7. Females of childbearing potential[1] who are sexually active, and who have not used any of the acceptable contraceptive methods[2] for at least 2 months prior to Day 1 (Month 0).
8. Females of childbearing potential who are sexually active, and who refuse to use an acceptable contraceptive method up to 6 weeks post-second vaccination.
9. Deprived of freedom by administrative or court order, or in an emergency setting, or hospitalized involuntarily.
10. Current alcohol abuse or drug addiction that may interfere with the subject's ability to comply with trial procedures.
11. Identified as an employee of the Investigator or trial center, with direct involvement in the proposed trial or other trials under the direction of that Investigator or trial center.

There may be instances when individuals meet all entry criteria except one that relates to transient clinical circumstances (eg, temperature elevation or recent use of excluded medication or vaccine). Under these circumstances, a subject may be considered eligible for trial entry or first vaccination, as applicable, if the appropriate window for delay has passed, inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

Booster phase (Parts 4 and 5)

Any subjects who are assigned to receive a booster dose of trial vaccines (TDV or placebo) will not qualify for entry into the booster phase of the trial if they meet any of the following criteria:

1. Febrile illness (temperature ≥38°C) or moderate or severe acute illness or infection at the time of enrollment in the booster phase of the trial.
2. History or any illness that, in the opinion of the Investigator, might interfere with the results of the booster phase of the trial or pose an additional risk to the subject due to participation in the booster phase of the trial, including but not limited to:
    a. Known hypersensitivity or allergy to any of the vaccine components.
    b. Female subjects (post-menarche) who are pregnant or breastfeeding.
    c. Individuals with any serious chronic or progressive disease according to judgment of the Investigator (eg, neoplasm, insulin-dependent diabetes, cardiac, renal or hepatic disease, neurologic or seizure disorder or Guillain-Barré syndrome).
    d. Known or suspected impairment/alteration of immune function, including:
        i. Chronic use of oral steroids (equivalent to 20 mg/day prednisone ≥12 weeks/ ≥2 mg/kg body weight/day prednisone ≥2 weeks) within 60 days prior to Day 1b (Month 0b) (use of inhaled, intranasal, or topical corticosteroids is allowed).
        ii. Receipt of parenteral steroids (equivalent to 20 mg/day prednisone ≥12 weeks/ ≥2 mg/kg body weight/day prednisone ≥2 weeks) within 60 days prior to Day 1b (Month 0b).

[1] Defined as status post onset of menarche and not meeting any of the following conditions: bilateral tubal ligation (at least 1 year previously), bilateral oophorectomy (at least 1 year previously) or hysterectomy.
[2] Hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring); barrier (condom with spermicide or diaphragm with spermicide) each and every time during intercourse; intrauterine device (IUD); monogamous relationship with vasectomized partner (partner must have been vasectomized for at least 6 months prior to Day 1 [Month 0]). Other contraceptive methods may be considered in agreement with the Sponsor and will be approved by the appropriate ethics committee.

iii. Receipt of immunoglobulins and/or any blood products since Day 120 (Month 4) (ie, 30 days after the second dose of trial vaccine) or planned administration during the booster phase of the trial.
iv. Receipt of immunostimulants within 60 days prior to Day 1b (Month 0b).
v. Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within 6 months prior to Day 1b (Month 0b).
vi. HIV infection or HIV-related disease.
vii. Genetic immunodeficiency.

3. Receipt of any other vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to Day 1b (Month 0b), or planning to receive any vaccine within 28 days after Day 1b (Month 0b).
4. Participation in any clinical trial with another investigational product at any time during participation in this trial or intent to participate in another clinical trial at any time during the conduct of the booster phase of this trial.
5. Participation in any clinical trial of a dengue candidate vaccine other than the current trial, or receipt of a dengue vaccine other than the trial vaccine at any time during participation in this trial.
6. First degree relatives of individuals involved in trial conduct.
7. Females of childbearing potential who are sexually active, and who have not used any of the acceptable contraceptive methods as specified under the criteria for entry into the trial, for at least 2 months prior to Day 1b (Month 0b) (see also trial entry exclusion criteria #7).
8. Females of childbearing potential who are sexually active, and who refuse to use an acceptable contraceptive method up to 6 weeks post-booster vaccination.
9. Deprived of freedom by administrative or court order, or in an emergency setting, or hospitalized involuntarily at any time during participation in this trial.
10. Current alcohol abuse or drug addiction that may interfere with the subject's ability to comply with trial procedures for the booster phase of the trial.
11. Identified as an employee of the Investigator or trial center, with direct involvement in the present trial or other trials under the direction of that Investigator or trial center.

There may be instances when individuals meet all entry criteria for the booster phase of the trial except one that relates to transient clinical circumstances (eg, temperature elevation or recent use of excluded medication or vaccine). Under these circumstances, a subject may be considered eligible for booster vaccination if the appropriate window for delay has passed, inclusion/exclusion criteria for the booster phase have been rechecked, and if the subject is confirmed to be eligible for participation in the booster phase of the trial.

Criteria for delay of second trial vaccination:

If any of the below criteria occur at the time scheduled for second vaccination, the subject may be vaccinated at a later date as long the subject is otherwise eligible to continue trial participation. In certain situations, the period of delay may lead to deviations from the time window for second vaccination. The decision to vaccinate in those situations will be taken by the Investigator. The following clinical circumstances warrant a delay for administration of the second trial vaccination:

1. Body temperature ≥38.0°C within 3 days of intended trial vaccination.
2. Receipt of blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation within 2 weeks of intended trial vaccination.
3. Receipt of any vaccine other than the trial vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) of intended trial vaccination.
4. Receipt of oral or parenteral steroids or immunosuppressive therapy within 1 month of intended trial vaccination; dosage and duration of treatments for steroids are specified under the exclusion criteria.

There are also circumstances under which receipt of second vaccination is a contraindication in this trial. These circumstances include anaphylaxis or severe hypersensitivity reactions following the first vaccination. If these reactions occur, the subject must not receive second vaccination but is encouraged to continue trial participation to enable continued surveillance for dengue.

Criteria for delay of booster vaccination:

If any of the below criteria occur at the time scheduled for the booster vaccination, the subject may be vaccinated at a later date as long the subject is otherwise eligible to continue participation in the booster phase of the trial.

1. Body temperature ≥38.0°C within 3 days of intended booster vaccination.
2. Receipt of any vaccine other than the trial vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) of intended booster vaccination.
3. Use of antipyretics and/or analgesic medication within 24 hours prior to booster vaccination.

There are also circumstances under which receipt of a booster dose of trial vaccine is a contraindication in this trial. These circumstances include anaphylaxis or severe hypersensitivity reactions following the first or second vaccination. If these reactions occur, the subject must not receive the booster vaccination.

Investigational Vaccine:

Parts 1, 2, and 3

- The Investigational Product is TDV, a tetravalent dengue vaccine comprised of 4 recombinant, live attenuated dengue virus strains: ~2 x 10^4, 5 x 10^3, 1 x 10^5 and 3 x 10^5 plaque forming units (PFU) per dose of TDV-1, TDV-2, TDV-3 and TDV-4, respectively.
- Control: Placebo was Normal Saline for injection (0.9% sodium chloride solution).

Booster phase (Parts 4 and 5)

- The Investigational Product is TDV, a tetravalent dengue vaccine comprised of 4 recombinant, live attenuated dengue virus strains with potencies of not less than 3.3, 2.7, 4.0, and 4.5 $\log_{10}$ PFU per dose of TDV-1, TDV-2, TDV-3, and TDV-4, respectively.
- Control: Placebo will be normal saline for injection (0.9% sodium chloride solution).

Duration of the Trial:

Parts 1, 2, and 3

For each participant, at least 42 months after the completion of Part 1 (at least 6 months in Part 2 and approximately 3 years in Part 3). The minimum duration of Part 1 will be approximately 15 months (including minimum 12 months after the second vaccination for each subject) but may be longer depending on the time taken to fulfill criteria for the end of Part 1. Hence, it is not explicitly defined. There is a possibility that when end of Part 1 is determined, certain subjects who were randomized earlier might have already completed the 6 months of active surveillance required for Part 2. The transition to Part 3 (ie, modified active surveillance) will occur at that point for those subjects.

The end of Part 3 will be the end of the trial for subjects not participating in the booster phase of the trial.

Booster phase (Parts 4 and 5)

For each participant, the duration of the booster phase of the trial (Part 4 and 5), will be approximately 760 days (approximately 25 months) including booster vaccination (Day 1b [Month 0b]) and follow-up through Day 760b (Month 25b).

Period of Evaluation:

For the duration of a subject's participation.

Main Criteria for Evaluation and Analyses:

Primary endpoint:

Efficacy

VE of 2 doses of TDV in preventing virologically confirmed dengue fever induced by any dengue serotype occurring from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 1, with VE defined as $1 - (\lambda_V/\lambda_C)$ (where λ_V and λ_C denote the hazard rates for the TDV and placebo arms, respectively).

Secondary endpoints:

Efficacy

- VE of 2 doses of TDV in preventing virologically-confirmed dengue fever induced by each dengue serotype from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 2.
- VE of 2 doses of TDV in preventing virologically-confirmed dengue fever induced by any dengue serotype from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 2 in subjects dengue seronegative at baseline.
- VE of 2 doses of TDV in preventing virologically-confirmed dengue fever induced by any dengue serotype from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 2 in subjects dengue seropositive at baseline.
- VE of 2 doses of TDV in preventing hospitalization due to virologically-confirmed dengue fever induced by any dengue serotype from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 2.
- VE of 2 doses of TDV in preventing virologically-confirmed severe dengue fever induced by any dengue serotype from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 2.

Safety

Subset (post-first and post-second vaccinations):

- Frequency and severity of solicited local (injection site) AEs for 7 days (day of vaccination + 6 subsequent days) and solicited systemic AEs for 14 days (day of vaccination + 13 subsequent days) post-vaccination.
- Percentage of subjects with any unsolicited AEs for 28 days (day of vaccination + 27 subsequent days) post- vaccination.

All subjects:

- Percentage of subjects with SAEs during Parts 1 and 2, Part 1 and Part 2 combined.
- Percentage of subjects with fatal SAEs and related SAEs during the first and second half of Part 3.

Immunogenicity

Subset (post-first and post-second vaccinations):

- Seropositivity rate (% of seropositive subjects) for each of the 4 dengue serotypes at pre-vaccination on Day 1 (Month 0), post-first vaccination on Day 30 (Month 1), pre-vaccination on Day 90 (Month 3); post-second vaccination at Day 120 (Month 4), Day 270 (Month 9), Day 450 (Month 15), and then annually.
- Seropositivity rate (% of seropositive subjects) for multiple (any 2, 3 or 4) dengue serotypes at pre- vaccination on Day 1 (Month 0), post-first vaccination on Day 30 (Month 1), pre-vaccination on Day 90 (Month 3); post-second vaccination at Day 120 (Month 4), Day 270 (Month 9), Day 450 (Month 15), and then annually.

  Note: Seropositivity is defined as a reciprocal neutralizing titer ≥10.
- Geometric mean titers (GMTs) of neutralizing antibodies (MNT_{50}) for each dengue serotype at pre-vaccination on Day 1 (Month 0), post-first vaccination on Day 30 (Month 1), pre-vaccination on Day 90 (Month 3); post- second vaccination at Day 120 (Month 4), Day 270 (Month 9), Day 450 (Month 15), and then annually.

Exploratory endpoints:

Parts 1, 2, and 3

- VE of TDV in preventing virologically-confirmed dengue fever identified between the first and second vaccinations.
- VE of TDV in preventing virologically-confirmed dengue fever identified from first vaccination until the end of Part 2.
- To describe virologically confirmed and hospitalized dengue fever identified during the first half (18 months) of Part 3.

- To describe virologically-confirmed and hospitalized dengue fever identified during the second half (18 months) of Part 3.
- To describe virologically-confirmed dengue fever induced by any dengue serotype identified during first half (18 months) of Part 3.
- To describe virologically-confirmed dengue fever induced by any dengue serotype identified during second half (18 months) of Part 3.

  Note: It is anticipated that some subjects eligible for the booster phase may not complete Part 3 of the trial. The endpoint assessment duration for these subjects will be detailed in the SAP.

Post-first and post-second vaccinations:

- To examine the relationship between dengue neutralizing antibodies (MNT_{50}) and protection from dengue infection (correlate of protection).
- To describe the profiles of IgG, IgM and NS1 antigen during episodes of febrile illness.

Booster phase (Parts 4 and 5)

Efficacy

All subjects in the booster phase:

- VE of a TDV booster dose in preventing virologically confirmed dengue fever induced by any dengue serotype from 30 days post-booster vaccination (Day 30 booster (Month 1b) until the end of Part 4 and Part 5 separately, and for Parts 4 and 5 combined.
- VE of a TDV booster dose in preventing virologically confirmed dengue fever induced by each dengue serotype from 30 days post-booster vaccination (Day 30b [Month 1b]) until the end of Part 4 and Part 5 separately, and for Parts 4 and 5 combined.
- VE of a TDV booster dose in preventing virologically confirmed dengue fever induced by any and each dengue serotype in dengue seronegative subjects at baseline from 30 days post-booster vaccination (Day 30b [Month 1b]) until the end of Part 4 and Part 5 separately, and for Parts 4 and 5 combined.
- VE of a TDV booster dose in preventing virologically confirmed dengue fever induced by any and each dengue serotype in dengue seropositive subjects at baseline from 30 days post-booster vaccination (Day 30b [Month 1b]) until the end of Part 4 and Part 5 separately, and for Parts 4 and 5 combined.
- VE of a TDV booster dose in preventing hospitalization due to virologically confirmed dengue fever induced by any dengue serotype from 30 days post-booster vaccination (Day 30b [Month 1b]) until the end of Part 4 and Part 5 separately, and for Parts 4 and 5 combined.
- VE of a TDV booster dose in preventing virologically confirmed severe dengue fever induced by any dengue serotype from 30 days post-booster vaccination (Day 30b [Month 1b]) until the end of Part 4 and Part 5 separately, and for Parts 4 and 5 combined.

Safety

Booster immunogenicity subset:

- Frequency and severity of solicited local (injection site) AEs for 7 days (day of booster vaccination + 6 subsequent days) and solicited systemic AEs for 14 days (day of booster vaccination + 13 subsequent days) post-vaccination.
- Percentage of subjects with any unsolicited AEs for 28 days (day of booster vaccination + 27 subsequent days) post-vaccination.

All subjects in the booster phase:

- Percentage of subjects with SAEs during Part 4 and Part 5 separately, and for Parts 4 and 5 combined.
- Percentage of subjects with fatal SAEs and related SAEs during Part 4 and Part 5 separately, and for Parts 4 and 5 combined.

Booster immunogenicity:

Booster immunogenicity subset:

- Seropositivity rate (% of seropositive subjects) for each of the 4 dengue serotypes at pre-booster vaccination on Day 1b (Month 0b) and post-booster vaccination on Day 30b (Month 1b), Day 180b (Month 6b), Day 395b (Month 13b), and Day 760b (Month 25b).
- Seropositivity rate (% of seropositive subjects) for multiple (any 2, 3 or 4) dengue serotypes at pre-booster vaccination on Day 1b (Month 0b) and post-booster vaccination on Day 30b (Month 1b), Day 180b (Month 6b), Day 395b (Month 13b), and Day 760b (Month 25b).

Note: Seropositivity is defined as a reciprocal neutralizing titer ≥10.

- GMTs of neutralizing antibodies (MNT_{50}) for each dengue serotype at pre-booster vaccination on Day 1b (Month 0b) and post-booster vaccination on Day 30b (Month 1b), Day 180b (Month 6b), Day 395b (Month 13b), and Day 760b (Month 25b).
- GMR of neutralizing antibodies (MNT50) for each dengue serotype at pre-booster vaccination on Day 1b (Month 0b) versus post-booster vaccination on Day 30b (Month 1b).
- GMR of neutralizing antibodies (MNT_{50}) for each dengue serotype at pre-booster vaccination on Day 1b (Month 0b) versus post-booster vaccination on Day 180b (Month 6b).
- GMR of neutralizing antibodies (MNT_{50}) for each dengue serotype at pre-booster vaccination on Day 1b (Month 0b) versus post-booster vaccination on Day 395b (Month 13b).
- GMR of neutralizing antibodies (MNT_{50}) for each dengue serotype at pre-booster vaccination on Day 1b (Month 0b) versus post-booster vaccination on Day 760b (Month 25b).

Post-booster vaccination:

- To examine the relationship between dengue neutralizing antibodies (MNT_{50}) and protection from dengue infection (correlate of protection).
- To describe the profiles of IgG, IgM and NS1 antigen during episodes of hospitalized febrile illness.

Statistical considerations:

Analysis sets – Parts 1, 2, and 3

Safety Set (SS): The SS will consist of all randomized subjects who received at least 1 dose of the trial vaccines (TDV or placebo). For analyses of solicited AEs (reactogenicity) and unsolicited non-serious AEs, only subjects in the subset will be included. For all subjects in the SS, SAEs will be assessed during Parts 1, 2, and 3.

Full Analysis Set (FAS): The FAS will include all randomized subjects who received at least 1 dose of the trial vaccines (TDV or placebo).

Full Analysis Set for Immunogenicity (FASI): The FASI will include all randomized subjects in the subset who received at least 1 dose of the trial vaccines (TDV or placebo) and for whom valid pre-dosing and at least 1 post-dosing blood sample have been received for immunogenicity.

PPS: The PPS will include all subjects in the FAS who have no major protocol violations. The major protocol violation criteria will be defined as part of the blinded data review prior to the unblinding of the subject's trial vaccine assignment. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving the wrong trial vaccine, (3) receiving prohibited therapies, (4) not receiving 2 doses of trial vaccine or receiving the second vaccination inadmissibly outside of the visit window, and (5) other major protocol violations that may be identified during blinded data reviews.

Per-Protocol Set for Immunogenicity (PPSI): The PPSI will consist of all subjects in the FASI who have no major protocol violations.

The primary analysis of VE of 2 doses of TDV in preventing virologically confirmed dengue fever induced by any dengue serotype and occurring from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 1 will be performed on the PPS.

Analysis sets – Booster phase (Parts 4 and 5)

Safety Set-Booster (SS-B): The SS-B will consist of all subjects 4 to 11 years of age at the time of randomization in the trial (Day 1 [Month 0]) who are included in the PPS and who received the booster dose of trial vaccine (TDV or placebo). For analyses of solicited AEs (reactogenicity) and unsolicited non-serious AEs, only subjects in the booster immunogenicity subset will be included. For all subjects in the SS-B, SAEs will be assessed during Parts 4 and 5.

Full Analysis Set-Booster (FAS-B): The FAS-B will consist of all subjects 4 to 11 years of age at the time of randomization in the trial (Day 1 [Month 0]) who are included in the PPS and who received the booster dose of trial vaccine (TDV or placebo).

Full Analysis Set for Immunogenicity-Booster (FASI-B): The FASI-B will consist of subjects from the FAS-B who were included in the booster immunogenicity subset and for whom there is a valid pre-booster measurement and at least 1 valid post-booster measurement for immunogenicity assessments.

Per-Protocol Set-Booster (PPS-B): The PPS-B will include all subjects in the FAS-B who have no major protocol violations. The major protocol violation criteria will be defined as part of the blinded data review prior to the unblinding of the subject's trial vaccine assignment. The categories of major protocol violations include: (1) not meeting selected entry criteria for the booster phase (Parts 4 and 5), (2) receiving the wrong booster trial vaccine, (3) receiving prohibited therapies, (4) not receiving the booster dose of trial vaccine or receiving the booster vaccination inadmissibly outside of the visit window, and (5) other major protocol violations that may be identified during blinded data reviews.

Per-Protocol Set for Immunogenicity-Booster (PPSI-B): The PPSI-B will consist of all subjects in the FASI-B who have no major protocol violations.

Analysis of demographics and other baseline characteristics

Parts 1, 2, and 3

Age, gender, race, and other baseline characteristics will be summarized descriptively by group for all randomized subjects, and for each of the analysis sets (ie, SS, FAS, FASI, PPS, and PPSI).

Booster phase (Parts 4 and 5):

Pre-booster baseline characteristics will be summarized descriptively by group for all subjects enrolled in the booster phase of the trial (Parts 4 and 5), and for each of the booster analysis sets (ie, SS-B, FAS-B, FASI-B, PPS-B, and PPSI-B).

Efficacy analysis

Parts 1, 2, and 3

The primary analysis of VE will occur after both of the following 2 criteria for the end of Part 1 are fulfilled: (1) 120 cases of virologically confirmed dengue have accrued, and (2) a minimum duration of subject follow-up of 12 months post-second vaccination.

For the primary efficacy evaluation, a case of virologically confirmed dengue is defined as febrile illness with a positive serotype-specific RT-PCR and occurring at any time starting from 30 days post-second vaccination (Day 120 [Month 4]) through the end of Part 1. The primary analysis will be performed on the PPS. The primary analysis method will be based on a Cox proportional hazard model with trial group as a factor, adjusted for age, and stratified by region, with 2-sided 95% confidence intervals (CIs) provided for the estimate of VE. The primary efficacy objective is considered to be met if the lower bound of the 95% CI for the VE is above 25%, where VE is defined as $1 – (\lambda_V / \lambda_C)$, where λ_V and λ_C denote the hazard rates for the TDV and placebo arms, respectively. A similar approach will be used to analyze the secondary efficacy endpoints.

Sensitivity analyses of the primary endpoint include: (1) analysis using exact 95% CIs, (2) analysis based on the FAS, and (3) analysis including cases of virologically confirmed dengue occurring at any time post-second vaccination (ie, starting on Day 90 ([Month 3]).

Evaluation of secondary efficacy endpoints will be based on the PPS and will be assessed using data from Parts 1 and 2. Secondary VE endpoints will be analyzed using a similar approach as for the primary endpoint described

above, except that statistical significance will be concluded if the lower bound of the corresponding CI is > 0. Some of the secondary endpoints will be considered as key secondary endpoints and family-wise type I error will be controlled for these endpoints. These endpoints will only be tested if statistical significance is achieved for the primary endpoint. Details on key secondary endpoints and control of the type I error will be provided in the SAP.

The number and percentage of subjects with virologically confirmed dengue will be summarized in the timeframes post-first vaccination (Day 1 [Month 0]) until the end of Part 2 and between administration of the first vaccination and second vaccination on Day 1(Month 0) and Day 90 (Month 3), respectively.

At the time of primary analysis of VE following the completion of Part 1 of the trial, external vendors (Clinical Research Organizations [CROs]) who are involved in the analyses will be unblinded at an individual subject level in order to analyze and summarize the trial data. Takeda will receive summary tables containing aggregated data by trial group for the primary analysis of Part 1 and at the time of any subsequent analyses. A small group of Takeda personnel will also have access to individual level unblinded data. In order to maintain the double-blind design, investigators, site staff, subjects, as well as Takeda staff and external vendors advising sites on trial conduct will remain blinded to individual subject level trial group allocation for the trial duration. There will be blinded and unblinded trial teams at Takeda and within the external vendors. The blinded team may have access to group unblinded results (eg., publications) but will remain blinded to subject level data for the duration of the trial and will remain responsible for all further activities during trial conduct after unblinding for the primary analysis.

The number of virologically confirmed cases of dengue fever identified by the time of the primary endpoint analysis may not be sufficient to assess less common events such as dengue fever due to a specific serotype or severe dengue. Therefore, it is proposed that active surveillance will continue for an additional 6 months after the analysis of the primary endpoint. Consequently, analysis of the secondary efficacy endpoints would then be based on cases occurring at any time from 1 month after the second vaccination (Day 120 [Month 4]) until 6 months after the end of Part 1 (ie, until the end of Part 2).

As a result, data from the additional 6 months surveillance for secondary efficacy endpoints will not be available at the same time as the primary endpoint.

Assuming a 1.0% incidence rate by the end of Part 1 (minimum 12 months after the second vaccination for each subject), it is estimated that approximately 180 evaluable cases will accrue by the end of the additional 6 months of observation (ie, an additional ~60 cases). These additional cases will improve the power for assessment of secondary endpoints, including serotype-specific efficacy.

In addition, the number and percentage of subjects with virologically confirmed dengue, virologically confirmed and hospitalized dengue as well as subjects with fatal SAEs and related SAEs will be summarized for the first half (18 months) and second half (18 months) of Part 3 when such data become available.

Booster phase (Parts 4 and 5)

Evaluation of exploratory efficacy endpoints will be based on the PPS-B and will be assessed using data from Parts 4 and 5. Exploratory VE endpoints will be analyzed using a similar approach as for exploratory VE endpoints during Parts 1, 2, and 3.

The number and percentage of subjects with virologically confirmed dengue will be summarized in the timeframes post-booster vaccination (Day 1b [Month 0b]) until the end of Part 5).

At the time of interim analyses for the booster phase of the trial, external vendors (CROs) who are involved in the analyses will be unblinded at an individual subject level in order to analyze and summarize the trial data. Takeda will receive summary tables containing aggregated data by trial group. A small group of Takeda personnel will also have access to individual level unblinded data. In order to maintain the double-blind design, investigators, site staff, subjects, as well as Takeda staff and external vendors advising sites on trial conduct will remain blinded to individual subject level trial group allocation for the trial duration. There will be blinded and unblinded trial teams at Takeda and within the external vendors. The blinded team may have access to group unblinded results (eg, via publications) but will remain blinded to subject level data for the duration of the trial and will remain responsible for all further activities during trial conduct after unblinding for the exploratory analyses.

Vaccine immunogenicity analysis

Parts 1, 2, and 3

For immunogenicity endpoints including seropositivity rate and GMTs for dengue neutralizing antibodies, descriptive statistics and 95% CIs will be provided by trial group and visit for subjects in the subset. Seropositivity is defined as a reciprocal neutralizing titer ≥10.

Correlate of protection

Immunogenicity data from subjects with confirmed dengue as well as those in the subset will be used to evaluate a potential correlate of protection. Details on the analysis of correlate of protection will be provided in the SAP.

Booster phase (Parts 4 and 5)

For exploratory immunogenicity endpoints including seropositivity rate and GMTs for dengue neutralizing antibodies, descriptive statistics and 95% CIs will be provided by trial group and visit for subjects in the booster immunogenicity subset.

Seropositivity is defined as a reciprocal neutralizing titer ≥10.

For the visit comparisons, GMRs will be summarized descriptively, including 95% CIs.

Correlate of protection

Details on the analysis of correlate of protection related to the booster phase will be provided in the SAP.

Safety Analysis

Parts 1, 2, and 3

All summaries of safety data will be based on the SS. Unless otherwise specified, the safety data will be summarized by trial group.

Reactogenicity

For subjects in the subset, solicited local AEs (injection site pain, injection site erythema, and injection site swelling) and solicited systemic AEs (child < 6 years: fever, irritability/fussiness, drowsiness and loss of appetite; child ≥ 6 years: asthenia, fever, headache, malaise and myalgia) will be assessed for 7 days and 14 days, respectively, following each vaccination (vaccination day included) via collection of diary cards.

For each solicited AE, the percentage of subjects will be summarized by event severity for each day after each vaccination (Days 1 to 7 for local AEs and Days 1 to 14 days for systemic AEs), and overall. A summary of the first onset of each event will also be provided. The number of days subjects experienced each event will also be summarized for each trial group. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

Unsolicited AEs

Unsolicited AEs (subset only) and SAEs (all subjects) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) for each trial group. AEs leading to withdrawal from the trial will also be summarized.

All unsolicited AEs up to 28 days after each vaccination will be included in the analyses of all AEs. For SAEs and AEs leading to subject withdrawal from the trial, Parts 1, 2, and 3 will be included.

In general, unsolicited AEs will be tabulated at each of the following levels: overall summary (subject with at least 1 AE) and by SOC and PT. Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once. Unsolicited AEs will be summarized as follows: by PT including events with frequency greater than 2%; by SOC and PT; by SOC, PT, and severity; and by SOC, PT, and relationship to the investigational vaccine. Unless otherwise specified, unsolicited AEs will be summarized in the following 3 ways: 1) overall up to 28 days post-vaccination, 2) with onset between 1 and 14 days post-vaccination, and 3) with onset between 15 and 28 days post-vaccination.

Booster phase (Parts 4 and 5)

All summaries of safety data from Parts 4 and 5 will be based on subjects in the SS-B. Unless otherwise specified, the safety data will be summarized by trial group.

Reactogenicity

For subjects in the booster immunogenicity subset, solicited local AEs (injection site pain, injection site erythema, and injection site swelling) and solicited systemic AEs (asthenia, fever, headache, malaise and myalgia) will be assessed for 7 days and 14 days, respectively, following booster vaccination (booster vaccination day included) via collection of diary cards.

For each solicited AE, the percentage of subjects will be summarized by event severity for each day after booster vaccination (Days 1 to 7 for local AEs and Days 1 to 14 days for systemic AEs), and overall. A summary of the first onset of each event will also be provided. The number of days subjects experienced each event will also be summarized for each trial group. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

Unsolicited AEs

Unsolicited AEs (booster immunogenicity subset only) and SAEs (all subjects in the booster phase) will be coded according to MedDRA and summarized by SOC and PT) for each trial group. AEs leading to withdrawal from the booster phase of the trial will also be summarized.

All unsolicited AEs up to 28 days after booster vaccination will be included in the analyses of all AEs. For SAEs and AEs leading to subject withdrawal from the booster phase of the trial, the Parts 4 and 5 will be included.

In general, unsolicited AEs will be tabulated at each of the following levels: overall summary (subject with at least 1 AE) and by SOC and PT. Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once. Unsolicited AEs will be summarized as follows: by PT including events with frequency greater than 2%; by SOC and PT; by SOC, PT, and severity; and by SOC, PT, and relationship to the investigational vaccine. Unless otherwise specified, unsolicited AEs will be summarized overall up to 28 days post-booster vaccination.

Interim Analyses and reporting:

Interim analyses are planned for Part 1, Part 2, 2-year follow-up post-second dose, 3-year follow-up post-second dose, at the end of Part 3, 30 days (1 month) post-booster vaccination, and Part 4. A final analysis will be performed upon trial completion (ie, at the end of Part 5).

At the time of this protocol amendment, an Interim Clinical Study Report (CSR) has been prepared for the results from the dry-run, Part 1, and Part 2 and a second Interim CSR has been prepared for data until 6 months after the end of Part 2 (2-year follow-up post-second dose). A third interim CSR will be prepared for data until 18 months after the end of Part 2 (3-year follow-up post-second dose). Additional reports for the results from Parts 3, 4, and 5, including further Interim CSRs, will be prepared if required for internal use and/or for regulatory submission. A Final CSR will be prepared upon trial completion and will include results for the trial duration.

Sample size justification:

Parts 1, 2, and 3

This is a partially case-driven trial as described above.

Assuming true VE of 60% and a randomization ratio of 2:1 (TDV:placebo), a total of 120 virologically confirmed cases of dengue fever induced by any dengue serotype occurring from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 1 would provide at least 90% power to rule out a vaccine effect of ≤25% (with a 2-sided significance level of 0.05). Assuming a background incidence rate of 1.0% by the end of Part 1 (minimum 12 months after the second vaccination for each subject), randomization of 20,100 subjects in a 2:1 ratio with

follow-up for a minimum of 12 months would allow accrual of at least 120 dengue fever cases. Exclusion of subjects from the PPS will be compensated by a potentially longer duration of Part 1.

Booster phase (Parts 4 and 5)

No formal sample size calculations were performed for the booster phase and the evaluation is exploratory. The booster phase is planned in a subset of the trial subjects based on feasibility considerations and a higher number of subjects will allow estimation of the overall VE and VE in various planned sub-group analyses with higher precision. However, some assumptions were made based on the number of subjects who may be willing to continue in the booster phase. At the time of drafting the protocol amendment, the ongoing trial had approximately 12,500 active PPS subjects in the 4 to 11 years age group. Assuming a 16% dropout, approximately 10,500 subjects are likely to continue in the booster phase. Multiple scenarios of decreasing sample sizes were assessed to estimate the number of dengue fever cases that could be accrued from 30 days post-booster vaccination to the end of Part 4 (with a follow-up period of 12 months) and the associated power, assuming a ratio of 2:1 (TDV:placebo) as on Day 1 (Month 0). These scenarios are summarized in Table 2.c, considering varying true VEs (60% and 70%) and background incidence rates (1% and 2%), with a 2-sided significance level of 0.05 and a lower bound limit of the 95% CI around the estimated VE of 0%.

Table 2.c Number of Virologically Confirmed Dengue Cases Accrued and Power Estimations for Various Scenarios to Demonstrate Booster Effect (Approximately 1 Year Evaluation)

Sample Size [a]	Efficacy	Incidence Rate	Cases Accrued	Power (%)
12,500	60%	1%	67	95
		2%	135	99
	70%	1%	60	99
		2%	120	99
11,500	60%	1%	62	93
		2%	124	99
	70%	1%	55	99
		2%	110	99
10,500	60%	1%	56	89
		2%	113	99
	70%	1%	50	98
		2%	100	99
9,500	60%	1%	51	86
		2%	102	99
	70%	1%	45	97
		2%	91	99
8,500	60%	1%	45	85
		2%	91	99
	70%	1%	40	96
		2%	81	99
7,500	60%	1%	40	80
		2%	81	98
	70%	1%	36	91
		2%	72	99

[a] Assuming a ratio of 2:1 (TDV:placebo) as on Day 1 (Month 0), 2-sided significance level of 0.05, and a lower bound limit of the 95% CI around the estimated VE of 0%.

Data Monitoring Committee:

A Data Monitoring Committee (DMC) will have oversight of this trial. The DMC functions at a program level and further information is available in the DMC Charter. Criteria to classify dengue severity will be defined by the DMC and will be documented in an appendix to the DMC Charter. An Adjudication Committee will assess the severity of individual confirmed dengue cases.

2.1 Schedule of Trial Procedures

Table 2.d presents the schedule of trial procedures for Parts 1, 2, and 3. Table 2.e presents the schedule of trial procedures for the booster phase (Parts 4 and 5).

Table 2.d Schedule of Trial Procedures for Parts 1, 2 and 3

	Possible dry-run for surveillance between enrollment and vaccination	Active surveillance							Modified active surveillance			Follow up visit [d]
		Part 1 [a]						Part 2 [b]	Part 3 [c]			
		Day 1 (Month 0) (Visit 1)	Day 30 (Month 1) (Visit 2)	Day 90 (Month 3) (Visit 3)	Day 120 (Month 4) (Visit 4)	Day 270 (Month 9) (Visit 5)	Day 450 (Month 15) (Visit 6)		Y 1 D815 (M27) (V7)	Y 2 D1180 (M39) (V8)	Y3 D1545 (M51) (V9)	
	Procedure for all subjects											
Visit window			-1 day/ +7 days	±15 days	-1 day/ +7 days	±21 days	±30 days		±45 days		±45 days [e] -45 days/ +180 days [f]	
Visits	X	X	X	X	X			NA				
End of trial phone Contact											X [g]	
Signed informed consent/ assent [h]	X	X										
Assessment of eligibility criteria [h]	X	X										
Check contraindications to vaccination				X								
Check criteria for delay of vaccination				X								
Demographics	X	X										
Medical history	X	X		X								X
Concomitant medications [i]	X	X	X	X	X							X
Complete physical examination [-j]	X	X		X								
Targeted physical examination [k]			X		X							X
Pregnancy test [l]	X	X		X								

Continued

Table 2.d Schedule of Trial Procedures for Parts 1, 2 and 3 (continued)

	Possible dry-run for surveillance between enrollment and vaccination	Active surveillance							Modified active surveillance			Follow up visit [d]
		Part 1 [a]						Part 2 [b]	Part 3 [c]			
		Day 1 (Month 0) (Visit 1)	Day 30 (Month 1) (Visit 2)	Day 90 (Month 3) (Visit 3)	Day 120 (Month 4) (Visit 4)	Day 270 (Month 9) (Visit 5)	Day 450 (Month 15) (Visit 6)		Y 1 D815 (M27) (V7)	Y 2 D1180 (M39) (V8)	Y3 D1545 (M51) (V9)	
	Procedure for all subjects											
Visit window			-1 day/ +7 days	±15 days	-1 day/ +7 days	±21 days	±30 days		±45 days		±45 days [e] -45 days/ +180 days [f]	
Visits	X	X	X	X	X			NA				
Randomization [m]		X										
Vaccine administration		X		X								
Surveillance for dengue fever [n]	X											
Blood sample [o] (8 mL)		X			X							
Febrile illness blood sample [p]	X											
SAEs [q]	X											
	Additional procedures for the subset											
Visits						X	X	NA	X	X	X	
Targeted physical examination [k]						X	X		X	X	X	X
Injection site evaluation [r]		X	X	X	X							
Diary card distribution [s]		X		X								
Diary card collection and review			X		X							
Documentation of AEs [s] [t]			X		X							
Blood sample [u] (5 mL)			X	X		X	X		X	X	X [v]	

AEs = adverse events, D = Day, M = Month, NA = not applicable, V = Visit, Y = Year
Note: when a site visit cannot be carried out due to the coronavirus disease 2019 (COVID-19) pandemic, alternative methods of contact (eg, telephone contact) will be made for subjects who are still under monitoring for safety reporting.

(a) Part 1 will end once both of the 2 following criteria are fulfilled: (1) 120 cases of dengue fever are confirmed, and (2) a minimum duration of subject follow-up of 12 months post-second vaccination.
(b) Part 2 will start after the completion of Part 1 and will last 6 months.
(c) Part 3 will start after the completion of the active surveillance period (i.e. end of Part 2) and will last for approximately 3 years.
(d) Follow-up visit is only applicable if the subject terminates early.
(e) For subjects not participating in the booster phase of the trial (Parts 4 and 5).
(f) For subjects participating in the booster phase of the trial (Parts 4 and 5). See also footnotes g and v.
(g) Between 4 years and approximately 4.5 years post-dose 2 in Part 3, the parent/guardian of subjects who are not included in the subset from Parts 1, 2, and 3 (see footnote 'm') but are included in the PPS and were 4 to 11 years of age at the time of randomization in the trial (Day 1 [Month 0]) will be asked to allow their child/ward to receive the booster dose of trial vaccine (TDV or placebo), depending on the assignment on Day 1 (Month 0) (see footnote 'm'). Regardless of the willingness to participate in the booster phase of this trial, all subjects will continue trial participation for febrile surveillance and safety follow-up.
(h) Eligibility by review of inclusion/exclusion criteria will be documented before randomization. Eligibility assessment performed prior to the dry-run must be repeated on Day 1 (Month 0). For subjects participating in dry-run, informed consent/assent must be obtained prior to entry into the dry-run.
(i) History of vaccination against Japanese Encephalitis or against Yellow Fever until Day 120 (Month 4) irrespective of time of administration and including the vaccine type as well as any additional supportive documentation for these vaccinations, all concomitant medications and vaccine history from 1 month (minimum 28 days) prior to administration of each dose of TDV or placebo up to 1 month (minimum 28 days) thereafter, steroids and immunostimulants within 60 days prior to Day 1 (Month 0), immunoglobulins and blood products within 3 months prior to Day 1 (Month 0), and immunosuppressive therapy within 6 months prior to Day 1 (Month 0).
(j) Physical examination including measurement of weight and height; body mass index will be calculated automatically. Measurement of height is not required at Day 90 (Month 3).
(k) Vital signs including (but not limited to) the measurement of systolic blood pressure/diastolic blood pressure, heart rate, temperature, height and weight. Measurement of height is not required at Day 30 (Month 1) for all subjects, and at Day 270 (Month 9) for the subset.
(l) Pregnancy testing (serum or urine) for females of childbearing potential. Results must be confirmed and documented as negative prior to trial entry (if dry-run is applicable) and prior to each trial vaccine administration.
(m) After eligibility is assessed and written informed consent/assent has been obtained, subjects will be randomized 1) to receive either 2 doses of Takeda's TDV or placebo by subcutaneous (SC) injection in the upper arm, and 2) to be included in the subset.
(n) The subject AND/OR the subject's parent/guardian will be contacted at least weekly during the dry-run, Parts 1, 2, and 3. Contacts will be made through appropriate methods that may differ in each site (eg, phone calls, text messaging, home visits, school-based surveillance). The text messaging system, if used, will be identified and evaluated by the Sponsor before use.
(o) Blood samples for dengue neutralizing antibodies will be collected for all subjects at pre-vaccination (Day 1 [Month 0]) and post-second vaccination on Day 120 (Month 4). The Day 30 (Month 1) and Day 120 (Month 4) blood samples should be taken at least 28 days after the first and second trial vaccination, respectively.
(p) For subjects presenting with febrile illness (fever ≥38°C on any 2 of 3 consecutive days or clinically suspected dengue) during the dry-run and Parts 1 and 2, or with febrile illness requiring hospitalization during Part 3, a blood sample will be collected during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever) and a convalescent blood sample will be collected between 7 and 14 days after the acute sample. For subjects presenting with febrile illness (fever ≥ 38°C on any 2 of 3 consecutive days or clinically suspected dengue) during Part 3 not requiring hospitalization will have 1 blood sample taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever) unless there is an alternate laboratory confirmed etiology.
(q) Serious adverse events (SAEs) will be reported to the Sponsor within 24 hours of the Investigator becoming aware of the event.

(r) At 30 minutes after vaccine administration on the day of vaccinations.
(s) Diary cards will be distributed for the collection of solicited local adverse events (AEs) until Day 7 (day of vaccination + 6 subsequent days), and of solicited systemic AEs until Day 14 (day of vaccination + 13 subsequent days) after each vaccination.
(t) Unsolicited AEs will be collected up to 28 days after each vaccination by interview.
(u) Additional blood samples for dengue neutralizing antibodies will be collected for subjects in the subset post first vaccination on Day 30 (Month 1), pre-vaccination on Day 90 (Month 3), post-second vaccination on Day 270 (Month 9), Day 450 (Month 15), and then every 12 months until the end of Part 3.
(v) Between 4 years and approximately 4.5 years post-dose 2 in Part 3, the parent/guardian of subjects who are included in the subset from Parts 1, 2, and 3 (see footnote 'm') and the PPS, and were 4 to 11 years of age at the time of randomization in the trial (Day 1 [Month 0]) will be asked to allow their child/ward to receive the booster dose of TDV or placebo, depending on the assignment on Day 1 (Month 0) (see footnote 'm'). Regardless of the willingness to participate in the booster phase of this trial, all subjects will continue trial participation for febrile surveillance and safety follow-up. This visit will correspond to the first trial visit of the booster phase of the trial if by that time the current protocol amendment has been approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC). It is anticipated that some subjects eligible for the booster phase may have or may not have completed Part 3 of the trial by the time the protocol amendment is implemented and it is feasible to enroll them into the booster phase for ethical and scientific reasons. Those subjects may be enrolled into the booster phase provided the IRBs/IECs approved the current protocol amendment, the subjects meet the entry criteria, and the global enrollment into the booster phase is ongoing. Details on data analysis for subjects who do not complete Part 3 of the trial will be provided in the Statistical Analysis Plan.

Table 2.e Schedule of Trial Procedures for the Booster Phase (Parts 4 and 5) – Subjects Between 4 and 11 Years of Age at the Time of Randomization in the Trial (Day 1 [Month 0])

	Modified active surveillance [a]					Follow up visit [c]
	Part 4				Part 5	
	Day 1b (Month 0b) (Visit 1b)	Day 30b (Month 1b) (Visit 2b)	Day 180b (Month 6b) (Visit 3b)	Day 395b (Month 13b) (Visit 4b)	Day 760b (Month 25b) (Visit 5b)	
	Procedure for all subjects					
Visit window		-1 day/+7 days	± 21 days	±30 days	± 45 days	
Visits	X	X				
Signed informed consent/assent [b]	X					
Assessment of eligibility criteria [d]	X					
Check contraindications to vaccination	X					
Check criteria for delay of vaccination	X					
Medical history	X					X
Concomitant medications [e]	X	X				X
Complete physical examination [f]	X					
Targeted physical examination [g]		X				X
Pregnancy test [h]	X					
Enrollment in the booster phase [i]	X					
Vaccine administration	X					
Surveillance for dengue fever [j]	X					
Blood sample [k] (9 mL)	X					
Blood sample [k] (6 mL)		X				
Febrile illness blood sample [l]	X					
SAEs [m]	X					
	Additional procedures for the booster immunogenicity subset					
Visits			X	X	X	
Targeted physical examination [g]			X	X	X	X
Injection site evaluation	X [n]	X				
Diary card distribution [o]	X					
Diary card collection and review		X				
Documentation of adverse events [o] [p]		X				
Blood sample [q] (6 mL)			X	X	X	

Notes:

- No new randomization will be performed for the booster phase of the trial. Only subjects from the Per-Protocol Set

who were 4 to 11 years of age at the time of randomization in the trial on Day 1 (Month 0) (see Table 2.d) will receive the booster vaccination between 4 years and approximately 4.5 years post-dose 2.
- The blood sampling will be re-set based on the day of booster vaccination ('b' will be used to denote trial visits of the booster phase – eg, Visit 1b, Day 1b, Month 0b).
- A subset of subjects who were 4 to 11 years of age at the time of randomization in the trial on Day 1 (Month 0) will be assigned to the booster immunogenicity subset for specific safety and immunogenicity evaluations. Assignment to the booster immunogenicity subset (approximately 2100 subjects) is also based on the randomization performed on Day 1 (Month 0) (see Table 2.d).
- When a site visit cannot be carried out due to the coronavirus disease 2019 (COVID-19) pandemic, alternative methods of contact (eg, telephone contact) will be made for subjects who are still under monitoring for safety reporting.

(a) The modified active surveillance will be performed as in Part 3 of the trial (see Table 2.d). The modified active surveillance during Parts 4 and 5 will maintain at least weekly contacts, but the intensity of investigation will be modified based on the need for hospitalization. Surveillance will identify febrile illness of any severity that could potentially be due to dengue.
(b) If not obtained at the last trial visit of Part 3 (see Table 2.d).
(c) Follow-up visit is only applicable if the subject terminates early.
(d) Eligibility by review of inclusion/exclusion criteria will be documented before enrollment in the booster phase.
(e) History of vaccination against Japanese Encephalitis or against Yellow Fever after Day 120 (Month 4) (see Table 2.d) until Day 30b (Month 1b) irrespective of time of administration and including the vaccine type as well as any additional supportive documentation for these vaccinations, all concomitant medications and other vaccine history from 1 month (minimum 28 days) prior to administration of the booster dose of TDV or placebo up to 1 month (minimum 28 days).
(f) Physical examination including measurement of weight and height; body mass index will be calculated automatically.
(g) Vital signs including (but not limited to) the measurement of systolic blood pressure/diastolic blood pressure, heart rate, temperature, height and weight. Measurement of height is not required at Day 30b (Month 1b).
(h) Pregnancy testing (serum or urine) for females of childbearing potential. Results must be confirmed and documented as negative prior to administration of the booster dose of trial vaccine (TDV or placebo).
(i) After eligibility is assessed and written informed consent/assent has been obtained, subjects will be enrolled in the booster phase to receive either the booster dose of Takeda's TDV or placebo by SC injection in the upper arm. Assignment of the booster dose of trial vaccine will be according to the randomization on Day 1 (Month 0) (see Table 2.d).
(j) The subject AND/OR the subject's parent/guardian will be contacted at least weekly during Parts 4 and 5. Contacts will be made through appropriate methods that may differ in each site (eg, phone calls, text messaging, home visits, school-based surveillance). The text messaging system, if used, will be identified and evaluated by the Sponsor before use.
(k) Blood samples for dengue neutralizing antibodies will be collected for all subjects at pre-booster vaccination (Day 1b [Month 0b]) and post-booster vaccination on Day 30b (Month 1b).
(l) For subjects presenting with febrile illness (fever ≥38°C on any 2 of 3 consecutive days or clinically suspected dengue) requiring hospitalization during Parts 4 and 5, a blood sample will be collected during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever) and a convalescent blood sample will be collected between 7 and 14 days after the acute sample. For subjects presenting with febrile illness (fever ≥ 38°C on any 2 of 3 consecutive days or clinically suspected dengue) during Parts 4 and 5 not requiring hospitalization will have 1 blood sample taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever) unless there is an alternate laboratory confirmed etiology
(m) SAEs will be reported to the Sponsor within 24 hours of the Investigator becoming aware of the event.
(n) At 30 minutes after vaccine administration on the day of vaccinations.
(o) Diary cards will be distributed for the collection of solicited local adverse events (AEs) until Day 7b (day of booster vaccination + 6 subsequent days) and solicited systemic AEs until Day 14b (day of booster vaccination + 13 subsequent days), and of unsolicited AEs (day of booster vaccination + 27 subsequent days).
(p) Unsolicited AEs will be collected up to 28 days (day of booster vaccination + 27 subsequent days) after booster vaccination by interview.
(q) Additional blood samples for dengue neutralizing antibodies will be collected for subjects in the booster immunogenicity subset at post booster vaccination on Day 180b (Month 6b), Day 395b (Month 13b) and Day 760b (Month 25b).

3.0 TRIAL REFERENCE INFORMATION

3.1 Trial-Related Responsibilities

The Sponsor will perform all trial-related activities with the exception of those identified in the Trial-Related Responsibilities template. The identified vendors in the template for specific trial-related activities will perform these activities in full or in partnership with the Sponsor.

3.2 Principal Investigators/Coordinating Investigators

Selection criteria for the principal investigators and coordinating investigators will include significant knowledge of the trial protocol, the investigational vaccine, their expertise in the therapeutic area and the conduct of clinical research as well as trial participation. Takeda will select one or more signatory/signatories from the investigators who participate in the study. The signatory coordinating investigator(s) will be required to review and sign the clinical protocol. The signatory coordinating investigator(s) will also be required to review and sign the Clinical Study Report(s) (CSR[s]) and by doing so agree(s) that it accurately describes the results of the trial.

3.3 List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CI	Confidence interval
CRO(s)	Clinical Research Organization(s)
CSR(s)	Clinical Study Report(s)
CYD-TDV	Chimeric yellow fever virus-dengue virus tetravalent dengue vaccine
DEN	Dengue serotype
DENV	Dengue virus (wild type virus strain)
DHF	Dengue hemorrhagic fever
DMC	Data Monitoring Committee
DSS	Dengue shock syndrome
E	Envelope
eCRF	electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FAS-B	Full Analysis Set-Booster
FASI	Full Analysis Set for Immunogenicity
FASI-B	Full Analysis Set for Immunogenicity-Booster
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMR	Geometric mean ratio
GMT	Geometric mean titer
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation of technical requirements for pharmaceuticals for human use
IEC	Independent Ethics Committee
Ig(s)	Immunoglobulin(s)
Inc	Incorporated
IRB	Institutional Review Board
IWRS	Interactive Web Response System
IVRS	Interactive Voice Response System
LFTs	Liver function tests

MedDRA	Medical Dictionary for Regulatory Activities
MNT_{50}	Microneutralization test 50%
N	Number
NS1	Nonstructural protein 1
PDK	Primary Dog Kidney
PFU	Plaque forming units
PPS	Per-Protocol Set
PPS-B	Per-Protocol Set-Booster
PPSI	Per-Protocol Set for Immunogenicity
PPSI-B	Per-Protocol Set for Immunogenicity-Booster
prM	pre-membrane
PT	Preferred Term
QTL	Quality Tolerance Limits
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SAE	Serious adverse event
SAGE	Strategic Advisory Group of Experts on Immunization
SAP	Statistical Analysis Plan
SC	Subcutaneous
SDV	Source data verification
SOC	System Organ Class
SS	Safety Set
SS-B	Safety Set-Booster
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDV	Tetravalent Dengue Vaccine Candidate
VE	Vaccine efficacy
WHO	World Health Organization
WT	Wild type

3.4 Corporate Identification

TV Takeda Vaccines, Inc.

4.0 INTRODUCTION

4.1 Background

Dengue fever is caused by infection with the dengue virus (DENV), a ribonucleic acid (RNA) virus that occurs as 4 recognized serotypes, DENV-1, DENV-2, DENV-3 or DENV-4. These dengue viruses are transmitted from human to human by mosquitoes (primarily *Aedes aegypti*). The 4 dengue viruses have spread worldwide and are endemic in Asia, Central and South America, the Caribbean, the Pacific Islands, parts of Australia, and parts of Africa. An estimated 50 - 100 million cases of dengue fever occur annually, which results in around 500,000 cases of dengue hemorrhagic fever (DHF) and an estimated 22,000 deaths, primarily in children. It is estimated that 2.5 billion people (40% of the world's population) live in areas at risk of dengue virus transmission [1-4].

Dengue fever is clinically defined as an acute febrile illness with 2 or more manifestations (headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, or leucopenia) and occurrence at the same location and time as other confirmed cases of dengue fever. The most severe forms of dengue infection – DHF and dengue shock syndrome (DSS) – are life threatening. Primary infection with any 1 of the 4 dengue serotypes is thought to result in life-long protection from re-infection by the same serotype, but does not protect against a secondary infection by 1 of the other 3 dengue serotypes and may lead to an increased risk of severe disease (DHF/DSS) [3-6].

Treatment of dengue fever is based solely on symptoms and signs, with fluid replacement required for hemorrhagic or shock cases. No antiviral therapy for dengue virus infection is available. Preventive measures that rely on mosquito control and individual protection, are of limited efficacy, complex to implement and questionable in terms of cost-effectiveness. There is a great unmet global public health need for a safe and effective vaccine that will protect against all serotypes of dengue infection, and thereby reduce the morbidity and mortality associated with dengue disease [1-7]. A first recombinant dengue vaccine (chimeric yellow fever virus-dengue virus tetravalent dengue vaccine [CYD-TDV]) has been approved since 2015 in several Asian and Latin American countries [8] as well as in the United States and in the European Union. Clinical data indicate an unfavorable risk-benefit profile for children aged <9 years with this first approved vaccine. Additionally, vaccine efficacy was different between serotypes and depended on dengue pre-exposure status [9]. More recent analyses found that people who had not been infected by dengue virus before vaccination had a higher risk of getting severe disease when they were infected with dengue virus after vaccination with CYD-TDV [10]. In a revised Strategic Advisory Group of Experts on Immunization (SAGE) recommendation in April 2018, the SAGE concluded that for countries considering CYD-TDV vaccination as part of their dengue control program, a "pre-vaccination screening strategy" would be the preferred option, in which only dengue-seropositive persons are vaccinated [11].

Hence, there is a continued unmet public health need for safer and more efficacious dengue vaccines [12].

Takeda's Tetravalent Dengue Vaccine Candidate (TDV) Background:

TDV consists of a mixture of 4 live, attenuated recombinant dengue virus strains expressing surface antigens corresponding to the 4 recognized dengue serotypes 1-4. The serotype 2 strain is based upon the attenuated laboratory-derived virus, DEN-2 Primary Dog Kidney (PDK)-53, originally isolated at Mahidol University, Bangkok, Thailand [13]. The chimeric, attenuated vaccine strains for dengue serotypes 1, 3 and 4 were engineered by replacing the DEN-2 structural genes, pre-membrane (prM) and envelope (E), with the prM and E genes of the wild-type (WT) virus strains, DENV-1 16007, DENV-3 16562 or DENV-4 1036 virus, respectively [14]. TDV is thus comprised of 4 recombinant, live attenuated dengue virus strains: a molecularly characterized, attenuated DEN-2 strain (TDV-2), a DEN-2/1 chimera (TDV-1), a DEN-2/3 chimera (TDV-3) and a DEN-2/4 chimera (TDV-4).

Nonclinical studies carried out in mice and nonhuman primates demonstrated an acceptable safety, immunogenicity, and efficacy profile of Takeda's TDV.

Data from 3 phase I trials and a phase II trial have shown satisfactory reactogenicity, safety and immunogenicity of Takeda's TDV in adults in non-endemic areas as well as in adults and children in endemic areas in Asia and Latin America. At the time of the current protocol amendment, the phase II trial that has enabled the selection of a final TDV dose formulation for use in the pivotal program has been finalized.

In Part 1 of the present ongoing Phase III trial, the primary endpoint was achieved with an overall vaccine efficacy (VE) of 80.2% (95% CI: 73.3 to 85.3). In Part 2, the analysis of secondary endpoints showed efficacies of 76.1% (95%CI: 68.5 to 81.9) in subjects who were seropositive at baseline, 66.2% (95% CI: 49.1 to 77.5) in subjects who were seronegative at baseline, 90.4% (95% CI: 82.6 to 94.7) against hospitalized dengue, and 85.9% (95% CI: 31.9 to 97.1) against dengue hemorrhagic fever. Vaccine efficacy varied by individual serotypes. Cumulative rates of serious adverse events (SAEs) were similar in TDV (4.0%) and placebo (4.8%) recipients, and were consistent with expected medical disorders in the trial population [15].

In Part 3 (yearly exploratory analysis), the overall VE for Year 2 (ie., during 12 months after the end of Part 1) compared to Year 1 (ie., 30 days post-second dose up to end of Part 1) was 56.2% (95% CI: 42.3 to 66.8) versus 80.2% (95% CI: 73.3 to 85.3). The Year 2 versus Year 1 analysis also showed efficacies of 60.3% (95% CI: 44.7 to 71.5) versus 82.2% (95% CI: 74.5 to 87.6) in subjects who were seropositive at baseline, and 45.3% (95% CI: 9.9 to 66.8) versus 74.9% (95% CI: 57.0 to 85.4) in subjects who were seronegative at baseline. The efficacy against hospitalized dengue for Year 2 was 76.1% (95% CI: 50.8 to 88.4%) versus 95.4% (95% CI: 88.4-98.2) for Year 1 [15, 16].

The current Investigator Brochure of Takeda's TDV contains additional product information and a more detailed review of pre-clinical and clinical trials [17].

4.2 Rationale for the Proposed Phase III Efficacy Trial

Given the accelerating spread of dengue in the world, there is an urgent need for an effective dengue vaccine, not only for those who live in dengue endemic areas, but also for those who travel to those areas. In the absence of a correlate of protection, the World Health Organization (WHO) recommends that phase III dengue trials are performed in dengue endemic areas, where vaccinated and control individuals are at equal risk of acquiring the disease allowing assessment of VE.

Although the ultimate goal of a dengue vaccine is to protect against all 4 serotypes, it is unlikely that a single trial will be sufficiently powered to demonstrate VE against each dengue serotype. Therefore, the WHO recommends a primary objective of VE measured against laboratory-confirmed dengue illness caused by any of the 4 serotypes.

The trial will be conducted in accordance with the protocol, the International Council for Harmonisation of technical requirements for pharmaceuticals for human use - Good Clinical Practice (ICH-GCP) Guidelines and any applicable regulatory requirements.

4.2.1 Parts 1, 2, and 3

This phase III trial is comprised of at least 3 parts for all subjects. Part 1 will assess VE against symptomatic dengue illness due to any serotype, and will provide data to support licensure based on WHO recommendations outlined above. An extended follow-up is planned in Part 2, aimed at providing additional data to allow a more precise assessment of VE against each serotype. Part 3 fulfils the WHO recommendation of long-term follow-up to evaluate safety.

In order to maintain the double-blind design, a placebo (Normal Saline) was used in this trial. A placebo had been chosen to avoid the use of a number of active vaccine comparators that would be required due to the wide age range of subjects (4 to 16 years of age) and the diverse countries participating. As no active comparator was possible as part of the trial design, a licensed vaccine will be offered to all subjects, irrespective of their full participation in this trial and at least 6 months after any protocol defined vaccination. The choice of this vaccine was discussed between the Sponsor and the Investigator, and was approved by the appropriate ethics committee. This vaccine will be used according to the labeling approved in the country (see also Section 9.3.3).

4.2.2 Booster Phase (Parts 4 and 5)

The booster phase of this phase III trial is comprised of 2 parts (Parts 4 and 5). Parts 4 and 5 will assess VE of a booster dose of TDV against symptomatic dengue illness due to any serotype, and will provide data on the effect of a booster dose on VE after a 2-dose vaccination regimen with TDV (2 single doses 3 months apart). Subjects will receive a single dose of TDV or placebo, depending on the assignment at the time of randomization in the trial (Day 1 [Month 0]). The trial blind will be maintained.

No new randomization will be performed for the booster phase of the trial. Only subjects from the Per-Protocol Set (PPS) who were 4 to 11 years of age at the time of randomization in the trial

(Day 1 [Month 0]) (see also Section 6.2.2) will receive the booster vaccination between 4 years and approximately 4.5 years post-dose 2.

As no active comparator was possible as part of the trial design, a licensed vaccine will be offered to all subjects at least 6 months after any protocol defined vaccination. A similar offer will be given to subjects participating in the booster phase. A licensed vaccine will be offered according to local regulations to all subjects irrespective of their full participation in the booster phase and at least 6 months after booster vaccination. The choice of this vaccine will be discussed between the Sponsor and the Investigator, and will be approved by the appropriate ethics committee. This vaccine will be used according to the labeling approved in the country.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To evaluate the efficacy of 2 doses of TDV in preventing symptomatic dengue fever of any severity and due to any of the 4 dengue virus serotypes in 4-16 year old subjects.

5.1.2 Secondary Objectives

To be assessed post-second vaccination:

Efficacy:

- To assess the efficacy of TDV in preventing symptomatic dengue fever of any severity induced by individual dengue serotypes.
- To assess the efficacy of TDV in preventing symptomatic dengue fever of any severity by dengue exposure status at baseline.
- To assess the efficacy of TDV in preventing hospitalization due to virologically confirmed dengue fever.
- To assess the efficacy of TDV in preventing severe dengue induced by any dengue serotype.

Safety:

- To describe the safety of TDV.
- To describe the reactogenicity of TDV in a subset of subjects.

Immunogenicity:

- To assess the immunogenicity of TDV in a subset of subjects.

5.1.3 Exploratory Objectives

5.1.3.1 Parts 1, 2, and 3

Efficacy:

- To describe the efficacy of TDV in preventing virologically confirmed dengue fever between first and second vaccinations.
- To describe the efficacy of TDV in preventing virologically confirmed dengue fever from first vaccination until end of Part 2.
- To describe virologically confirmed and hospitalized dengue fever identified during Part 3.
- To describe virologically confirmed dengue fever identified during Part 3.

- For the correlate of protection, a threshold antibody titer value may be evaluated to predict VE using descriptive methodology.
- To describe the profiles of immunoglobulin G (IgG), IgM, and nonstructural protein 1 (NS1) antigen during episodes of febrile illness.

5.1.3.2 Booster Phase (Parts 4 and 5)

Efficacy:

- To assess the efficacy of a TDV booster dose in preventing symptomatic dengue fever of any severity induced by any dengue serotype.
- To assess the efficacy of a TDV booster dose in preventing symptomatic dengue fever of any severity by dengue exposure status at baseline.
- To assess the efficacy of a TDV booster dose in preventing hospitalization due to virologically confirmed dengue fever induced by any dengue serotype.
- To assess the efficacy of a TDV booster dose in preventing severe dengue induced by any dengue serotype.

Safety:

- To describe the safety of a TDV booster dose.
- To describe the reactogenicity of a TDV booster dose in a subset of subjects.

Booster immunogenicity:

- To assess the immunogenicity of a TDV booster dose in a subset of subjects.

5.2 Endpoints

5.2.1 Primary Endpoint

Efficacy

VE of 2 doses of TDV in preventing virologically confirmed dengue fever induced by any dengue serotype occurring from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 1, with VE defined as $1 – (\lambda_V/\lambda_C)$ (where λ_V and λ_C denote the hazard rates for the TDV and placebo arms, respectively).

5.2.2 Secondary Endpoints

Efficacy

- VE of 2 doses of TDV in preventing virologically-confirmed dengue fever induced by each dengue serotype from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 2.

- VE of 2 doses of TDV in preventing virologically-confirmed dengue fever induced by any dengue serotype from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 2 in subjects dengue seronegative at baseline.
- VE of 2 doses of TDV in preventing virologically-confirmed dengue fever induced by any dengue serotype from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 2 in subjects dengue seropositive at baseline.
- VE of 2 doses of TDV in preventing hospitalization due to virologically-confirmed dengue fever induced by any dengue serotype from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 2.
- VE of 2 doses of TDV in preventing virologically-confirmed severe dengue fever induced by any dengue serotype from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 2.

Safety

Subset (post-first and post-second vaccinations):

- Frequency and severity of solicited local (injection site) AEs for 7 days (day of vaccination + 6 subsequent days) and solicited systemic AEs for 14 days (day of vaccination + 13 subsequent days) post-vaccination.
- Percentage of subjects with any unsolicited AEs for 28 days (day of vaccination + 27 subsequent days) post-vaccination.

All subjects:

- Percentage of subjects with SAEs during Parts 1 and 2, Part 1 and Part 2 combined.
- Percentage of subjects with fatal SAEs and related SAEs during the first and second half of Part 3.

Immunogenicity

Subset (post-first and post-second vaccinations):

- Seropositivity rate (% of seropositive subjects) for each of the 4 dengue serotypes at pre-vaccination on Day 1 (Month 0), post-first vaccination on Day 30 (Month 1), pre-vaccination on Day 90 (Month 3); post-second vaccination at Day 120 (Month 4), Day 270 (Month 9), Day 450 (Month 15), and then annually.
- Seropositivity rate (% of seropositive subjects) for multiple (any 2, 3 or 4) dengue serotypes at pre-vaccination on Day 1 (Month 0), post-first vaccination on Day 30 (Month 1), pre-vaccination on Day 90 (Month 3); post-second vaccination at Day 120 (Month 4), Day 270 (Month 9), Day 450 (Month 15), and then annually.

Note: Seropositivity is defined as a reciprocal neutralizing titer ≥10.

- Geometric mean titers (GMTs) of neutralizing antibodies (microneutralization test 50% [MNT_{50}]) for each dengue serotype at pre-vaccination on Day 1 (Month 0), post-first vaccination on Day 30 (Month 1), pre-vaccination on Day 90 (Month 3); post-second vaccination at Day 120 (Month 4), Day 270 (Month 9), Day 450 (Month 15), and then annually.

5.2.3 Exploratory Endpoints

5.2.3.1 Parts 1, 2 and 3

- VE of TDV in preventing virologically-confirmed dengue fever identified between the first and second vaccinations.
- VE of TDV in preventing virologically-confirmed dengue fever identified from first vaccination until the end of Part 2.
- To describe virologically confirmed and hospitalized dengue fever identified during the first half (18 months) of Part 3.
- To describe virologically-confirmed and hospitalized dengue fever identified during the second half (18 months) of Part 3.
- To describe virologically-confirmed dengue fever induced by any dengue serotype identified during first half (18 months) of Part 3.
- To describe virologically-confirmed dengue fever induced by any dengue serotype identified during second half (18 months) of Part 3.

Note: It is anticipated that some subjects eligible for the booster phase may not complete Part 3 of the trial. The endpoint assessment duration for these subjects will be detailed in the Statistical Analysis Plan (SAP).

Post-first and post-second vaccinations:

- To examine the relationship between dengue neutralizing antibodies (MNT_{50}) and protection from dengue infection (correlate of protection).
- To describe the profiles of IgG, IgM and NS1 antigen during episodes of febrile illness.

5.2.3.2 Booster Phase (Parts 4 and 5)

Efficacy

All subjects in the booster phase:

- VE of a TDV booster dose in preventing virologically confirmed dengue fever induced by any dengue serotype from 30 days post-booster vaccination (Day 30 booster [b] (Month 1b)) until the end of Part 4 and Part 5 separately, and for Parts 4 and 5 combined.
- VE of a TDV booster dose in preventing virologically confirmed dengue fever induced by each dengue serotype from 30 days post-booster vaccination (Day 30b [Month 1b]) until the end of Part 4 and Part 5 separately, and for Parts 4 and 5 combined.
- VE of a TDV booster dose in preventing virologically confirmed dengue fever induced by any and each dengue serotype in dengue seronegative subjects at baseline from 30 days post-booster vaccination (Day 30b [Month 1b]) until the end of Part 4 and Part 5 separately, and for Parts 4 and 5 combined.
- VE of a TDV booster dose in preventing virologically confirmed dengue fever induced by any and each dengue serotype in dengue seropositive subjects at baseline from 30 days post-booster vaccination (Day 30b [Month 1b]) until the end of Part 4 and Part 5 separately, and for Parts 4 and 5 combined.
- VE of a TDV booster dose in preventing hospitalization due to virologically confirmed dengue fever induced by any dengue serotype from 30 days post-booster vaccination (Day 30b [Month 1b]) until the end of Part 4 and Part 5 separately, and for Parts 4 and 5 combined.
- VE of a TDV booster dose in preventing virologically confirmed severe dengue fever induced by any dengue serotype from 30 days post-booster vaccination (Day 30b [Month 1b]) until the end of Part 4 and Part 5 separately, and for Parts 4 and 5 combined.

Safety

Booster immunogenicity subset:

- Frequency and severity of solicited local (injection site) AEs for 7 days (day of booster vaccination + 6 subsequent days) and solicited systemic AEs for 14 days (day of booster vaccination + 13 subsequent days) post-vaccination.
- Percentage of subjects with any unsolicited AEs for 28 days (day of booster vaccination + 27 subsequent days) post-vaccination.

All subjects in the booster phase:

- Percentage of subjects with SAEs during Part 4 and Part 5 separately, and for Parts 4 and 5 combined.
- Percentage of subjects with fatal SAEs and related SAEs during Part 4 and Part 5 separately, and for Parts 4 and 5 combined.

Booster immunogenicity

Booster immunogenicity subset:

- Seropositivity rate (% of seropositive subjects) for each of the 4 dengue serotypes at pre-booster vaccination on Day 1b (Month 0b) and post-booster vaccination on Day 30b (Month 1b), Day 180b (Month 6b), Day 395b (Month 13b), and Day 760b (Month 25b).
- Seropositivity rate (% of seropositive subjects) for multiple (any 2, 3 or 4) dengue serotypes at pre-booster vaccination on Day 1b (Month 0b) and post-booster vaccination on Day 30b (Month 1b), Day 180b (Month 6b), Day 395b (Month 13b), and Day 760b (Month 25b).

Note: Seropositivity is defined as a reciprocal neutralizing titer ≥10.

- GMTs of neutralizing antibodies (MNT_{50}) for each dengue serotype at pre-booster vaccination on Day 1b (Month 0b) and post-booster vaccination on Day 30b (Month 1b), Day 180b (Month 6b), Day 395b (Month 13b), and Day 760b (Month 25b).
- GMR of neutralizing antibodies (MNT_{50}) for each dengue serotype at pre-booster vaccination on Day 1b (Month 0b) versus post-booster vaccination on Day 30b (Month 1b).
- GMR of neutralizing antibodies (MNT_{50}) for each dengue serotype at pre-booster vaccination on Day 1b (Month 0b) versus post-booster vaccination on Day 180b (Month 6b).
- GMR of neutralizing antibodies (MNT_{50}) for each dengue serotype at pre-booster vaccination on Day 1b (Month 0b) versus post-booster vaccination on Day 395b (Month 13b).
- GMR of neutralizing antibodies (MNT_{50}) for each dengue serotype at pre-booster vaccination on Day 1b (Month 0b) versus post-booster vaccination on Day 760b (Month 25b).

Post-booster vaccination:

- To examine the relationship between dengue neutralizing antibodies (MNT_{50}) and protection from dengue infection (correlate of protection).
- To describe the profiles of IgG, IgM and NS1 antigen during episodes of hospitalized febrile illness.

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a phase III, double-blind, randomized, placebo-controlled trial with 2 parallel groups. The trial includes for all subjects at least 3 time periods (Parts 1, 2 and 3) for surveillance of febrile illness with potential dengue etiology. The trial includes 2 additional time periods (Parts 4 and 5) for surveillance of febrile illness with potential dengue etiology for subjects participating in the booster phase of the trial.

The trial design and subject population for Parts 1, 2, and 3 of the trial and the booster phase (Parts 4 and 5) are in Section 6.1.1 and Section 6.1.2, respectively.

6.1.1 Parts 1, 2, and 3

Part 1 constitutes the primary analysis period, including primary efficacy analysis. Part 2 constitutes a period of additional active surveillance for secondary efficacy analyses. Part 3 constitutes modified active surveillance for the assessment of long-term safety.

- Part 1: Active surveillance for the primary assessment of efficacy in all subjects. During this time subjects will be contacted at least weekly to ensure identification of febrile illness that could potentially be due to dengue. This part will commence on the day of vaccination and finish once both of the following 2 criteria are fulfilled:
  1. 120 cases of dengue fever are confirmed.
  2. Minimum duration of subject follow-up of 12 months post-second vaccination.

  The end of Part 1 will be defined for each subject so that the duration of follow up after the second vaccination will be approximately the same for all subjects. Virologically confirmed cases in Part 1 count towards the primary efficacy objective if occurring at least 30 days post-second vaccination.
- Part 2: Active surveillance for an additional 6 months for each subject following the completion of Part 1. During this time subjects will be contacted at least weekly to ensure identification of febrile illness that could potentially be due to dengue.

  Virologically confirmed cases in Parts 1 and 2 contribute towards the secondary efficacy objectives.
- Part 3: Modified active surveillance for the assessment of safety in all subjects following the completion of Part 2 and lasting approximately 3 years for each subject. The modified active surveillance during Part 3 will maintain at least weekly contacts through Part 3 of the trial, but the intensity of investigation will be modified based on the need for hospitalization. Surveillance will identify febrile illness of any severity that could potentially be due to dengue.

Subjects may be enrolled into a dry-run to commence and test febrile surveillance methodology. This dry-run will involve pre-vaccination surveillance for dengue and may be conducted for up

to 10 months prior to vaccination on Day 1. It may not be required in all sites and may not be applicable to all subjects at the trial sites where it is conducted. The need for and duration of the dry-run at an individual site will depend on the experience of the site in conducting similar trials. For ease of terminology, trial time points will use the date of first vaccination (Day 1) as the reference point, so activities occurring prior to the day of first vaccination (Day 1) will be referred to as Day –x to Day -1 (the day before first vaccination).

The target sample of 20,100 healthy children and adolescents aged between 4 and 16 years will be randomized to receive either TDV or placebo in a 2:1 ratio (13,400 TDV; 6700 placebo). Randomization by using an interactive system (Interactive Web Response System [IWRS] or Interactive Voice Response System [IVRS]) will be stratified by region and age range (children aged 4-5 years, 6-11 years, and 12-16 years) to ensure each age range has the appropriate ratio of TDV to placebo in each region. In addition, recruitment will follow an enrollment plan to ensure representative enrollment across the age ranges and regions. This is considered necessary to mitigate the relative difficulty of recruitment of subjects at the extremes of the age-ranges in this trial. Each subject will receive TDV or placebo by a subcutaneous (SC) injection into the upper arm. A subset of the same subjects (number [N]=4,000) will be included in specific safety and immunogenicity evaluations (safety/ immunogenicity subset, hereafter referred to as 'subset'). This subset will also be selected randomly using IWRS or IVRS and stratified by region and age range (children aged 4-5 years, 6-11 years, and 12-16 years).

Aspects of active surveillance (dry-run, Parts 1 and 2):

Definition of active surveillance

During active surveillance (dry-run, Parts 1 and 2), any subject with febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) will be asked to return to the site for dengue fever evaluation by the Investigator. Subjects/guardians will be contacted at least weekly to ensure robust identification of febrile illness by reminding subjects/guardians of their obligation to return to the site in case of febrile illness. This contact will be implemented through appropriate methods that may differ in each trial site (eg, phone calls, text messaging, home visits, school-based surveillance). The text messaging system, if used, will be identified and evaluated by the Sponsor before use. Each trial site will have locally-developed Standard Procedures (ie, Internal Operating Procedures) that details the local healthcare map relevant to the trial (as assessed by the trial site), methodology of febrile illness surveillance and case handling.

Duration of active surveillance

Active surveillance for febrile illness will commence at the dry-run or on Day 1 (Part 1) and will continue until the end of Part 2.

Part 1 is designed to support the primary objective of assessment of efficacy of the vaccine candidate in preventing virologically confirmed dengue fever induced by any dengue serotype, and will include active surveillance until the 2 conditions described above are fulfilled.

Part 2 is designed to provide additional data regarding the secondary efficacy objectives detailed in Section 5.1.2. These analyses involve subsets of dengue cases, such as dengue due to a single serotype, and will therefore be less precise than the primary efficacy endpoint which considers

dengue cases regardless of severity or serotype. A longer surveillance period enables the identification of additional dengue cases, thereby improving the precision of the secondary efficacy objectives. For this reason, all subjects will continue active surveillance for 6 months following the completion of Part 1.

Aspects of modified active surveillance (Part 3):

Modified active surveillance will start after the completion of Part 2, and will last for approximately 3 years. Modified active surveillance will be implemented to detect dengue cases of any severity in a tiered approach based on the need for hospitalization. Any subject with febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) will be asked to return to the site for evaluation by the Investigator. Subjects presenting with febrile illness not requiring hospitalization will be screened for dengue disease (by reverse transcriptase polymerase chain reaction [RT-PCR]) unless there is alternate laboratory confirmed etiology. They will undergo local laboratory evaluations as per standard medical practice. Subjects with febrile illness requiring hospitalization will be evaluated as during active surveillance (ie, dry-run, Parts 1 and 2). During Part 3, there will be a minimum frequency of 1 contact every week through appropriate methods that may differ in each trial site (see above). Modified active surveillance will be performed according to locally-developed Standard Procedures as described above.

The trial design (Parts 1, 2, and 3) is presented below in Figure 6.a. Differences between active surveillance (dry-run, Parts 1 and 2) and modified active surveillance (Part 3) are summarized in Table 6.a.

Figure 6.a Schematic Showing Parts 1, 2, 3

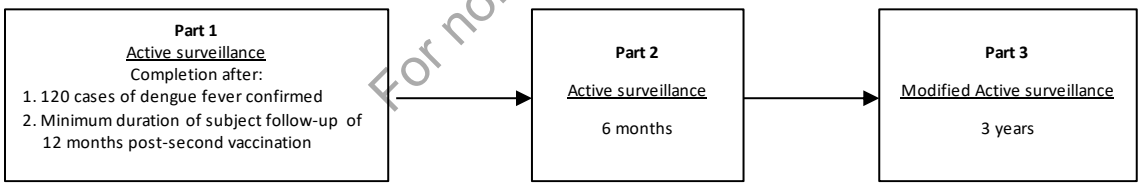


Table 6.a Differences between Active Surveillance (Dry-Run, Parts 1 and 2) and Modified Active Surveillance (Part 3)

	Active Surveillance (dry-run, Parts 1 and 2)	Modified Active Surveillance (Part 3)	
Contact frequency	At least weekly	At least weekly	
Threshold for evaluation	All febrile illness (irrespective of need for hospitalization)	Febrile illness requiring hospitalization	Febrile illness not requiring hospitalization (unless the febrile illness has an alternate laboratory confirmed etiology).
Laboratory evaluations	- Within 5 days: RT-PCR, NS1 antigen, IgM, IgG ELISA (central laboratory); and platelet count, hematocrit, ALT, and AST (locally) - 7-14 days after the acute sample: IgM and IgG ELISA (central laboratory); and platelet count, hematocrit, ALT, and AST (locally) - Other laboratory evaluations as per standard of care (locally)		- Within 5 days: RT-PCR (central laboratory) - Other laboratory evaluations as per standard of care (locally)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ELISA = enzyme-linked immunosorbent assay; IgG/IgM = Immunoglobulin G/M; NS1 = nonstructural protein 1; RT-PCR = reverse transcriptase polymerase chain reaction

Case definition for efficacy objectives:

A virologically confirmed dengue case is defined as febrile illness (defined as temperature ≥ 38°C on any 2 of 3 consecutive days) or illness clinically suspected to be dengue by the Investigator with a positive serotype-specific RT-PCR. The presence of febrile illness or clinically suspected dengue will be recorded in the electronic Case Report Form (eCRF) by the Investigator.

Handling of febrile illness cases (suspected dengue cases):

Subjects presenting with febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) or clinically suspected dengue during the dry-run, Parts 1 and 2 or requiring hospitalization during Part 3 will have 2 blood samples taken to confirm dengue infection, in addition to those taken as part of the clinical care of the subject. The first or acute blood sample will be taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever). Testing will include dengue IgM and IgG enzyme-linked immunosorbent assay (ELISA), dengue NS1 antigen ELISA, dengue RT-PCR, hematocrit, platelet count and liver function tests (LFTs [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)]). The second or convalescent blood sample will be taken during the convalescent phase of the disease (ie, between 7 and 14 days after the acute sample) and will be tested for dengue IgM/IgG by ELISA, hematocrit, platelet count, and LFTs (as above).

Local standards of care may require additional tests, based on clinical presentation and at medical discretion. Additional dengue neutralizing antibody and other laboratory tests may be performed. In addition to blood tests, clinical evaluation will be performed for signs of hemorrhage or plasma leakage as well as any other abnormal signs or symptoms.

In addition, during Part 3, subjects presenting with febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) or clinically suspected dengue and not requiring hospitalization will have 1 blood sample taken for dengue infection confirmation by RT-PCR unless there is an

alternate laboratory confirmed etiology. The blood sample will be taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever). Febrile illness cases within 30 days after vaccination will be investigated for the presence of WT or vaccine-derived dengue virus. The testing algorithm is described in the serology plan. Clinical evaluation will be performed for signs of hemorrhage or plasma leakage as well as any other abnormal signs or symptoms. Local standards of care may require additional tests, based on clinical presentation and at medical discretion.

A febrile illness as described above will require an interval of at least 14 days from a previous febrile illness to avoid overlap of acute and convalescent visits from 1 episode with those from a second episode.

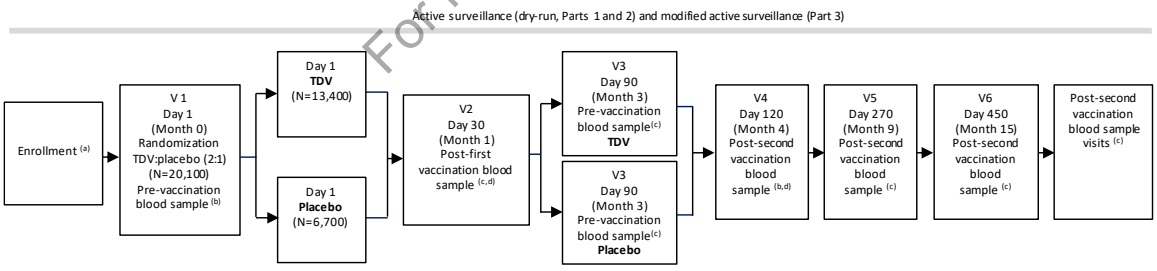
Procedures

After informed consent/assent has been obtained (which may be up to 10 months prior to vaccination on Day 1 [Month 0] as described above and as a result of the dry-run) each subject will be assessed for eligibility to participate in the trial. On Day 1 (Month 0) a pre-vaccination blood sample will be taken, randomization to TDV or placebo, and vaccination will occur. A second vaccination will be administered at Day 90 (Month 3). Subjects included in the subset (see above) will also be randomly selected using the IWRS or IVRS.

Any withdrawals from enrollment until Day 1 will be replaced so that 20,100 subjects are randomized and vaccinated; any withdrawals after randomization will not be replaced.

The trial schedule (subject flow and visits) is presented below in Figure 6.b.

Figure 6.b Schematic to Show Subject Flow Through the Trial (Parts 1, 2, and 3)



Note: (i) Any subjects who withdraw between enrollment and randomization will be replaced so that 20,100 subjects are randomized; subjects who withdraw after randomization will not be replaced.
(ii) Subjects presenting with febrile illness (defined as temperature ≥38°C on any two of three consecutive days) or clinically suspected dengue during the dry-run, Parts 1 and 2, or with febrile illness requiring hospitalization during Part 3 will have two blood samples taken to confirm dengue infection. The first or acute blood sample will be taken during the acute phase of the disease (i.e., as soon as possible and preferably within 5 days after the onset of fever); the second or convalescent blood sample will be taken during the convalescent phase of the disease (i.e., between 7 to 14 days after the acute sample).
(iii) During Part 3, subjects presenting with febrile illness (defined as temperature ≥38°C on any two of three consecutive days) or clinically suspected dengue and not requiring hospitalization will have one blood sample taken during the acute phase of the disease (i.e., as soon as possible and preferably within 5 days after the onset of fever) unless there is an alternate laboratory confirmed etiology.
[a]Prior to entry into the dry-run or Day 1 (Month 0)
[b]Blood sample for dengue neutralizing antibodies for all subjects
[c] Additional blood samples for dengue neutralizing antibodies will be taken in the subset on Day 30 (Month 1), Day 90 (Month 3), Day 270 (Month 9), Day 450 (Month 15), and then every 12 months until the end of Part 3.
[d] Day 30 (Month 1) and Day 120 (Month 4) blood samples should be taken at least 28 days after the first and second vaccination, respectively.
V= Visit

Between 4 years and approximately 4.5 years post-dose 2 in Part 3, the parent/guardian of subjects who are included in the PPS and who were 4 to 11 years of age at the time of randomization in the trial on Day 1 (Month 0) will be asked to allow their child/ward to receive the booster dose of trial vaccine (TDV or placebo) (see Section 6.1.2). It is anticipated that some subjects eligible for the booster phase of the trial may have or may not have completed Part 3 of

the trial by the time the protocol amendment is implemented and it is feasible to enroll them into the booster phase for ethical and scientific reasons. Those subjects may be enrolled into the booster phase provided the Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) approved the current protocol amendment, the subjects meet the entry criteria (see Section 7.1.2), and the global enrollment into the booster phase is ongoing. Details on data analysis for subjects who do not complete Part 3 of the trial will be provided in the SAP.

Immunogenicity evaluation (MNT_{50}):

All subjects:

- Blood samples will be collected pre-vaccination on Day 1 (Month 0) and post-second vaccination on Day 120 (Month 4).

Subset:

- Additional blood samples will be collected post-first vaccination on Day 30 (Month 1), pre-vaccination on Day 90 (Month 3), post-second vaccination on Day 270 (Month 9) and Day 450 (Month 15), and then every 12 months until the end of Part 3.

Safety evaluation:

All subjects:

- Identification of febrile episodes with potential dengue etiology for the trial duration.
- Blood samples will be collected in the event of febrile illness as described above.
- Documentation of all SAEs during Parts 1 and 2. During Part 3, investigators will be required to report all deaths as well as SAEs assessed as related, or deemed relevant by the Investigator in the context of vaccine safety.

Subset:

- Subjects will be provided with a diary card for the recording of:
  - Solicited local AEs for 7 days following each vaccination (day of vaccination + 6 subsequent days). These will include:
    - Injection site pain, injection site erythema and injection site swelling.
  - Solicited systemic AEs for 14 days following each vaccination (day of vaccination + 13 subsequent days). These will include:
    - Child <6 years: fever, irritability/fussiness, drowsiness and loss of appetite.
    - Child ≥6 years: asthenia, fever, headache, malaise and myalgia.
- Unsolicited AEs for 28 days following each vaccination (day of vaccination + 27 subsequent days) will be collected by interview (ie, at Day 30 [Month 1] and Day 120 [Month 4], as applicable).

6.1.2 Booster Phase (Parts 4 and 5)

Parts 4 and 5 constitute a period of modified active surveillance for exploratory efficacy, immunogenicity and safety analyses post-booster vaccination.

- Part 4: Modified active surveillance post-booster vaccination and lasting minimum 13 months for each subject.
- Part 5: Modified active surveillance following the completion of Part 4 and lasting 1 year for each subject.

  The modified active surveillance during Parts 4 and 5 will maintain at least weekly contacts through Parts 4 and 5 of the trial, but the intensity of investigation will be modified based on the need for hospitalization. Surveillance will identify febrile illness of any severity that could potentially be due to dengue.

No new randomization will be performed for the booster phase of the trial. Only subjects from the PPS who were 4 to 11 years of age at the time of randomization in the trial on Day 1 [Month 0]) (see Section 6.1.1) can participate in the booster phase of this trial. Subjects assigned to participate in the booster phase of the trial will receive a single dose of TDV or placebo, depending on the assignment at the time of randomization in the trial (Day 1 [Month 0]) (see Section 6.1.1). The target sample size for the booster phase is approximately 10,500 subjects (TDV: approximately 7,000 subjects, placebo: approximately 3500 subjects). The booster dose will be administered between 4 years and approximately 4.5 years post-dose 2 (see Section 6.1.1). A subset of subjects who were 4 to 11 years of age at the time of randomization on Day 1 (Month 0) will be assigned to the booster immunogenicity subset for specific safety and immunogenicity evaluations. Assignment to the booster immunogenicity subset (approximately 2100 subjects) is also based on randomization performed in Part 1 on Day 1 (Month 0) (see Section 6.1.1).

For ease of terminology, trial time points will use the date of booster vaccination (Day 1b) as the reference point, so activities occurring prior to the day of booster vaccination (Day 1b) will be referred to as Day –x to Day -1b (the day before booster vaccination).

Aspects of modified active surveillance in the booster phase of the trial (Parts 4 and 5):

Modified active surveillance will continue after the completion of Part 3 and will last for approximately 25 months to detect dengue cases of any severity in a tiered approach based on the need for hospitalization post-booster vaccination. Any subject with febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) will be asked to return to the site for evaluation by the Investigator. Subjects presenting with febrile illness not requiring hospitalization will be screened for dengue disease (by RT-PCR) unless there is alternate laboratory confirmed etiology. They will undergo local laboratory evaluations as per standard medical practice. Subjects with febrile illness requiring hospitalization will be evaluated as during active surveillance (ie, dry-run, Parts 1 and 2). During Parts 4 and 5, there will be a minimum frequency of 1 contact every week through appropriate methods that may differ in each trial site (see above). Modified active

surveillance will be performed according to locally-developed Standard Procedures as described above.

The trial design (Parts 4 and 5) is presented below in Figure 6.c. Modified active surveillance (Parts 4 and 5) is summarized in Table 6.b.

Figure 6.c Schematic Showing Parts 4 and 5

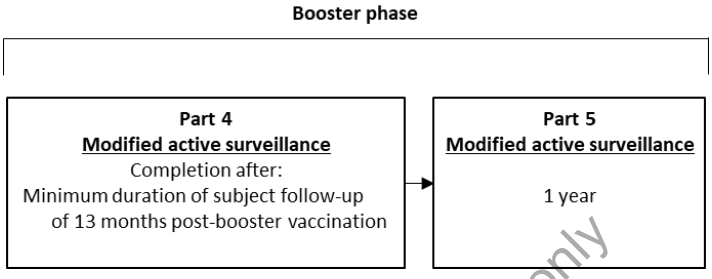


Table 6.b Modified Active Surveillance (Parts 4 and 5)

	Modified Active Surveillance (Parts 4 and 5)	
Contact frequency	At least weekly	
Threshold for evaluation	Febrile illness requiring hospitalization	Febrile illness not requiring hospitalization (unless the febrile illness has an alternate laboratory confirmed etiology).
Laboratory evaluations	- Within 5 days: RT-PCR, NS1 antigen, IgM, IgG ELISA (central laboratory); and platelet count, hematocrit, ALT, and AST (locally) - 7-14 days after the acute sample: IgM and IgG ELISA (central laboratory); and platelet count, hematocrit, ALT, and AST (locally) - Other laboratory evaluations as per standard of care (locally)	- Within 5 days: RT-PCR (central laboratory) - Other laboratory evaluations as per standard of care (locally)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ELISA = enzyme-linked immunosorbent assay; IgG/IgM = Immunoglobulin G/M; NS1 = nonstructural protein 1; RT-PCR = reverse transcriptase polymerase chain reaction

Handling of febrile illness cases (suspected dengue cases):

Subjects presenting with febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) requiring hospitalization during Parts 4 and 5 will have 2 blood samples taken to confirm dengue infection, in addition to those taken as part of the clinical care of the subject. The first or acute blood sample will be taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever). Testing will include dengue IgM and IgG ELISA, dengue NS1 antigen ELISA, dengue RT-PCR, hematocrit, platelet count and LFTs (AST and ALT). The second or convalescent blood sample will be taken during the convalescent phase of the disease (ie, between 7 and 14 days after the acute sample) and will be tested for dengue IgM/IgG by ELISA, hematocrit, platelet count, and LFTs (as above). In some circumstances, additional investigations (including additional PCR and viral genome sequencing) will be performed to further characterize the detected infectious dengue virus.

Local standards of care may require additional tests, based on clinical presentation and at medical discretion. Additional dengue neutralizing antibody and other laboratory tests may be performed. In addition to blood tests, clinical evaluation will be performed for signs of hemorrhage or plasma leakage as well as any other abnormal signs or symptoms.

Subjects presenting with febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) or clinically suspected dengue and not requiring hospitalization during Parts 4 and 5 will have 1 blood sample taken for dengue infection confirmation by RT-PCR unless there is an alternate laboratory confirmed etiology. The blood sample will be taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever). Febrile illness cases within 30 days after vaccination will be investigated for the presence of WT or vaccine-derived dengue virus. The testing algorithm is described in the serology plan. Clinical evaluation will be performed for signs of hemorrhage or plasma leakage as well as any other abnormal signs or symptoms. Local standards of care may require additional tests, based on clinical presentation and at medical discretion.

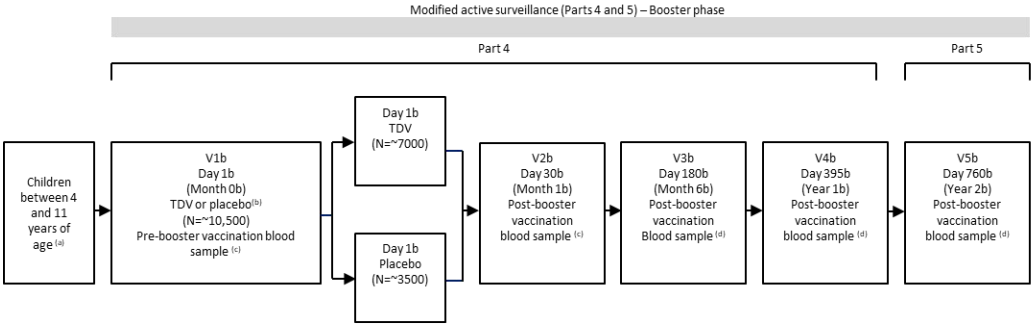
A febrile illness as described above will require an interval of at least 14 days from a previous febrile illness to avoid overlap of acute and convalescent visits from 1 episode with those from a second episode.

Procedures

After informed consent/assent has been obtained for the booster phase of the trial, each subject will be assessed for eligibility to participate in the booster phase. On Day 1b (Month 0b) a pre-booster vaccination blood sample will be taken and booster vaccination will occur.

The trial schedule (subject flow and visits) for the booster phase of the trial (Parts 4 and 5) is presented below in Figure 6.d.

Figure 6.d Schematic to Show Subject Flow Through the Booster Phase of the Trial (Parts 4 and 5)



Note: (i) The blood sampling will be re-set based on the day of booster vaccination ('b' will be used to denote booster visits – e.g., V1b, Day 1b, Month 0b)
(ii) Subjects presenting with febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) requiring hospitalization will have two blood samples taken to confirm dengue infection. The first blood sample will be taken during the acute phase (ie, as soon as possible and preferably within 5 days after the onset of fever); the second sample will be taken during the convalescent phase (ie., between 7 to 14 days after the first blood sample). Subjects presenting with febrile illness (defined as temperature ≥38 °C on any 2 of 3 consecutive days) or clinically suspected dengue and not requiring hospitalization during Parts 4 and 5 will have 1 blood sample taken for dengue infection confirmation by RT-PCR unless there is an alternate laboratory confirmed etiology. The blood sample will be taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever).

a. Subjects who are included in the Per-Protocol Set and were 4 to 11 years of age at the time of randomization in the trial (see Figure 6.b) .
b. Subjects will receive a booster dose of TDV or placebo, depending on the assignment at the time of randomization in the trial (see Figure 6.b).
c. Blood sample for dengue neutralizing antibodies for all subjects.
d. Additional blood sample for dengue neutralizing antibodies in the booster immunogenicity subset.

Booster immunogenicity evaluation (MNT_{50}):

Note: 'b' will be used to denote trial visits of the booster phase.

All subjects in the booster phase:

- Blood samples will be collected pre-booster vaccination on Day 1b (Month 0b) and post-booster vaccination on Day 30b (Month 1b).

Booster immunogenicity subset:

- Additional blood samples will be collected post-booster vaccination on Day 180b (Month 6b), Day 395b (Month 13b), and Day 760b (Month 25b).

Safety evaluation:

All subjects in the booster phase:

- Identification of febrile episodes with potential dengue etiology for the trial duration.
- Blood samples will be collected in the event of febrile illness as described above.
- Documentation of all SAEs during Parts 4 and 5.

Booster immunogenicity subset:

- Subjects will be provided with a diary card for the recording of:
  - Solicited local AEs for 7 days following booster vaccination (day of booster vaccination + 6 subsequent days). These will include:
    - Injection site pain, injection site erythema and injection site swelling.
  - Solicited systemic AEs for 14 days following booster vaccination (day of booster vaccination + 13 subsequent days). These will include:
    - Asthenia, fever, headache, malaise and myalgia.
- Unsolicited AEs for 28 days following booster vaccination (day of booster vaccination + 27 subsequent days) will be collected by interview (ie, at Day 30b [Month 1b]).

6.2 Justification for Trial Design, Dose, and Endpoints

An efficacy trial is required due to the absence of a correlate of protection, so the primary objective of this trial is to assess the efficacy of 2 doses of TDV in preventing dengue fever of any severity and any serotype in subjects 4 to 16 years of age. This is consistent with WHO recommendations. The trial includes a booster phase for exploratory analysis of the efficacy, immunogenicity and safety of a TDV booster dose when given between 4 years and approximately 4.5 years post-dose 2 to subjects who were 4 to 11 years of age at the time of randomization in the trial on Day 1 (Month 0). The trial is split into 5 main parts for the reasons described in Section 6.2.1 and 6.2.2.

6.2.1 Parts 1, 2, and 3

- Part 1 is designed to support the primary objective through active surveillance of febrile illness intended to detect dengue fever. The duration of Part 1 will ensure that there are

sufficient cases of dengue identified to enable a powered assessment of VE while also ensuring an adequate duration of surveillance following vaccination, both at an individual and a group level.

- Part 2 adds an extra 6 months of active surveillance in order to provide additional data for the secondary objective of assessment of efficacy of the vaccine candidate (see Section 5.1.2). As dengue cases due to individual serotypes are both less common and less predictable in epidemiological terms than a composite assessment of dengue regardless of serotype, it is likely a surveillance duration that supports the later will be inadequate for the former. Part 2 will identify additional cases of dengue to minimize this risk.
- Part 3 fulfils the WHO recommendation of long-term safety follow-up by continuing surveillance for approximately 3 years. The modified active surveillance aims to capture dengue fever of any severity with higher focus on hospitalized dengue fever which has more clinical relevance and societal impact than mild dengue fever managed as an outpatient. Identification of all symptomatic dengue cases will allow monitoring of disease severity over time. However, the surveillance mechanism is modified to lessen burden on subjects and parent/guardian, with the potential to ensure greater compliance to longer term active follow-up. Febrile illness with an alternate laboratory confirmed etiology and not requiring hospitalization will be of lesser clinical relevance in the context of long-term safety assessment of the trial vaccine.

The age range of 4 to 16 years of age has been chosen based on the epidemiology of dengue in the Asian and Latin American countries included in the trial. Symptomatic dengue is most common during a second infection, less common during a primary infection and unusual during a third or fourth infection. Efficacy assessment based on detection of symptomatic dengue is therefore best performed in age groups for which a secondary infection is likely. The peak of symptomatic dengue tends to be younger in Asia (where dengue incidence is higher) and older in Latin America (where incidence is lower, leading to 'delayed' secondary and symptomatic infections). An age range of 4 to 16 years enables some overlap of this epidemiology in the 2 regions and is also an age range for which febrile surveillance and long-term follow-up is more successful.

For the efficacy endpoint, case detection will be supported by a combination of a highly sensitive clinical case definition and a highly specific confirmation method. Febrile episodes will be confirmed virologically by specific RT-PCR to detect specific serotypes and distinguish vaccine-derived from WT viruses. Serological diagnosis will be performed as part of the standard of care but will not be used to confirm cases because the vaccine and other flavivirus infections may induce IgM and IgG responses thereby reducing specificity.

All efforts will be made to detect any possible febrile case as early as possible to optimize the chances of virological confirmation in a timely fashion. However, there may be situations where fever is not documented or may not persist for 2 consecutive days, or atypical presentations trigger the Investigator's suspicion of dengue. To increase the likelihood of capturing more dengue cases, a more flexible criteria that specifies fever on 'any 2 of 3 consecutive days' rather

than '2 consecutive days' and the addition of the Investigator's suspicion of dengue will be used. These cases will be unambiguously recorded by the Investigator using a check box in the eCRF.

In order to maintain the double-blind design, a placebo (Normal Saline) was used in this trial. A placebo had been chosen to avoid the use of a number of active vaccine comparators that would be required due to the wide age range of subjects (4 to 16 years of age) and the diverse countries participating. As no active comparator was possible as part of the trial design, a licensed vaccine will be offered to all subjects, irrespective of their full participation in this trial and at least 6 months after any protocol defined vaccination. The choice of this vaccine was discussed between the Sponsor and the Investigator, and was approved by the appropriate ethics committee. This vaccine will be used according to the labeling approved in the country.

The collection of solicited and unsolicited AEs following each vaccination is consistent with vaccine evaluation trials, and with those collected in earlier trials with TDV.

6.2.2 Booster Phase (Parts 4 and 5)

Parts 4 and 5 are designed for exploratory analysis of the efficacy, immunogenicity and safety of a TDV booster dose when given between 4 years and approximately 4.5 years post-dose 2.

Subjects who were 4 to 11 years of age at the time of randomization in the trial have been chosen for booster vaccination based on potential retention issues in subjects who were 12 to 16 years of age at the time of randomization in the trial.

For the efficacy endpoints, case detection will be supported by a combination of a highly sensitive clinical case definition and a highly specific confirmation method. Febrile episodes will be confirmed virologically by specific RT-PCR to detect specific serotypes and distinguish vaccine-derived from WT viruses. Serological diagnosis will be performed as part of the standard of care but will not be used to confirm cases because the vaccine and other flavivirus infections may induce IgM and IgG responses thereby reducing specificity.

All efforts will be made to detect any possible febrile case as early as possible to optimize the chances of virological confirmation in a timely fashion. However, there may be situations where fever is not documented or may not persist for 2 consecutive days, or atypical presentations trigger the Investigator's suspicion of dengue. To increase the likelihood of capturing more dengue cases, a more flexible criteria that specifies fever on 'any 2 of 3 consecutive days' rather than '2 consecutive days' and the addition of the Investigator's suspicion of dengue will be used. These cases will be unambiguously recorded by the Investigator using a check box in the eCRF.

The double-blind design will be maintained in the booster phase of the trial. Subjects will receive a single dose of TDV or placebo, depending on the assignment at the time of randomization performed on Day 1 (Month 0) (see Section 6.1.1). At randomization on Day 1 (Month 0), a placebo was chosen to avoid the use of a number of active vaccine comparators that would have been required due to the wide age range of subjects and the diverse countries participating. As no active comparator was possible as part of the trial design, a licensed vaccine will be offered to all subjects at least 6 months after any protocol defined vaccination. A similar offer will be given to

subjects participating in the booster phase. A licensed vaccine will be offered according to local regulations to all subjects irrespective of their full participation in the booster phase and at least 6 months after booster vaccination. The choice of this vaccine will be discussed between the Sponsor and the Investigator, and will be approved by the appropriate ethics committee. This vaccine will be used according to the labeling approved in the country.

The collection of solicited and unsolicited AEs following booster vaccination is consistent with vaccine evaluation trials, and with those collected in earlier trials with TDV.

6.3 Duration of Subject's Expected Participation in the Entire Trial

6.3.1 Parts 1, 2, and 3

For each participant, at least 42 months after the completion of Part 1 (at least 6 months in Part 2 and approximately 3 years in Part 3). The minimum duration of Part 1 will be approximately 15 months (including minimum 12 months after the second vaccination for each subject) but may be longer depending on the time taken to fulfill criteria for the end of Part 1. Hence, it is not explicitly defined. There is a possibility that when end of Part 1 is determined, certain subjects who were randomized earlier might have already completed the 6 months of active surveillance required for Part 2. The transition to Part 3 (ie, modified active surveillance) will occur at that point for those subjects.

The end of Part 3 will be the end of the trial for subjects not participating in the booster phase of the trial.

6.3.2 Booster Phase (Parts 4 and 5)

For each participant, the duration of the booster phase of the trial (Part 4 and 5), will be approximately 760 days (approximately 25 months) including booster vaccination (Day 1b [Month 0b]) and follow-up through Day 760b (Month 25b).

6.4 Premature Termination or Suspension of Trial or Investigational Site

6.4.1 Criteria for Premature Termination or Suspension of the Trial

The trial will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the trial.

- New information or other evaluation regarding the safety or efficacy of the investigational vaccine that indicates a change in the known risk/benefit profile, such that the risk/benefit is no longer acceptable for subjects participating in the trial.
- Significant violation of GCP that compromises the ability to achieve the primary trial objectives or compromises subject safety.

6.4.2 Criteria for Premature Termination or Suspension of Investigational Sites

A trial site may be terminated prematurely or suspended if the site (including the Investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the trial, or as otherwise permitted by the contractual agreement.

A trial site that enrolls subjects prior to randomization may not be able to continue participation in the trial. Examples of reason for non-continuation include failure to adequately implement febrile surveillance or a change in the local standard of care such as availability of a licensed dengue vaccine.

6.4.3 Procedures for Premature Termination or Suspension of the Trial or the Participation of Investigational Site(s)

In the event that the Sponsor, IRB/IEC or regulatory authority elects to terminate or suspend the trial or the participation of an investigational site, a trial-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable investigational sites during the course of termination or trial suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including pregnancy test results (if applicable), need to be confirmed prior to randomization.

Note that enrollment into the trial could occur up to 10 months prior to Day 1 (Month 0) (ie, as a result of the dry-run for pre-vaccination surveillance for dengue) (see Section 6.1), and that entry criteria will be re-confirmed at Day 1 (Month 0) prior to vaccination.

7.1 Inclusion Criteria

7.1.1 Trial Entry

Subject eligibility is determined according to the following criteria:

1. The subject is aged 4 to 16 years, inclusive, at the time of randomization.
2. Individuals who are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs) and clinical judgment of the Investigator.
3. The subject and/or the subject's parent/guardian signs and dates an assent/written informed consent form where applicable, and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements (Appendix C).
4. Individuals who can comply with trial procedures and are available for the duration of follow-up.

7.1.2 Booster Phase (Parts 4 and 5)

Subject eligibility for enrollment in the booster phase of the trial is determined according to the following criteria:

1. The subject is included in the PPS of the trial.
2. The subject was aged 4 to 11 years at the time of randomization in the trial (Day 1 [Month 0]).
3. The subject and/or the subject's parent/guardian signs and dates an assent/written informed consent form where applicable, and any required privacy authorization prior to the initiation of any trial procedures for the booster phase of the trial, after the nature of the booster phase of the trial has been explained according to local regulatory requirements (Appendix C).
4. Individuals who can comply with trial procedures for the booster phase and are available for the duration of follow-up post-booster vaccination.

7.2 Exclusion Criteria

7.2.1 Trial Entry

Any subject who meets any of the following criteria will not qualify for entry into the trial:

1. Febrile illness (temperature ≥38°C) or moderate or severe acute illness or infection at the time of randomization.
2. History or any illness that, in the opinion of the Investigator, might interfere with the results of the trial or pose an additional risk to the subject due to participation in the trial, including but not limited to:
    a. Known hypersensitivity or allergy to any of the vaccine components.
    b. Female subjects (post-menarche) who are pregnant or breastfeeding.
    c. Individuals with any serious chronic or progressive disease according to judgment of the Investigator (eg, neoplasm, insulin-dependent diabetes, cardiac, renal or hepatic disease, neurologic or seizure disorder or Guillain-Barré syndrome).
    d. Known or suspected impairment/alteration of immune function, including:
        i. Chronic use of oral steroids (equivalent to 20 mg/day prednisone ≥ 12 weeks/ ≥ 2 mg/kg body weight/day prednisone ≥ 2 weeks) within 60 days prior to Day 1 (Month 0) (use of inhaled, intranasal, or topical corticosteroids is allowed).
        ii. Receipt of parenteral steroids (equivalent to 20 mg/day prednisone ≥ 12 weeks/ ≥ 2 mg/kg body weight/day prednisone ≥ 2 weeks) within 60 days prior to Day 1 (Month 0).
        iii. Administration of immunoglobulins and/or any blood products within the 3 months prior to Day 1 (Month 0) or planned administration during the trial.
        iv. Receipt of immunostimulants within 60 days prior to Day 1 (Month 0).
        v. Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within 6 months prior to Day 1 (Month 0).
        vi. Human immunodeficiency virus (HIV) infection or HIV-related disease.
        vii. Genetic immunodeficiency.
3. Receipt of any other vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to Day 1 (Month 0) or planning to receive any vaccine within 28 days after Day 1 (Month 0).
4. Participation in any clinical trial with another investigational product 30 days prior to Day 1 (Month 0) or intent to participate in another clinical trial at any time during the conduct of this trial.

5. Previous participation in any clinical trial of a dengue candidate vaccine, or previous receipt of a dengue vaccine.
6. First degree relatives of individuals involved in trial conduct.
7. Females of childbearing potential who are sexually active, and who have not used any of the acceptable contraceptive methods for at least 2 months prior to Day 1 (Month 0).
    a. Of childbearing potential is defined as status post onset of menarche and not meeting any of the following conditions: bilateral tubal ligation (at least 1 year previously), bilateral oophorectomy (at least 1 year previously) or hysterectomy.
    b. Acceptable birth control methods are defined as 1 or more of the following:
        i. Hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring).
        ii. Barrier (condom with spermicide or diaphragm with spermicide) each and every time during intercourse.
        iii. Intrauterine device (IUD).
        iv. Monogamous relationship with vasectomized partner (partner must have been vasectomized for at least six months prior to Day 1 [Month 0]).

    Other contraceptive methods may be considered in agreement with the Sponsor and will be approved by the appropriate ethics committee.
8. Females of childbearing potential who are sexually active, and who refuse to use an acceptable contraceptive method up to 6 weeks post-second vaccination.
9. Deprived of freedom by administrative or court order, or in an emergency setting, or hospitalized involuntarily.
10. Current alcohol abuse or drug addiction that may interfere with the subject's ability to comply with trial procedures.
11. Identified as an employee of the Investigator or trial center, with direct involvement in the proposed trial or other trials under the direction of that Investigator or trial center.

There may be instances when individuals meet all entry criteria except one that relates to transient clinical circumstances (eg, temperature elevation or recent use of excluded medication or vaccine). Under these circumstances, a subject may be considered eligible for trial entry or first vaccination, as applicable, if the appropriate window for delay has passed, inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

7.2.2 Booster Phase (Parts 4 and 5)

Any subjects who are assigned to receive a booster dose of trial vaccines (TDV or placebo) will not qualify for entry into the booster phase of the trial if they meet any of the following criteria:

1. Febrile illness (temperature ≥38°C) or moderate or severe acute illness or infection at the time of enrollment in the booster phase of the trial.
2. History or any illness that, in the opinion of the Investigator, might interfere with the results of the booster phase of the trial or pose an additional risk to the subject due to participation in the booster phase of the trial, including but not limited to:
    a. Known hypersensitivity or allergy to any of the vaccine components.
    b. Female subjects (post-menarche) who are pregnant or breastfeeding.
    c. Individuals with any serious chronic or progressive disease according to judgment of the Investigator (eg, neoplasm, insulin-dependent diabetes, cardiac, renal or hepatic disease, neurologic or seizure disorder or Guillain-Barré syndrome).
    d. Known or suspected impairment/alteration of immune function, including:
        i. Chronic use of oral steroids (equivalent to 20 mg/day prednisone ≥12 weeks/ ≥2 mg/kg body weight/day prednisone ≥2 weeks) within 60 days prior to Day 1b (Month 0b) (use of inhaled, intranasal, or topical corticosteroids is allowed).
        ii. Receipt of parenteral steroids (equivalent to 20 mg/day prednisone ≥12 weeks/ ≥2 mg/kg body weight/day prednisone ≥2 weeks) within 60 days prior to Day 1b (Month 0b).
        iii. Receipt of immunoglobulins and/or any blood products since Day 120 (Month 4) (ie, 30 days after the second dose of trial vaccine) or planned administration during the booster phase of the trial.
        iv. Receipt of immunostimulants within 60 days prior to Day 1b (Month 0b).
        v. Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within 6 months prior to Day 1b (Month 0b).
        vi. HIV infection or HIV-related disease.
        vii. Genetic immunodeficiency.
3. Receipt of any other vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to Day 1b (Month 0b), or planning to receive any vaccine within 28 days after Day 1b (Month 0b).
4. Participation in any clinical trial with another investigational product at any time during participation in this trial or intent to participate in another clinical trial at any time during the conduct of the booster phase of this trial.
5. Participation in any clinical trial of a dengue candidate vaccine other than the current trial, or receipt of a dengue vaccine other than the trial vaccine at any time during participation in this trial.

6. First degree relatives of individuals involved in trial conduct.
7. Females of childbearing potential who are sexually active, and who have not used any of the acceptable contraceptive methods as specified under the criteria for entry into the trial, for at least 2 months prior to Day 1b (Month 0b) (see also trial entry exclusion criteria #7).
8. Females of childbearing potential who are sexually active, and who refuse to use an acceptable contraceptive method up to 6 weeks post-booster vaccination.
9. Deprived of freedom by administrative or court order, or in an emergency setting, or hospitalized involuntarily at any time during participation in this trial.
10. Current alcohol abuse or drug addiction that may interfere with the subject's ability to comply with trial procedures for the booster phase of the trial.
11. Identified as an employee of the Investigator or trial center, with direct involvement in the present trial or other trials under the direction of that Investigator or trial center.

There may be instances when individuals meet all entry criteria for the booster phase of the trial except one that relates to transient clinical circumstances (eg, temperature elevation or recent use of excluded medication or vaccine). Under these circumstances, a subject may be considered eligible for booster vaccination if the appropriate window for delay has passed, inclusion/exclusion criteria for the booster phase have been rechecked, and if the subject is confirmed to be eligible for participation in the booster phase of the trial.

7.3 Criteria for Delay of Vaccination and Contraindications

7.3.1 Second Vaccination (Day 90 [Month 3])

If any of the below criteria occur at the time scheduled for second vaccination, the subject may be vaccinated at a later date as long the subject is otherwise eligible to continue trial participation. In certain situations, the period of delay may lead to deviations from the time window for second vaccination. The decision to vaccinate in those situations will be taken by the Investigator. The following clinical circumstances warrant a delay for administration of the second trial vaccination:

1. Body temperature ≥38.0°C within 3 days of intended trial vaccination.
2. Receipt of blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation within 2 weeks of intended trial vaccination.
3. Receipt of any vaccine other than the trial vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) of intended trial vaccination.
4. Receipt of oral or parenteral steroids or immunosuppressive therapy within 1 month of intended trial vaccination; dosage and duration of treatments for steroids are specified under the exclusion criteria.

There are also circumstances under which receipt of second vaccination is a contraindication in this trial. These circumstances include anaphylaxis or severe hypersensitivity reactions following the first vaccination. If these reactions occur, the subject must not receive second vaccination but is encouraged to continue trial participation to enable continued surveillance for dengue.

7.3.2 Booster Vaccination (Day 1b [Month 0b]

If any of the below criteria occur at the time scheduled for the booster vaccination, the subject may be vaccinated at a later date as long the subject is otherwise eligible to continue participation in the booster phase of the trial.

1. Body temperature ≥38.0°C within 3 days of intended booster vaccination.
2. Receipt of any vaccine other than the trial vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) of intended booster vaccination.
3. Use of antipyretics and/or analgesic medication within 24 hours prior to booster vaccination.

There are also circumstances under which receipt of a booster dose of trial vaccine is a contraindication in this trial. These circumstances include anaphylaxis or severe hypersensitivity reactions following the first or second vaccination. If these reactions occur, the subject must not receive the booster vaccination.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the trial should be recorded in the eCRF using the following categories. For screen failure subjects, refer to Section 9.1.11. For booster screen failure subjects, refer to Section 9.1.12.

1. Protocol violation: The subject may remain in the trial unless continuation in the trial jeopardizes the subject's health, safety or rights.
2. AE: The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue and/or subject's parent/guardian is unwilling for the subject to continue because of the AE.
3. Lost to follow-up: The subject did not return to the clinic and attempts to contact the subject and/or subject's parent/guardian were unsuccessful. Attempts to contact the subject and/or subject's parent/guardian must be documented. Lost to follow up status will only be confirmed at the time of Last Subject Last Visit at the particular trial site.
4. Withdrawal by subject and/or subject's parent/guardian: The subject wishes to withdraw and/or subject's parent/guardian wishes to withdraw the subject from the trial. The reason for withdrawal, if provided, should be recorded in the eCRF.
    a. Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be

recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

b. Note: subjects will be considered as participating in the trial until the end of Part 3 unless they explicitly withdraw their consent (febrile surveillance will continue and febrile episodes will be recorded in the eCRF per protocol definition).

5. Study terminated by Sponsor.
6. Pregnancy: Any subject who, despite the requirement for adequate contraception, becomes pregnant during the trial will not receive further investigational vaccines and trial interventions except for febrile surveillance and safety follow-up if the subject and/or the subject's parent/guardian agrees. The site should maintain contact with the pregnant subject and should complete a "Clinical Trial Pregnancy Form" as soon as possible. In addition, the subject should be followed-up until the birth of the child, or spontaneous or voluntary termination; when pregnancy outcome information becomes available, the information should be captured using the same form. The subject should be reported as a withdrawal from trial and the reason for withdrawal (ie, pregnancy) recorded in detail on the Trial Termination eCRF and subject' medical records.
7. Other. (Note: The specific reasons should be recorded in the "specify" field of the eCRF).

7.5 Procedures for Discontinuation or Withdrawal of a Subject

7.5.1 Parts 1, 2, and 3

The Investigator may terminate a subject's trial participation at any time during the trial when the subject meets trial termination criteria described in Section 7.4. In addition, a subject and/or the subject's parent/guardian may discontinue the subject's trial participation at any time during the trial without giving a reason. Should a subject's participation be discontinued, the primary criterion for termination must be recorded. In addition, efforts should be made to perform all procedures as scheduled for the Follow-up Visit (see Table 2.d).

Until the time of randomization, discontinued or withdrawn subjects will be replaced; after that time, discontinued or withdrawn subjects will not be replaced.

All withdrawn and discontinued subjects after vaccination on Day 1 (Month 0) will be followed for safety monitoring until the end of Part 3 (ie, the end of the trial for subjects not participating in the booster phase of the trial) unless subjects are lost to follow up or specifically withdrawn from febrile surveillance and safety follow up. Those withdrawn or discontinued prior to vaccination will not be followed up for safety.

7.5.2 Booster Phase (Parts 4 and 5)

The Investigator may terminate a subject's trial participation at any time during the booster phase of the trial when the subject meets trial termination criteria described in Section 7.4. In addition, a subject and/or the subject's parent/guardian may discontinue the subject's trial participation at any time during the booster phase of the trial without giving a reason. Should a subject's

participation be discontinued, the primary criterion for termination must be recorded. In addition, efforts should be made to perform all procedures as scheduled for the Follow-up Visit (see Table 2.e).

Refer to Section 9.1.4 for follow-up of subjects whose parent/guardian does not want to participate in the booster phase of this trial. For subjects from whom a signed informed consent form/assent for participation in the booster phase has been obtained but who are withdrawn or discontinued prior to receipt of the booster vaccination will no longer be follow-up for febrile surveillance and safety monitoring.

All withdrawn and discontinued subjects after booster vaccination on Day 1b (Month 0b) will be followed for febrile surveillance and safety monitoring until the end of Part 5 (ie, the end of the trial for subjects participating in the booster phase of the trial) unless subjects are lost to follow-up or specifically withdrawn from febrile surveillance and safety follow-up.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all vaccines and materials provided directly by the Sponsor, and/or sourced by other means, that are required by the trial protocol, including important sections describing the management of clinical trial material.

8.1 Investigational Vaccine(s) and Materials

8.1.1 Parts 1, 2, and 3

The Investigational Product is TDV, a tetravalent dengue vaccine comprised of 4 recombinant, live attenuated dengue virus strains: ~2 x 10^4, 5 x 10^3, 1 x 10^5 and 3 x 10^5 plaque forming units (PFU) per dose of TDV-1, TDV-2, TDV-3 and TDV-4, respectively.

All doses should be prepared at the time of administration by the unblinded pharmacist (or administrator) per the Pharmacy Manual. Each vial and carton will contain a label that includes pertinent trial information and caution statements. The label text will be in the specific country language, depending on local requirements.

8.1.2 Booster Phase (Parts 4 and 5)

The Investigational Product is TDV, a tetravalent dengue vaccine comprised of 4 recombinant, live attenuated dengue virus strains with potencies of not less than 3.3, 2.7, 4.0, and 4.5 $\log_{10}$ PFU per dose of TDV-1, TDV-2, TDV-3, and TDV-4, respectively.

All doses should be prepared at the time of administration by the unblinded pharmacist (or administrator) per the Pharmacy Manual. Each vial and carton will contain a label that includes pertinent trial information and caution statements. The label text will be in the specific country language, depending on local requirements.

8.1.2.1 Dosage Form, Manufacturing, Packaging, and Labeling

This trial will involve the use of TDV for SC administration. Manufacturing of monovalent bulk drug substances of TDV, mixing of the 4 TDV drug substances, filling into vials, and lyophilization of TDV drug product is done at IDT Biologika GmbH, Germany.

8.1.2.1.1 Parts 1, 2, and 3

- **Investigational TDV**

TDV is lyophilized and presented in a labeled, single-use, 2 mL glass vial with a FluroTec-coated butyl rubber stopper and flip-top aluminum over seal that once reconstituted will contain a single 0.5 mL liquid dose for SC injection. TDV will be reconstituted by adding 0.7 mL diluent to facilitate the withdrawal of 1 dose (0.5 mL).

The doses should be prepared at the time of administration by the unblinded pharmacist (or administrator) per the Pharmacy Manual. TDV will be provided by the Sponsor in a uniquely numbered carton and will be dispensed in a blinded manner by the IWRS/IVRS.

- **Placebo (Normal Saline) control**

The placebo was normal saline for injection (0.9% sodium chloride solution). Placebo will be presented in a 2 mL glass vial to deliver a single dose (0.5 mL) for SC injection. Placebo will be provided by the Sponsor in a uniquely numbered carton and will be dispensed in a blinded manner by the IWRS/IVRS.

Refer to Section 8.6 for accountability of Sponsor-supplied vaccines.

8.1.2.1.2 Booster Phase (Parts 4 and 5)

- **Investigational TDV**

TDV is lyophilized and presented in a labeled, single-use, 2 mL glass vial with a FluroTec-coated butyl rubber stopper and flip-top aluminum over seal that once reconstituted will contain a single 0.5 mL liquid dose for SC injection. TDV will be reconstituted by adding diluent to facilitate the withdrawal of 1 dose (0.5 mL).

The doses should be prepared at the time of administration by the unblinded pharmacist (or administrator) per the Pharmacy Manual.

TDV will be provided by the Sponsor in a uniquely numbered carton and will be dispensed in a blinded manner by the IWRS/IVRS.

- **Placebo (Normal Saline) control**

Normal saline for injection (0.9% sodium chloride solution) will be used as placebo. The placebo is presented as single dose units for 0.5 mL dosing. Placebo will be provided by the Sponsor in a uniquely numbered carton and will be dispensed in a blinded manner by the IWRS/IVRS.

8.1.2.2 Storage

8.1.2.2.1 Parts 1, 2, and 3

The placebo, TDV and diluent will be shipped in refrigerated containers at 2 to 8°C. From receipt and prior to use, lyophilized TDV kits must be protected from light and stored at 2°C to 8°C in a refrigerator.

8.1.2.2.2 Booster Phase (Parts 4 and 5)

The trial vaccines, consisting of TDV with diluent, and placebo will be shipped as per the Pharmacy Manual. From receipt and prior to use, the trial vaccines must be stored as per the label and Pharmacy Manual.

8.1.2.2.3 Parts 1, 2, and 3 and Booster Phase (Parts 4 and 5)

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used, destroyed or returned to the Sponsor or designee for destruction. All Sponsor-supplied vaccines must be stored under the conditions specified on the label, and remain in the original

container until dispensed. A daily temperature log of the vaccine storage area must be maintained every working day.

8.1.2.3 Dose and Regimen

8.1.2.3.1 Parts 1, 2, and 3

Subjects will receive a 2-dose regimen (Day 1 [Month 0]) and Day 90 [Month 3]) with either TDV or placebo according to their random assignment on Day 1 (Month 0).

8.1.2.3.2 Booster Phase (Parts 4 and 5)

Subjects assigned to receive the booster dose of trial vaccine will receive a single dose of TDV or placebo, depending on the assignment at the time of randomization in the trial (Day 1 [Month 0]).

8.2 Investigational Vaccine Assignment and Dispensing Procedures

At Day 1 (Month 0), the Investigator or designee will access the IWRS/IVRS at subject enrollment to obtain the subject number. This number will be used throughout the trial.

The Investigator or designee will utilize the IWRS/IVRS to randomize the subject into the trial on the day of first dosing. During this contact, the Investigator or designee will provide the necessary subject identifying information.

Subjects assigned to participate in the booster phase of the trial will receive a single dose of TDV or placebo, depending on the assignment at the randomization performed on Day 1 (Month 0) by IWRS/IVRS.

The investigator or the investigator's designee will access the IWRS or IVRS at each dispensing visit to obtain the Vaccination Identification number for the vaccine dose. The vaccines will be prepared and administered by the unblinded pharmacist or unblinded administrator according to the instructions in the Pharmacy Manual or per manufacturer's instructions.

The Investigator or designee will be responsible for overseeing the administration of vaccine to subjects randomized in the trial according to the procedures stipulated in this trial protocol. All vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable laws and regulations for that specific trial. The unblinded personnel who administer the vaccine will not assess AEs.

If Sponsor-supplied vaccine is lost or damaged, the site can request a replacement. Expired vaccines must not be administered.

8.3 Randomization Code Creation and Storage

8.3.1 Parts 1, 2, and 3

Randomization personnel of the Sponsor or designee will generate the randomization schedule(s). Randomization information will be stored in a secured area, accessible only by authorized personnel.

Randomization will be stratified by region and age range (children aged 4-5 years, 6-11 years, and 12-16 years). Subjects included in the subset will be randomly selected using the IWRS/IVRS.

8.3.2 Booster Phase (Parts 4 and 5)

No new randomization will be performed for the booster phase of the trial. A subset of subjects who were 4 to 11 years of age at the time of randomization on Day 1 (Month 0) will be assigned to the booster immunogenicity subset (approximately 2100 subjects) based on the randomization performed on Day 1 (Month 0) (see Section 6.1.1).

8.4 Investigational Vaccine Blind Maintenance.

The investigational vaccine blind will be maintained using the IWRS/IVRS. The subjects, data collectors (eg, Investigator), and data evaluators (eg, trial statisticians) are blinded. One or more designated pharmacists/ vaccine administrators will be unblinded at the site. These unblinded designees will maintain the investigational vaccine blind and will have no role in the assessment of subject safety.

The investigational vaccine blind will be maintained in the booster phase of the trial (Parts 4 and 5).

8.5 Unblinding Procedure

The investigational vaccine blind shall not be broken by the Investigator unless information concerning the investigational vaccine is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible, the medical monitor should be contacted before the investigational vaccine blind is broken to discuss the need for unblinding.

For unblinding a subject, the investigational vaccine blind can be obtained by the Investigator, by accessing the IVRS/IWRS.

The Sponsor's Pharmacovigilance Department must be notified as soon as possible if the investigational vaccine blind is broken by the Investigator and the completed SAE form must be sent within 24 hours (Refer to Section 10.4.3). The date, time, and reason the blind is broken must be recorded in the source document and the same information (except the time) must be recorded on the eCRF.

In the event of accidental unblinding of the investigational vaccine, the Sponsor shall be immediately contacted for further decision about the subjects' eligibility to continue in the trial.

Further details regarding the unblinding procedure for the primary analysis after Part 1 can be found in Section 13.2.

8.6 Accountability and Destruction of Sponsor-Supplied Vaccine(s)

Vaccine supplies will be counted and reconciled at the site before being destroyed or returned to the Sponsor or designee as noted below. Sites will maintain source documents in addition to entering data in the IVRS/IWRS.

The Investigator or designee must ensure that the Sponsor-supplied vaccines are used in accordance with the approved protocol and is administered only to subjects randomized in the trial. To document appropriate use of Sponsor-supplied vaccine(s) (TDV, diluent and placebo), the Investigator must maintain records of all Sponsor-supplied vaccine delivery to the site, site inventory, administration and use by each subject, and destruction or return to the Sponsor or designee.

Upon receipt of Sponsor-supplied vaccine(s), the Investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the investigational vaccine is received within the labeled storage conditions, and is in good condition. If quantity and conditions are acceptable, the Investigator or designee will acknowledge receipt of the shipment by recording in IVRS/IWRS.

If there are any discrepancies between the packing list versus the actual product received, the Sponsor or designee must be contacted to resolve the issue. The packing list should be filed in the Investigator's essential document file.

The Investigator must maintain 100% accountability for all Sponsor-supplied vaccines received and administered during his or her entire participation in the trial. Proper vaccine accountability includes, but is not limited to:

- Verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the vaccine lot number used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the Sponsor must be notified immediately.

The Investigator or designee must record the current inventory of all Sponsor-supplied vaccines (TDV and placebo) on a Sponsor-approved vaccine accountability log. The following information will be recorded at a minimum: protocol number and title, name of the Investigator, site identifier and number, description of Sponsor-supplied vaccine(s), expiry date and/or retest date and amount. The IVRS/IWRS should include all required information as a separate entry for each subject to whom Sponsor-supplied vaccine is administered.

Prior to site closure or at appropriate intervals throughout the trial, before any clinical trial materials are returned to the Sponsor or its designee for destruction, a representative from the

Sponsor or its designee will perform clinical trial material accountability and reconciliation. The Investigator will retain a copy of the documentation regarding clinical trial material accountability, return, and/or destruction, and originals will be sent to the Sponsor or designee.

The pharmacist (or designated individual) at each site will be responsible for vaccine accountability and will document receipt, use, return, or destruction of TDV and placebo. Vaccine accountability documentation will be reviewed by the unblinded monitor during clinical monitoring visits.

9.0 TRIAL PLAN

9.1 Trial Procedures

The following sections describe the trial procedures and data to be collected. For each procedure, subjects are to be assessed by the same Investigator or site personnel whenever possible. The Schedule of Trial Procedures is located in Section 2.1.

9.1.1 Informed Consent/Assent

The requirements of the informed consent/assent are described in Section 15.2.

9.1.1.1 Parts 1, 2, and 3

Informed consent/assent must be obtained prior to the subject entering into the trial, and before any protocol-directed procedures are performed. Note that this may be up to 10 months prior to first vaccination as a result of the dry-run for pre-vaccination surveillance for dengue or prior to Day 1 (Month 0). Informed consent/assent already obtained prior to the dry-run will not need to be repeated on Day 1 (Month 0) unless there is an amendment to the informed consent/assent forms.

After informed assent/consent has been obtained, the IVRS/IWRS will assign a unique identification number (screening number) to each subject. If all eligibility criteria are fulfilled, this will become the definitive subject number to be used throughout the trial. Subject numbers assigned to subjects who fail screening should not be reused (Section 9.1.11), and similarly subject numbers assigned to subjects who withdraw or are discontinued between enrollment and Day 1 (Month 0) should not be reused.

9.1.1.2 Booster Phase (Parts 4 and 5)

Additional informed consent/assent must be obtained prior to the subject entering into the booster phase of the trial, and before any protocol-directed procedures are performed for the booster phase. Subjects will keep the same unique identification number assigned at the time of trial entry. Subjects who would become of legal age (18 years of age in all participating countries) during the booster phase of the trial will be asked to provide informed consent as legal adults, ideally within approximately 3 weeks after the 18th birthday, to remain in the trial.

9.1.2 Demographics, Medical History and Prior Medications

9.1.2.1 Parts 1, 2, and 3

Demographic information to be obtained will include date of birth, gender, and race as described by the subject and/or the subject's parent/guardian.

Medical history will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for trial participation such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. Relevant medical history can also

include any medical history that contributes to the understanding of an AE that occurs during trial participation, if it represents an exacerbation of an underlying disease/preexisting problem.

History of vaccination against Japanese Encephalitis or against Yellow Fever until Day 120 (Month 4) will be recorded in the eCRF irrespective of time of administration and including the vaccine type (Japanese Encephalitis: inactivated, live-attenuated, live recombinant or other; Yellow fever: live-attenuated or other). Additionally, any supportive documentation for these vaccinations will be recorded in the eCRF.

All concomitant medications and any vaccine taken/received during the period starting 1 month (minimum 28 days) prior to administration of trial vaccine (Day 1 [Month 0] and Day 90 [Month 3]) and ending 1 month (minimum 28 days) after each trial vaccination are to be recorded on the relevant sections of the eCRF. Medications/treatments specifically contraindicated at trial entry and time of first vaccination including steroids and immunostimulants within 60 days prior to Day 1 (Month 0), immunoglobulins and blood products within 3 months prior to Day 1 (Month 0), and immunosuppressive therapy within 6 months prior to Day 1 (Month 0) are to be recorded on the relevant sections of the eCRF (See also Section 7.2). The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source documents. Trial vaccination should be delayed if subjects have used antipyretics and/or analgesic medication within 24 hours prior to vaccine administration.

Medications taken for prophylaxis are those intended to prevent the onset of AEs following vaccination. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

Prohibited therapies (see also Section 7.2):

- Parenteral immunoglobulin preparation, blood products, and/or blood-derived products within the 3 months prior to Day 1 (Month 0).
- Immunosuppressive therapy within 6 months or systemic (eg, oral or parenteral) corticosteroid treatment within 60 days prior to Day 1 (Month 0) or immunostimulants within 60 days prior to Day 1 (Month 0).
- Any vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to Day 1 (Month 0) and Day 90 (Month 3), and 28 days after each trial vaccination.
- Receipt of any other clinical trial product within 30 days prior to Day 1 (Month 0).

These data must be written in the source documents.

Medical history (including corresponding medication) to be obtained will include any significant conditions or diseases that have disappeared or resolved at or prior to signing of informed consent/assent. Additionally, reasons for delay of second trial vaccination and contraindications for second vaccination must be recorded in the eCRF (see Section 7.3).

9.1.2.2 Booster Phase (Parts 4 and 5)

Medical history will also be collected, including but not limited to any medical history that may be relevant to subject eligibility for participation in the booster phase of the trial such as prior vaccinations, concomitant medications, and previous and ongoing illnesses or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during participation in the booster phase of the trial, if it represents an exacerbation of an underlying disease/preexisting problem.

History of vaccination against Japanese Encephalitis or against Yellow Fever after Day 120 (Month 4) until Day 30b (Month 1b) will be recorded in the eCRF irrespective of time of administration and including the vaccine type (Japanese Encephalitis: inactivated, live-attenuated, live recombinant or other; Yellow fever: live-attenuated or other). Additionally, any supportive documentation for these vaccinations will be recorded in the eCRF.

All concomitant medications and any vaccine taken/received during the period starting 1 month (minimum 28 days) prior to administration of the booster dose of trial vaccine (Day 1b [Month 0b]) and ending 1 month (minimum 28 days) after the booster vaccination or early termination visit if applicable are to be recorded on the relevant sections of the eCRF. The use of antipyretics and/or analgesic medications within 24 hours prior to booster vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source documents. Booster vaccination should be delayed if subjects have used antipyretics and/or analgesic medication within 24 hours prior to booster vaccine administration.

Medications taken for prophylaxis are those intended to prevent the onset of AEs following booster vaccination. Medications taken for treatment are intended to reduce or eliminate the presence of symptoms that are present.

Prohibited therapy (see also Section 7.2):

- Immunoglobulins and/or any blood products at any time during participation in this trial.
- Immunosuppressive therapy within 6 months or systemic (eg, oral or parenteral) corticosteroid treatment within 60 days prior to Day 1b (Month 0b) or immunostimulants within 60 days prior to Day 1b (Month 0b).
- Any vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to Day 1b (Month 0b), and 28 days after the booster vaccination.
- Receipt of any other clinical trial product within 30 days prior to Day 1b (Month 0b).

These data must be written in the source documents.

Medical history (including corresponding medication) to be obtained will include any significant conditions or diseases that have disappeared or resolved at or prior to signing of informed consent/assent for the booster phase of the trial. Additionally, reasons for delay of booster vaccination and contraindications for booster vaccination must be recorded in the eCRF (see Section 7.3).

9.1.3 Documentation of Trial Entrance/Randomization

Only subjects for whom a signed informed consent form/assent has been obtained, and meet all of the other inclusion criteria and none of the exclusion criteria are eligible for trial entry/randomization into the vaccination phase. The list of randomization assignments is produced by IVRS/IWRS.

If the subject is found to be not eligible for randomization/trial phase, the Investigator should record the primary reason for failure on the screening log.

9.1.4 Documentation of Enrollment in the Booster Phase (Parts 4 and 5)

Between 4 years and approximately 4.5 years post-dose 2 in Part 3, the parent/guardian of subjects who are included in the PPS and who were 4 to 11 years of age at the time of randomization in the trial (Day 1 [Month 0]) will be asked to allow their child/ward to receive the booster dose of trial vaccine (TDV or placebo) (see Section 6.1.2). If the subject's parent/guardian does not allow the participation of their child/ward in the booster phase of this trial, the Investigator should record this in the eCRF. Regardless of the willingness to participate in the booster phase of this trial, all subjects will continue trial participation for febrile surveillance and safety follow-up.

On Day 1b (Month 0b), only subjects who are assigned to receive a booster dose of trial vaccines (TDV or placebo) and from whom a signed informed consent form/assent for participation in the booster phase has been obtained, and who meet all of the other inclusion criteria and none of the exclusion criteria are eligible for enrollment in the booster phase of the trial.

If on Day 1b (Month 0b) a subject assigned to receive the booster dose of trial vaccines is found not eligible for enrollment in the booster phase, the Investigator should record the primary reason for failure on the booster enrollment log and the eCRF.

9.1.5 Physical Examination

Physical examinations must be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Site Responsibility Delegation Log.

A complete physical examination includes but is not limited to: auscultation of heart and lungs, palpation of the abdomen, inspection of extremities (including skin over intended vaccination site(s)), and a check of general appearance. Additional physical examinations may be performed if indicated by review of the subject's medical history. The performance of the physical examination must be recorded in the eCRF (Yes/No). The findings should be documented in the subject's source document.

A targeted physical examination includes but is not limited to measurement of vital signs (see Section 9.1.6).

9.1.5.1 Parts 1, 2, and 3

Complete physical examination will be performed prior to the dry-run, on Day 1 (Month 0), and on Day 90 (Month 3). A targeted physical examination will be performed for all subjects on Day 30 (Month 1), Day 120 (Month 4), and in the subset at all trial visits subsequent to Visit 4 (Day 120 [Month 4]).

9.1.5.2 Booster Phase (Parts 4 and 5)

Complete physical examination will be performed prior to booster vaccination on Day 1b (Month 0b). A targeted physical examination will be performed for all subjects on Day 30b (Month 1b), and for the booster immunogenicity subset also at all subsequent visits.

9.1.6 Vital Signs

9.1.6.1 Parts 1, 2, and 3

During the physical examination (see Section 9.1.5.1), a subject should have their vital signs measured. These will include (but are not limited to) systolic blood pressure/diastolic blood pressure, heart rate, temperature, height and weight.

9.1.6.2 Booster Phase (Parts 4 and 5)

During the physical examination (see Section 9.1.5.2), a subject should have their vital signs measured. These will include (but are not limited to) systolic blood pressure/diastolic blood pressure, heart rate, temperature, height and weight. Measurement of height is not required at Day 30b (Month 1b).

9.1.6.3 Parts 1, 2, and 3 and Booster Phase (Parts 4 and 5)

Temperature measurement will be described in Procedures Manuals.

9.1.7 Immunogenicity Assessments

9.1.7.1 Vaccine Immunogenicity

9.1.7.1.1 Parts 1, 2, and 3

All subjects will undergo blood sampling for serological immunogenicity testing at pre-vaccination on Day 1 (Month 0) and on Day 120 (post-second vaccination [Month 4]). Additional samples will be collected from the subset post first-vaccination on Day 30 (Month 1), pre-vaccination on Day 90 (Month 3), post-second vaccination on Day 270 (Month 9) and Day 450 (Month 15), and then every 12 months until the end of Part 3.

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood taken for immunogenicity at any single visit is approximately 8 mL at Day 1 (Month 0) and Day 120 (Month 4) for all subjects. The maximum volume of blood

taken for immunogenicity at other visits (subset only) is 5 mL. The approximate total volume of blood for the trial is 16 mL for subjects not included in the subset and 51 mL for subjects in the subset. Blood samples will be processed and stored at the trial site according to the Laboratory Guidelines as provided in the Laboratory Manual.

Blood samples taken at pre-vaccination on Day 1 (Month 0) of all subjects will be analyzed for evaluation of dengue serostatus at baseline. Day 120 (Month 4) samples for subjects not in the subset will be stored for future analysis. A higher blood volume for immunogenicity assessment (ie, approximately 8 mL vs. 5 mL) is collected on Day 1 (Month 0) and on Day 120 (Month 4) for all subjects in comparison to additional sampling time points (for the subset) to obtain additional serum to be stored for future analysis. This is considered essential in view of the evolving scientific field around dengue vaccine development (see also Section 9.4).

9.1.7.1.2 Booster Phase (Parts 4 and 5)

All subjects participating in the booster phase of the trial will undergo blood sampling for serological immunogenicity testing at pre-booster vaccination on Day 1b (Month 0b) and post-booster vaccination on Day 30b (Month 1b). Additional samples will be collected from the booster immunogenicity subset post-booster vaccination on Day 180b (Month 6b), Day 395b (Month 13b), and Day 760b (Month 25b).

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood taken for immunogenicity at any single visit is approximately 9 mL on Day 1b (Month 0b) for all subjects. The maximum volume of blood taken for immunogenicity at other visits is approximately 6 mL (Day 30b [Month 1b] for all subjects, and Day 180b [Month 6b], Day 395b [Month 13b], and Day 760b [Month 25b] in the booster immunogenicity subset only). The approximate total volume of blood for the booster phase of the trial is 15 mL for subjects not included in the booster immunogenicity subset and 33 mL for subjects in the booster immunogenicity subset. Blood samples will be processed and stored at the trial site according to the Laboratory Guidelines as provided in the Laboratory Manual.

Blood samples taken at pre-booster vaccination on Day 1b (Month 0b) and at 1 month post-booster vaccination on Day 30b (Month 1b) will only be analyzed for subjects in the booster immunogenicity subset. Samples from subjects not included in the booster immunogenicity subset will be stored for further analysis.

A higher blood volume for immunogenicity assessment (ie, approximately 9 mL vs. 6 mL) is collected on Day 1b (Month 0b) for all subjects in comparison to the Day 30b (Month 1b) sampling timepoint for all subjects and additional sampling time points for the booster immunogenicity subset to obtain additional serum to be stored for future analysis. This is considered essential in view of the evolving scientific field around dengue vaccine development (see also Section 9.4).

9.1.7.2 Handling of Febrile Illness Cases (Suspected Dengue Cases)

9.1.7.2.1 Parts 1, 2, and 3

Subjects presenting with febrile illness (defined as temperature ≥ 38°C on any 2 of 3 consecutive days) or clinically suspected dengue during the dry-run, Parts 1 and 2 or requiring hospitalization during Part 3 will have 2 blood samples taken to confirm dengue infection, in addition to those taken as part of the clinical care of the subject as outlined in Figure 6.b and detailed in the Laboratory Manual. The first or acute blood sample will be taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever). Testing will include dengue IgM and IgG ELISA, dengue NS1 antigen ELISA, dengue RT-PCR, hematocrit, platelet count and LFTs (AST and ALT). The second or convalescent blood sample will be taken during the convalescent phase of the disease (ie, between 7 and 14 days after the acute sample) and will be tested for dengue IgM/IgG ELISA, hematocrit, platelet count, and LFTs.

Local standards of care may require additional tests, based on clinical presentation and at medical discretion. Additional dengue neutralizing antibody and other laboratory tests may be performed. In addition to blood tests, clinical evaluation will be performed for signs of hemorrhage or plasma leakage as well as any other abnormal signs or symptoms.

In addition, during Part 3, subjects presenting with febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) or clinically suspected dengue and not requiring hospitalization will have 1 blood sample taken for dengue infection confirmation by RT-PCR unless there is an alternate laboratory confirmed etiology. The blood sample will be taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever). Febrile illness cases within 30 days after vaccination will be investigated for the presence of WT or vaccine-derived dengue virus. The testing algorithm is described in the serology plan. Clinical evaluation will be performed for signs of hemorrhage or plasma leakage as well as any other abnormal signs or symptoms. Local standards of care may require additional tests, based on clinical presentation and at medical discretion. Approximate blood volumes and analyses for febrile surveillance are presented in Table 9.a.

A febrile illness as described above will require an interval of at least 14 days from a previous febrile illness to avoid overlap of acute and convalescent visits from 1 episode with those from a second episode.

Table 9.a Blood Volumes and Analyses for Febrile Surveillance

Timing	Blood volume	Assessments
During the dry-run, Parts 1 and 2, and if hospitalization is required during Part 3		
Acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever)	4 mL	RT-PCR, NS1 antigen ELISA, IgM and IgG ELISA
	3-5 mL [(a)]	Hematocrit, platelet count and LFTs (AST and ALT)
Convalescent phase of the disease (ie, between 7 and 14 days after the acute sample)	3 mL	IgM and IgG ELISA
	3-5 mL [(a)]	Hematocrit, platelet count and LFTs (AST and ALT)
During Part 3 without alternate laboratory confirmed etiology and not requiring hospitalization		
Acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever)	3 mL	RT-PCR

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ELISA = enzyme-linked immunosorbent assay; IgG/IgM = Immunoglobulin G/M; LFT = liver function test; NS1 = nonstructural protein 1; RT-PCR = reverse transcriptase polymerase chain reaction
(a) Blood volume may be different as per local laboratory requirements.
Note: Only samples for RT-PCR, NS1 antigen ELISA, IgM ELISA and IgG ELISA will be sent to the central laboratory. Data from central laboratory will not be available for real time case management. Diagnostic tests are to be performed locally as per standard of care for case management.

9.1.7.2.2 Booster Phase (Parts 4 and 5)

Subjects presenting with febrile illness (defined as temperature ≥ 38°C on any 2 of 3 consecutive days) or clinically suspected dengue requiring hospitalization during Parts 4 and 5 will have 2 blood samples taken to confirm dengue infection, in addition to those taken as part of the clinical care of the subject as outlined in Figure 6.d and detailed in the Laboratory Manual. The first or acute blood sample will be taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever). Testing will include dengue IgM and IgG ELISA, dengue NS1 antigen ELISA, dengue RT-PCR, hematocrit, platelet count and LFTs (AST and ALT). The second or convalescent blood sample will be taken during the convalescent phase of the disease (ie, between 7 and 14 days after the acute sample) and will be tested for dengue IgM/IgG ELISA, hematocrit, platelet count, and LFTs. In some circumstances, additional investigations (including additional PCR and viral genome sequencing) will be performed to further characterize the detected infectious dengue virus.

In addition, subjects presenting with febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) or clinically suspected dengue and not requiring hospitalization during Parts 4 and 5 will have 1 blood sample taken for dengue infection confirmation by RT-PCR unless there is an alternate laboratory confirmed etiology. The blood sample will be taken during the acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever). Febrile illness cases within 30 days after vaccination will be investigated for the presence of WT or vaccine-derived dengue virus. The testing algorithm is described in the serology plan. Clinical

evaluation will be performed for signs of hemorrhage or plasma leakage as well as any other abnormal signs or symptoms. Local standards of care may require additional tests, based on clinical presentation and at medical discretion. Approximate blood volumes and analyses for febrile surveillance are presented in Table 9.b.

A febrile illness as described above will require an interval of at least 14 days from a previous febrile illness to avoid overlap of acute and convalescent visits from 1 episode with those from a second episode.

Table 9.b Blood Volumes and Analyses for Febrile Surveillance for all Subjects During the Booster Phase (Parts 4 and 5)

Timing	Blood volume	Assessments
If hospitalization is required		
Acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever)	5 mL	RT-PCR, NS1 antigen ELISA, IgM and IgG ELISA
	4-6 mL [(a)]	Hematocrit, platelet count and LFTs (AST and ALT)
Convalescent phase of the disease (ie, between 7 and 14 days after the acute sample)	4 mL	IgM and IgG ELISA
	4-6 mL [(a)]	Hematocrit, platelet count and LFTs (AST and ALT)
Without alternate laboratory confirmed etiology and not requiring hospitalization		
Acute phase of the disease (ie, as soon as possible and preferably within 5 days after the onset of fever)	4 mL	RT-PCR

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ELISA = enzyme-linked immunosorbent assay; IgG/IgM = Immunoglobulin G/M; LFT = liver function test; NS1 = nonstructural protein 1; RT-PCR = reverse transcriptase polymerase chain reaction
(a) Blood volume may be different as per local laboratory requirements.
Note: Only samples for RT-PCR, NS1 antigen ELISA, IgM ELISA and IgG ELISA will be sent to the central laboratory. Data from central laboratory will not be available for real time case management. Diagnostic tests are to be performed locally as per standard of care for case management.

9.1.7.3 Correlate of Protection

9.1.7.3.1 Parts 1, 2, and 3

The evaluation of the correlate of protection will be based on blood samples taken from the subset and from subjects who are subsequently identified with virologically confirmed dengue fever.

9.1.7.3.2 Booster Phase (Parts 4 and 5)

The evaluation of the correlate of protection will be based on blood samples taken from the booster immunogenicity subset and from subjects who are subsequently identified with virologically confirmed dengue fever.

9.1.8 Safety Assessments

Safety assessments will include collection and recording of solicited local (injection site) and systemic AEs, and unsolicited AEs (serious and non-serious). Solicited AEs and non-serious unsolicited AEs will be collected for the subjects in the subset.

For the booster phase of the trial (Parts 4 and 5), solicited AEs and non-serious unsolicited AEs will be collected for the subjects in the booster immunogenicity subset.

Refer to Section 10.1 for safety definitions. Details on collection and reporting of AEs are in Section 10.4.

9.1.9 Contraception and Pregnancy Avoidance Procedure

9.1.9.1 Parts 1, 2, and 3

For female subjects of child bearing potential, urine or serum pregnancy testing will be performed prior to entry into the dry-run and prior to each vaccination. Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign an assent/consent form (the same form as signed for trial entry) stating that they understand the requirements for avoidance of pregnancy and donation of ova. Refer also to Section 7.2.

9.1.9.2 Booster Phase (Parts 4 and 5)

For female subjects of child bearing potential, urine or serum pregnancy testing will be performed prior to booster vaccination. Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process for the booster phase of the trial and will be asked to sign an assent/consent form (the same form as signed for entry in the booster phase of the trial) stating that they understand the requirements for avoidance of pregnancy and donation of ova. Refer also to Section 7.2.

9.1.10 Pregnancy

To ensure subject safety and the safety of the unborn child, each pregnancy in a subject having received the investigational vaccine must be reported to the Sponsor within 24 hours of the site learning of its occurrence. The pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of safety follow-up for the trial has ended.

Any pregnancy occurring following investigational vaccine administration should be reported immediately, using a pregnancy notification form, to the contact listed in the Investigator Site File.

If pregnancy occurs after administration of a blinded investigational vaccine, the Investigator must inform the subject or parent/guardian of their right to receive trial vaccine information. If

the subject or parent/guardian chooses to receive unblinded trial vaccine information, the individual blind should be broken by the Investigator and procedures must be followed as described in Section 8.5.

9.1.11 Documentation of Subjects who are not Randomized

Investigators must account for all subjects for whom a signed informed consent/assent has been obtained. If a previously enrolled subject is found to be not eligible at Day 1 (Month 0), the Investigator should complete the eCRF. The IVRS/IWRS should be contacted as a notification of non-randomization.

The primary reason for non-randomization is recorded in the eCRF using the following categories:

- AEs prior to receipt of investigational vaccine.
- Screen failure (did not meet inclusion criteria or did meet exclusion criteria).
- Withdrawal by subject and/or subject's parent/guardian.
- Site terminated by Sponsor.
- Study terminated by Sponsor.
- Other (Note: The specific reason[s] should be recorded in the 'specify' field of the eCRF).

Subject numbers assigned to subjects who fail screening or who are withdrawn or discontinued between enrollment and Day 1 (Month 0) should not be reused.

9.1.12 Documentation of Subjects who are not Enrolled in the Booster Phase of the Trial (Parts 4 and 5)

Investigators must account for all subjects for whom a signed informed consent/assent has been obtained for the booster phase of the trial. If a previously enrolled subject for the booster phase of the trial is found to be not eligible at Day 1b (Month 0b), the Investigator should complete the eCRF. The IVRS should be contacted to notify that the subject is not enrolled in the booster phase of the trial.

The primary reason for not enrolling the subject in the booster phase is recorded in the eCRF using the following categories:

- AEs that constitute a contraindication to receipt of the booster dose of investigational vaccine. Refer also to Section 7.3.2.
- Booster screen failure (did not meet inclusion criteria or did meet exclusion criteria for the booster phase of the trial [Parts 4 and 5]).
- Withdrawal by subject and/or subject's parent/guardian.
- Site terminated by Sponsor.
- Study terminated by Sponsor.
- Other (Note: The specific reason[s] should be recorded in the 'specify' field of the eCRF).

9.2 Monitoring Subject Trial Vaccine Compliance

The Investigator must record each administration of trial vaccine (TDV or placebo) into the subject's source documents and eCRF.

9.3 Schedule of Observations and Procedures

The schedule for all trial-related procedures for all evaluations is shown in Section 2.1. Assessments should be completed at the designated visit/time point(s).

9.3.1 Parts 1, 2, and 3

When a site visit cannot be carried out due to the COVID-19 pandemic, alternative methods of contact (eg, telephone contact) will be made for subjects who are still under monitoring for safety reporting.

9.3.1.1 Enrollment (Day 1 [Month 0] or Prior to the Dry-Run) and Vaccination Procedures (Day 1 [Month 0] and Day 90 [Month 3])

All subjects:

- Prior to vaccination:
  - Before performing any other trial procedure, the signed informed consent/assent needs to be obtained (*prior to the dry-run or on Day 1 [Month 0]*). Refer to Section 9.1.1.
  - Collect demographic data (prior to the dry-run or Day 1 [Month 0]), medical history (*prior to the dry-run, Day 1 [Month 0], and Day 90 [Month 3]*), and concomitant medication (*prior to the dry-run, Day 1 [Month 0], and Day 90 [Month 3]*). Refer to Section 9.1.2.
  - Perform a complete physical examination (*prior to the dry-run, Day 1 [Month 0] and Day 90 [Month 3]*). Refer to Section 9.1.5.
  - Perform pregnancy testing (serum or urine) for female subjects of childbearing potential (*prior to the dry-run, Day 1 [Month 0], and Day 90 [Month 3]*). Refer to Section 9.1.10.
  - Check inclusion and exclusion criteria (*prior to the dry-run and on Day 1 [Month 0]*). Refer to Sections 7.1.1 and 7.2.1.
  - Check criteria for delay of second trial vaccination on Day 90 (Month 3). Refer to Section 7.3.1.
  - Check contraindications to second vaccination on Day 90 (Month 3). Refer to Section 7.3.1.
- If subject meets all eligibility criteria:
  - Randomize subject (*Day 1 [Month 0] only*). Refer to Section 9.1.3.
  - Collect blood sample (*Day 1 [Month 0]*). Refer to Section 9.1.7.

Blood should be taken from the subject using aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in Procedures Manuals.

- Vaccinate subject according to the assigned investigational vaccine or placebo (*Day 1 [Month 0] and Day 90 [Month 3]*). Refer to Section 8.1.2.3.
- Observe subject for at least 30 minutes after vaccination (Day 1 [Month 0] and Day 90 [Month 3]).
- The site should schedule the next trial activity clinic visit with the subject and/or the subject's parent/guardian (*Day 1 [Month 0] and Day 90 [Month 3]*).
- The subject and/or the subject's parent/guardian will receive a written reminder of the next planned trial activity (*Day 1 [Month 0] and Day 90 [Month 3]*).

The subject and/or the subject's parent/guardian will be instructed to come to the trial site if the subject experiences febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) for dengue fever evaluation by the Investigator. Refer to Section 9.1.7.2.

The subject and/or the subject's parent/guardian will receive a written reminder of the next planned trial activity. The subject and/or the subject's parent/guardian will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

Additional procedures for the subset (Day 1 [Month 0] and Day 90 [Month 3]):

- Collect blood sample (*Day 90 [Month 3]*) prior to vaccination. Refer to Section 9.1.7.

  Blood should be taken from the subject using aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in Procedures Manuals.
- Perform injection site evaluation. Refer to Section 10.1.2.
- Distribute diary cards and perform following procedures (see also Section 10.4.2):
  - Careful training of the subject and/or the subject's parent/guardian on how to measure local AEs and temperature, how to complete and how often to complete the diary card. Training should be directed at the individual(s) who will perform the measurements of local AEs and those who will enter the information into the diary card. This individual may not be the subject or the subject's parent/guardian, but if a person other than the subject or the subject's parent/guardian enters information into the diary card, this person's identity must be documented in the trial file and this person must receive training on the diary card. Training of the subject or the subject's parent/guardian on how to measure an injection site reaction should be performed while the subject is under observation after vaccination.

Diary card instruction must include the following:

– The subject and/or the subject's parent/guardian must understand that timely completion of the diary card on a daily basis is a critical component to trial participation. The subject and/or the subject's parent/guardian should also be instructed to write clearly and to complete the diary card in pen. Any corrections to the diary card that are performed by the person completing the diary card should include a single strikethrough line with a brief explanation for any change and be initialed and dated.

Please note:

Diary cards will be the only source document allowed for remote collection of solicited local and systemic AEs (including body temperature measurements, preferably by the oral route). The following additional rules apply to the documentation of safety information collected by diary card:

- The diary card should be reviewed with the subject and/or the subject's parent/guardian.
- No corrections or additions to the diary card will be allowed after it is reviewed with the investigator/designee.
- Any data that are identified as implausible or incorrect, and confirmed by the subject and/or the subject's parent/guardian to be a transcription error should be corrected by the subject or the subject's parent/guardian on the diary card (the correction should include a single strikethrough line and should be initialed and dated by the subject and/or the subject's parent/guardian).
- Any blank or illegible fields on the diary card not otherwise corrected as above will be missing in the eCRF.
- The site must enter all readable entries on the diary card into the eCRF.
- Any newly described solicited safety information should be added to the diary card by the subject and initialed and dated. Any new unsolicited safety information would be recorded in the subject source document as a verbally reported event and therefore captured as an AE and recorded in the AE eCRF.
- Starting on the day of vaccination, the subject and/or the subject's parent/guardian will check for specific types of reactions at the injection site (solicited local AEs), any specific generalized symptoms (solicited systemic AEs), body temperature (preferably to be taken orally), any other symptoms or change in the subject's health status, and any medications taken (excluding vitamins and minerals). These solicited AEs and body temperature will be recorded in the diary. Assessments should preferably take place in the evening at day's end.
- Temperature measurement is to be performed using the thermometer provided by the site, and preferably by the oral route. If the subject feels unusually hot or cold during the day, the subject and/or the subject's parent/guardian should check their temperature. If the subject has fever, the highest body temperature observed that day should be recorded on the diary card.

- The measurement of solicited local AEs (erythema and swelling) is to be performed using the ruler provided by the site.
- The collection on the diary card of body temperature (preferably oral) and of solicited systemic AEs will continue for a total of 14 days (day of vaccination + 13 subsequent days) following each vaccine administration. Collection of solicited local AEs will continue for a total of 7 days (day of vaccination + 6 subsequent days) following each vaccine administration.

The collection of unsolicited AEs and medications by interview will be done after 28 days (day of vaccination + 27 subsequent days) following each vaccine administration (ie, at Day 30 [Month 1] and Day 120 [Month 4], as applicable).

After each vaccination, the subject will be observed for at least 30 minutes including observation for unsolicited AEs, solicited AEs, and temperature measurement. Please take the opportunity to remind the subject and/or the subject's parent/guardian how to measure solicited AEs and temperature as part of this observation period. Record all safety data collected in the subject's source documents.

The site should schedule the next trial activity reminder call.

The subject and/or the subject's parent/guardian will receive a written reminder of the next planned trial activity. The subject and/or the subject's parent/guardian will be reminded to complete the diary card daily and to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. All contact details will be provided to the subject and/or the subject's parent/guardian.

9.3.1.2 Clinic Visit for all Subjects after Vaccination (Day 1 [Month 0] and Day 90 [Month 3]) on (Day 30 [Month 1] and Day 120 [Month 4])

All subjects:

- Perform a targeted physical examination. Refer to Section 9.1.5.
- Collect concomitant medication. Refer to Section 9.1.2.
- Collect blood sample at Day 120 (Month 4). Refer to Section 9.1.7.

Blood should be taken from the subject using aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in Procedures Manuals.

The subject and/or the subject's parent/guardian will be instructed to come to the trial site if their child/ward experience febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) for dengue fever evaluation by the Investigator. Refer to Section 9.1.7.2.

The site should schedule the next trial activity clinic visit with subject and/or the subject's parent/guardian.

The subject and/or the subject's parent/guardian will receive a written reminder of the next planned trial activity. The subject and/or the subject's parent/guardian will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

Additional procedures for the subset:

- Collect blood sample at Day 30 (Month 1). Refer to Section 9.1.7.
- Perform an evaluation of the injection site.
- The diary card will be reviewed. The healthcare professional reviewing these data will discuss the solicited AEs (if any) reported by the subject and/or the subject's parent/guardian and will determine if any additional diagnoses and/or AEs are present and/or concomitant medications have been used.
- Unsolicited AEs will be collected by interview.

Please note:

Diary cards will be the only source document allowed for solicited local and systemic AEs (including temperature measurements). The following additional rules apply to the documentation of safety information collected by diary card:

1. No corrections or additions to the diary card will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the diary card not otherwise corrected will be missing in the eCRF.
3. The site must enter all readable entries in the diary card into the eCRF.
4. Any illegible or implausible data should be reviewed with the subject or the subject's parent/guardian.

Any newly described solicited safety information should be added to the diary card by the subject and initialed and dated. Any new unsolicited safety information would be recorded in the subject's source document as a verbally reported event and therefore captured as an AE and recorded in the AE eCRF.

Perform brief symptom-directed physical assessment. Corresponding information is documented in the source documents and eCRFs.

9.3.1.3 Clinic Visits After Vaccination (Day 1 [Month 0] and Day 90 [Month 3]) for Subjects in the Subset of Parts 1, 2, and 3 (Day 270 [Month 9], Day 450 [Month 15], and Every 12 Months Until Completion of Part 3)

- Perform a targeted physical examination. Refer to Section 9.1.5.
- Collect blood sample. Refer to Section 9.1.7.

Blood should be taken from the subject using aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in Procedures Manuals.

The subject and/or the subject's parent/guardian will be instructed to come to the trial site if the subject experiences febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) for dengue fever evaluation by the Investigator. Refer to Section 9.1.7.2.

The subject and/or the subject's parent/guardian will receive a written reminder of the next planned trial activity. The subject and/or the subject's parent/guardian will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

Between 4 years and approximately 4.5 years post-dose 2 in Part 3, the parent/guardian of subjects who are included in the PPS and who were 4 to 11 years of age at the time of randomization in the trial (Day 1 [Month 0]) will be asked to allow their child/ward to receive the booster dose of trial vaccine (TDV or placebo) (see Section 6.1.2 and Section 9.3.2). Regardless of the willingness to participate in the booster phase of this trial, all subjects will continue trial participation for febrile surveillance and safety follow-up. The last protocol-scheduled visit in Part 3 (Day 1545 [Month 51]) will correspond to the first trial visit of the booster phase of the trial if by that time the current protocol amendment has been approved by the IRB/IEC. It is anticipated that some subjects eligible for the booster phase may have or may not have completed Part 3 of the trial by the time the protocol amendment is implemented and it is feasible to enroll them into the booster phase for ethical and scientific reasons. Those subjects may be enrolled into the booster phase provided the IRBs/IECs approved the current protocol amendment, the subjects meet the entry criteria (see Section 7.1.2), and the global enrollment into the booster phase is ongoing. Details on data analysis for subjects who do not complete Part 3 of the trial will be provided in the SAP.

9.3.1.4 Contacts During Surveillance (Dry-Run; Parts 1, 2 and 3)

The subject and/or the subject's parent/guardian will be contacted at least weekly during the dry-run, Parts 1, 2, and 3. Contacts with the subject and/or the subject's parent/guardian will be made through appropriate methods that may differ in each site (eg, phone calls, text messaging, home visits, school-based surveillance). The text messaging system, if used, will be identified and evaluated by the Sponsor before use.

The subject and/or the subject's parent/guardian will be instructed to come to the trial site if the subject experiences febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) for dengue fever evaluation by the Investigator. Each site will identify potential healthcare facilities other than the trial site (including those for hospitalization) in the locality where a subject may visit in case of febrile illnesses. This will enable the identification of subjects who present to a non-trial site, maximizing the detection of febrile illnesses satisfying trial criteria, and facilitating the collection of a sample for dengue infection confirmation by RT-PCR (i.e. as soon as possible and preferably within 5 days after onset of fever). Refer to Section 9.1.7.2.

The subject and/or the subject's parent/guardian will be reminded to contact the trial site if there are any questions and to contact the trial site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to hospitalization or an emergency room visit. All contact details will be given to the subject and/or the subject's parent/guardian.

Between 4 years and approximately 4.5 years post-dose 2 in Part 3, the parent/guardian of subjects who are included in the PPS and who were 4 to 11 years of age at the time of randomization in the trial (Day 1 [Month 0]) will be asked to allow their child/ward to receive the booster dose of trial vaccine (TDV or placebo) (see Section 6.1.2 and Section 9.3.2). Regardless of the willingness to participate in the booster phase of this trial, all subjects will continue trial participation for febrile surveillance and safety follow-up.

9.3.1.5 Follow-up Visit

If a subject is withdrawn or discontinues after vaccination, standard visit procedures should be performed if possible.

9.3.2 Booster Phase (Parts 4 and 5)

When a site visit cannot be carried out due to the COVID-19 pandemic, alternative methods of contact (eg, telephone contact) will be made for subjects who are still under monitoring for safety reporting.

9.3.2.1 Enrollment in the Booster Phase of the Trial (Parts 4 and 5) and Booster Vaccination Procedures (Day 1b [Month 0b])

All subjects:

- Prior to booster vaccination:
  - Before performing any other trial procedure, the signed informed consent/assent for the booster phase of the trial needs to be obtained. Refer to Section 9.1.1.
  - Collect medical history and concomitant medication. Refer to Section 9.1.2.
  - Perform a complete physical examination. Refer to Section 9.1.5.
  - Perform pregnancy testing (serum or urine) for female subjects of childbearing potential. Refer to Section 9.1.10.
  - Check inclusion and exclusion criteria for the booster phase of the trial. Refer to Sections 7.1.2 and 7.2.2.
  - Check criteria for delay of booster vaccination. Refer to Section 7.3.2.
  - Check contraindications to booster vaccination. Refer to Section 7.3.2.
- If subject meets all eligibility criteria:
  - Enroll the subject in the booster phase of the trial. Refer to Section 9.1.4.

– Collect blood sample. Refer to Section 9.1.7.

Blood should be taken from the subject using aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in Procedures Manuals.

- Vaccinate the subject. The booster dose (TDV or placebo) will depend on the assignment on Day 1 (Month 0). Refer to Section 8.1.2.3.
- Observe subject for at least 30 minutes after vaccination.
- The site should schedule the next trial activity clinic visit with the subject and/or the subject's parent/guardian.
- The subject and/or the subject's parent/guardian will receive a written reminder of the next planned trial activity.

The subject and/or the subject's parent/guardian will be instructed to come to the trial site if the subject experiences febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) for dengue fever evaluation by the Investigator. Refer to Section 9.1.7.2.

The subject and/or the subject's parent/guardian will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

Additional procedures for the booster immunogenicity subset (Day 1b [Month 0b]):

- Perform injection site evaluation. Refer to Section 10.1.2.
- Distribute diary cards (see also Section 10.4.2). Perform the same procedures and follow the same instructions as described in Section 9.3.1.1.

Please note:

- The collection on the diary card of body temperature (preferably oral) and of solicited systemic AEs will continue for a total of 14 days (day of booster vaccination + 13 subsequent days) following administration of the booster dose of trial vaccine.
- Collection of solicited local AEs will continue for a total of 7 days (day of booster vaccination + 6 subsequent days) following administration of the booster dose of trial vaccine.
- Assessment of solicited AEs and body temperature should preferably take place in the evening at day's end. If the subject feels unusually hot or cold during the day, the subject and/or the subject's parent/guardian should check their temperature. If the subject has fever, the highest body temperature observed that day should be recorded on the diary card.

The collection of unsolicited AEs and medications by interview will be done after 28 days (day of booster vaccination + 27 subsequent days) following administration of the booster dose of trial vaccine (ie, at Day 30b [Month 1b]).

After booster vaccination, the subject will be observed for at least 30 minutes including observation for unsolicited AEs, solicited AEs, and temperature measurement. Please take the

opportunity to remind the subject and/or the subject's parent/guardian how to measure solicited AEs and temperature as part of this observation period. Record all safety data collected in the subject's source documents.

The site should schedule the next trial activity reminder call.

The subject and/or the subject's parent/guardian will receive a written reminder of the next planned trial activity. The subject and/or the subject's parent/guardian will be reminded to complete the diary card daily and to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. All contact details will be provided to the subject and/or the subject's parent/guardian.

9.3.2.2 Clinic Visit for all Subjects after Booster Vaccination (Day 1b [Month 0b]) on Day 30b (Month 1b)

All subjects:

- Perform a targeted physical examination. Refer to Section 9.1.5.
- Collect concomitant medication. Refer to Section 9.1.2.
- Collect blood sample. Refer to Section 9.1.7.

  Blood should be taken from the subject using aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in Procedures Manuals.

The subject and/or the subject's parent/guardian will be instructed to come to the trial site if the subject experiences febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) for dengue fever evaluation by the Investigator. Refer to Section 9.1.7.2.

The subject and/or the subject's parent/guardian will receive a written reminder of the next planned trial activity. The subject and/or the subject's parent/guardian will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

Additional procedures for the booster immunogenicity subset:

- Perform an evaluation of the injection site. Refer to Section 10.1.2.
- The diary card will be reviewed. The healthcare professional reviewing these data will discuss the solicited AEs (if any) reported by the subject and/or the subject's parent/guardian and will determine if any additional diagnoses and/or AEs are present and/or concomitant medications have been used.
- Unsolicited AEs will be collected by interview.

Please note:

Diary cards will be the only source document allowed for solicited local and systemic AEs (including temperature measurements). The following additional rules apply to the documentation of safety information collected by diary card:

1. No corrections or additions to the diary card will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the diary card not otherwise corrected will be missing in the eCRF.
3. The site must enter all readable entries in the diary card into the eCRF.
4. Any illegible or implausible data should be reviewed with the subject or the subject's parent/guardian.

Any newly described solicited safety information should be added to the diary card by the subject and initialed and dated. Any new unsolicited safety information would be recorded in the subject's source document as a verbally reported event and therefore captured as an AE and recorded in the AE eCRF.

Perform brief symptom-directed physical assessment. Corresponding information is documented in the source documents and eCRFs.

9.3.2.3 Clinic Visits After Booster Vaccination (Day 1b [Month 0b]) for Subjects in the Booster Immunogenicity Subset (Day 180b [Month 6b], Day 395b [Month 13b], and Day 760b [Month 25b]

- Perform a targeted physical examination. Refer to Section 9.1.5.
- Collect blood sample. Refer to Section 9.1.7.

  Blood should be taken from the subject using aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in Procedures Manuals.

The subject and/or the subject's parent/guardian will be instructed to come to the trial site if the subject experiences febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) for dengue fever evaluation by the Investigator. Refer to Section 9.1.7.2.

The subject and/or the subject's parent/guardian will receive a written reminder of the next planned trial activity, as applicable. The subject and/or the subject's parent/guardian will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit.

9.3.2.4 Contacts During Modified Active Surveillance - Booster Phase (Parts 4 and 5)

The subject and/or the subject's parent/guardian will be contacted at least weekly during Parts 4 and 5. Contacts with the subject and/or the subject's parent/guardian will be made through appropriate methods that may differ in each site (eg, phone calls, text messaging, home visits,

school-based surveillance). The text messaging system, if not already in use, will be identified and evaluated by the Sponsor before use.

The subject and/or the subject's parent/guardian will be instructed to come to the trial site if the subject experiences febrile illness (defined as fever ≥38°C on any 2 of 3 consecutive days) for dengue fever evaluation by the Investigator. Each site will identify potential healthcare facilities other than the trial site (including those for hospitalization) in the locality where a subject may visit in case of febrile illnesses. This will enable the identification of subjects who present to a non-trial site, maximizing the detection of febrile illnesses satisfying trial criteria, and facilitating the collection of a sample for dengue infection confirmation by RT-PCR (i.e. as soon as possible and preferably within 5 days after onset of fever). Refer to Section 9.1.7.2.

The subject and/or the subject's parent/guardian will be reminded to contact the trial site if there are any questions and to contact the trial site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to hospitalization or an emergency room visit. All contact details will be given to the subject and/or the subject's parent/guardian.

9.3.2.5 Follow-up Visit

If a subject is withdrawn or discontinues after booster vaccination, standard visit procedures should be performed if possible.

9.3.3 Post-Trial Care

9.3.3.1 Parts 1, 2, and 3

No post-trial care will be provided except for the provision of a licensed vaccine to all subjects irrespective of their full participation in Parts 1, 2, and 3 of this trial. This licensed vaccine will be administered in the time period from at least 6 months after any protocol defined vaccination in Part 1 and before the end of Part 3 or booster vaccination, as applicable. The choice of this vaccine was discussed between the Sponsor and the Investigator, and was approved by the appropriate ethics committee. This vaccine will be used according to the labeling approved in the country. For subjects participating in the booster phase (see Section 9.3.3.2), this licensed vaccine will be administered outside the 14 days (for inactivated vaccines) or 28 days (for live vaccines) period prior to the booster vaccination on Day 1b (Month 0b) (see also Section 7.2.2 and Section 7.3.2).

Subjects in the placebo group not participating in the booster phase of the trial will have the option to receive TDV outside the context of the trial after completion of Part 3 and once TDV is approved in their respective countries.

9.3.3.2 Booster Phase (Parts 4 and 5)

No post-trial care will be provided except for the provision of a licensed vaccine to all subjects, irrespective of their full participation in Parts 4 and 5 of this trial. This licensed vaccine will be offered according to local regulations and administered in the time period from at least 6 months after the protocol defined booster vaccination and before the end of Part 5. The choice of this

vaccine will be discussed between the Sponsor and the Investigator, and will be approved by the appropriate ethics committee. This vaccine will be used according to the labeling approved in the country.

Subjects in the placebo group will have the option to receive TDV outside the context of the trial after completion of Part 5 and once TDV is approved in their respective countries.

9.4 Biological Sample Retention and Destruction

In this trial, specimens for immune response testing will be collected as described in Section 9.1.7. After blood draw and serum processing, the serum samples will be preserved and retained at a central laboratory that was contracted by the Sponsor for this purpose for up to but not longer than 20 years or as required by applicable law. Residual samples after analysis and back up samples may be analyzed to explore correlate of protection or additional research related to the TDV development program. Accountability of all samples will be documented from collection until analysis or destruction. The Sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered an investigational vaccine; it does not necessarily have to have a causal relationship with trial vaccine administration.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the administration of an investigational vaccine whether or not it is considered related to the investigational vaccine.

AEs will be graded by the Investigator in the following manner:

Mild	Grade 1	• Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities. Relieved with or without symptomatic treatment.
Moderate	Grade 2	• Sufficient discomfort is present to cause interference with normal activity. Only partially relieved with symptomatic treatment.
Severe	Grade 3	• Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities. Not relieved with symptomatic treatment

10.1.2 Solicited AEs

10.1.2.1 Parts 1, 2, and 3

The occurrence of selected indicators of safety will be measured/collected in the subset until Day 7 (solicited local reactions) and Day 14 (solicited systemic reactions) following each vaccination (vaccination day included) and will be recorded on the relevant sections of the eCRF as applicable as listed in Table 10.a. These will be summarized in the final report under the category "solicited AEs" to differentiate them from other AEs which were not solicited.

Table 10.a Local and Systemic AEs

Local AEs (injection site) (infant/toddler/child <6 years, child ≥6 years):	Pain Erythema Swelling
Systemic AEs (infant/toddler/child <6 years):	Fever [(a)] Irritability/fussiness Drowsiness Loss of appetite
Systemic AEs (child ≥6 years):	Fever [(a)] Headache Asthenia Malaise Myalgia

(a) Fever is defined as body temperature greater than or equal to 38.0°C (100.4°F) regardless of method taken [18].

The intensity of solicited safety parameters will be assessed in the subset as described in Table 10.b and Table 10.c.

Table 10.b Intensity Scales for Solicited Safety Parameters (Infant/Toddler/Child <6 Years)

AE	Intensity grade	Intensity
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
Erythema at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever [(a)]		Record temperature in °C/°F
Irritability/Fussiness	0	Behavior as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interferes with normal activity
	3	Severe: Crying that cannot be comforted/prevents normal activity
Drowsiness	0	Behavior as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all

(a) Fever is defined as body temperature greater than or equal to 38.0°C (100.4°F) regardless of method taken [18].

Table 10.c Intensity Scales for Solicited Safety Parameters (Child ≥6 Years)

AE	Intensity grade	Intensity
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities
	2	Moderate: Painful when limb is moved and interferes with every day activities
	3	Severe: Significant pain at rest. Prevents normal every day activities
Erythema at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever [(a)]		Record body temperature in °C/°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Asthenia	0	Normal
	1	Mild: Asthenia that is easily tolerated
	2	Moderate: Asthenia that interferes with normal activity
	3	Severe: Asthenia that prevents normal activity
Malaise	0	No symptoms
	1	Mild: Malaise that is easily tolerated
	2	Moderate: Malaise that interferes with normal activity
	3	Severe: Malaise that prevents normal activity
Myalgia	0	No symptoms
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity

(a) Fever is defined as body temperature greater than or equal to 38.0°C (100.4°F) regardless of method taken [18].

10.1.2.2 Booster Phase (Parts 4 and 5)

The occurrence of selected indicators of safety will be measured/collected in the booster immunogenicity subset until Day 7b (solicited local reactions) and Day 14b (solicited systemic reactions) following booster vaccination (booster vaccination day included) and will be recorded on the relevant sections of the eCRF as applicable as listed in Table 10.d. These will be summarized in the final report under the category "solicited AEs" to differentiate them from other AEs which were not solicited.

Table 10.d Local and Systemic AEs – Booster Phase (Parts 4 and 5) (Child ≥6 Years)

Local AEs (injection site):	Pain Erythema Swelling
Systemic AEs:	Fever [(a)] Headache Asthenia Malaise Myalgia

(a) Fever is defined as body temperature greater than or equal to 38.0°C (100.4°F) regardless of method taken [18].

The intensity of solicited safety parameters will be assessed in the booster immunogenicity subset as described in Table 10.c.

10.1.3 SAEs

An SAE is defined as any untoward medical occurrence that:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT in the offspring of a subject.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

10.2 Causality of AEs

Relatedness (causality) to vaccine will also be assessed by the Investigator. The relationship of each AE, including solicited systemic AEs (solicited local AEs are considered as related) to trial vaccine(s) will be assessed using the following categories:

Related:	There is suspicion that there is a relationship between the investigational vaccine and the AE (without determining the extent of probability); there is a reasonable possibility that the investigational vaccine contributed to the AE.
Not Related:	There is no suspicion that there is a relationship between the investigational vaccine and the AE; there are other more likely causes and administration of the investigational vaccine is not suspected to have contributed to the AE.

10.2.1 Relationship to Trial Procedures

Relationship (causality) to trial procedures should be determined for all AEs.

The relationship should be assessed as "Yes" if the Investigator considers that there is reasonable possibility that an event is due to a trial procedure. Otherwise, the relationship should be assessed as "No".

10.2.2 Outcome of AEs

Recovered:	The subject has fully recovered from the event or the condition has returned to the level observed at baseline
Recovering:	The event is improving but the subject is still not fully recovered
Not recovered:	The event is ongoing at the time of reporting and the subject has still not recovered
Recovered with sequelae:	As a result of the AE, the subject suffered persistent and significant disability/incapacity (eg, became blind, deaf or paralysed)
Fatal:	The subject died due to the event. If the subject died due to other circumstances than the event, the outcome of the event per se should be stated otherwise (eg, Not Recovered or Recovering)
Unknown:	If outcome is not known or not reported.

10.3 Additional Points to Consider for AEs

An untoward occurrence generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. Intermittent events for pre-existing conditions or underlying disease should not be considered as AEs.
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require vaccine discontinuation or a change in concomitant medication.

- Be considered unfavorable by the Investigator for any reason.

Diagnoses *vs.* signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, signs or symptoms should be recorded appropriately as an AE(s).

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after starting administration of the trial vaccine, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in trial vaccine, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences changes in severity of an AE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered AEs. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

10.4 Procedures

10.4.1 Collection and Reporting of AEs

All AEs, whether considered related with the use of the investigational vaccine or not, must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. All findings must be reported on an AE eCRF and on the SAE form, if necessary (see Section 10.4.3). All findings in subjects experiencing AEs must also be reported in the subject's source documents. Any unsolicited AEs will be collected in the subset for 28 days after each vaccination during site visits via interview.

The following information will be documented for each event:

- Reported term for the AE.
- Start and end date.
- Serious (Y/N).
- Severity.
- Investigator's opinion of the causality (relationship) between the event and administration of trial vaccine(s) ("related" or "not related").
- Investigator's opinion of the causality (relationship) to trial procedure(s), including the details of the suspected procedure.
- Action taken with the trial treatment (trial vaccine).
- Outcome of event.

10.4.2 Collection and Reporting of Solicited AEs

10.4.2.1 Parts 1, 2, and 3

The occurrence of selected indicators of safety will be collected on diary cards by the subjects in the subset until Day 7 (solicited local reactions) or Day 14 (solicited systemic reactions) following each vaccination (vaccination day included) and will be recorded on the relevant sections of the eCRF, as appropriate. Any solicited local or systemic AE observed as continuing on trial Day 7 (local reactions) or Day 14 (systemic reactions) will be recorded as an unsolicited AE on the AE eCRF. Any solicited local or systemic AE that resolved before that time but which recurs at a later time will be recorded as an unsolicited AE on the AE eCRF.

Any solicited AE that meets any of the following criteria must be entered as an AE on the AE eCRF.

- Solicited local or systemic AEs that lead the subject to withdraw from the trial.
- Solicited local or systemic AEs that lead to the subject being withdrawn from the trial by the Investigator.
- Solicited local and systemic AEs that otherwise meet the definition of an SAE (see Section 10.1.3).

10.4.2.2 Booster Phase (Parts 4 and 5)

The occurrence of selected indicators of safety will be collected on diary cards by the subjects in the booster immunogenicity subset until Day 7b (solicited local reactions) or Day 14b (solicited systemic reactions) following booster vaccination (booster vaccination day included) and will be recorded on the relevant sections of the eCRF, as appropriate. Any solicited local or systemic AE observed as continuing on trial Day 7b (local reactions) or Day 14b (systemic reactions) will be

recorded as an unsolicited AE on the AE eCRF. Any solicited local or systemic AE that resolved before that time but which recurs at a later time will be recorded as an unsolicited AE on the AE eCRF.

Any solicited AE that meets any of the following criteria must be entered as an AE on the AE eCRF.

- Solicited local or systemic AEs that lead the subject to withdraw from the trial.
- Solicited local or systemic AEs that lead to the subject being withdrawn from the trial by the Investigator.
- Solicited local and systemic AEs that otherwise meet the definition of an SAE (see Section 10.1.3).

10.4.3 Collection and Reporting of SAEs

10.4.3.1 Parts 1, 2, and 3

Collection of SAEs will commence from the time that the subject is first administered the investigational vaccine (Day 1 [Month 0]). Routine collection of all SAEs will continue during Parts 1 and 2. During Part 3, investigators will be required to report all deaths as well as SAEs assessed as related, or deemed relevant by the Investigator in the context of vaccine safety.

10.4.3.2 Booster Phase (Parts 4 and 5)

Collection of all SAEs will commence from the time that the subject is administered the booster dose of trial vaccine (TDV or placebo) on Day 1b (Month 0b) and will continue up to the end of the trial.

10.4.3.3 Parts 1, 2, 3, and Booster Phase (Parts 4 and 5)

SAEs should be reported according to the following procedure:

A Sponsor SAE form must be completed, in English, and signed by the Investigator immediately or within 24 hours of first onset or notification of the event. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number.
- Investigator's name.
- Name of the investigational vaccine(s) – if no unblinding is necessary, in a blinded way.
- Causality assessment.

The SAE form should be transmitted within 24 hours to the attention of the contact(s) in the list provided to each site.

10.5 Follow-up Procedures

10.5.1 AEs

All AEs will be monitored until resolution or a stable status is reached or until a formal diagnosis can be made. This could potentially be outside of this trial.

10.5.2 SAEs

If information not available at the time of the first report becomes available at a later date, the Investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, laboratory tests, discharge summary, postmortem results) should be sent to the Sponsor after redaction for privacy.

All SAEs should be followed up until resolution or permanent outcome of the event or is otherwise explained. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.5.3 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The Sponsor or designee will be responsible for the reporting of all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, Investigators and IRBs or IECs, as applicable, in accordance with national regulations. Relative to the first awareness of the event by/or further provision to the Sponsor or designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other SUSARs, unless otherwise required by national regulations. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the trial vaccine administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to their IRB or IEC in accordance with national regulations.

10.5.4 Post-Trial Events

Any AE that occurs outside of the protocol-specified observation period or after the end of the trial but considered to be caused by the investigational vaccine(s) must be reported to the Sponsor. These AEs will be processed by the Sponsor's Pharmacovigilance Department. Instructions for how to submit these AEs will be provided in a handout in the Investigator Site File.

11.0 TRIAL-SPECIFIC REQUIREMENT(S)

11.1 Trial-Specific Committees

11.1.1 Data Monitoring Committee

A Data Monitoring Committee (DMC) will have oversight of this trial. The DMC functions at a program level and further information is available in the DMC Charter. Criteria to classify dengue severity will be defined by the DMC and will be documented in an appendix to the DMC Charter. An Adjudication Committee will assess the severity of individual confirmed dengue cases.

12.0 DATA HANDLING AND RECORD-KEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, System Organ Class [SOC], High Level Group Term, High Level Term, Low Level Term, Preferred Term [PT], and their corresponding descriptive terms). Drugs will be coded using the WHO Drug Dictionary.

12.1 Electronic CRFs (eCRF)

Completed eCRFs are required for each subject for whom a signed informed assent/consent has been obtained.

The Sponsor or its designee will supply investigative sites with access to eCRFs. The Sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These eCRFs are used to transmit the information collected in the performance of this trial to the Sponsor and regulatory authorities. eCRFs must be completed in English. Data are entered directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Sponsor personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The Investigator or designee must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the Investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the trial site during periodic visits by trial monitors. The Sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the trial to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the Sponsor.

When a site visit cannot be carried out due to the COVID-19 pandemic, alternative methods of contact (eg, telephone contact) will be made for subjects who are still under monitoring for safety reporting. Refer also to Section 14.1.

12.2 Record Retention

The Investigator agrees to keep the records stipulated in Section 12.0 and those documents that include (but are not limited to) the trial-specific documents, the identification log of all participating subjects, medical records. Temporary media such as thermal sensitive paper should be copied and certified, source worksheets, all original signed and dated informed consent forms

and assent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copies of eCRFs, including the audit trail, and detailed records of vaccine disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. Furthermore, ICH E6 Section 4.9.5 requires the Investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified, or according to local regulation. In addition, ICH E6 Section 4.9.5 states that the trial records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the Investigator and Sponsor.

Refer to the Clinical Study Site Agreement for the Sponsor's requirements on record retention. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A SAP related to Parts 1, 2, and 3 was prepared and finalized prior to unblinding of subjects' vaccination assignment for the first interim analysis (see Section 13.2.3). This document provides further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

An amendment to the SAP will be prepared and finalized prior to unblinding of subjects' vaccination assignment for the first interim analysis of the booster phase of the trial (Parts 4 and 5) (see Section 13.2.3). This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

Blinded data reviews will be conducted prior to unblinding of subjects' vaccination assignments. These reviews will assess the accuracy and completeness of the trial database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

13.1.1.1 Parts 1, 2, and 3

Safety Set (SS): The SS will consist of all randomized subjects who received at least 1 dose of the trial vaccines (TDV or placebo). For analyses of solicited AEs (reactogenicity) and unsolicited non-serious AEs, only subjects in the subset will be included. For all subjects in the SS, SAEs will be assessed during Parts 1, 2, and 3.

Full Analysis Set (FAS): The FAS will include all randomized subjects who received at least 1 dose of the trial vaccines (TDV or placebo).

Full Analysis Set for Immunogenicity (FASI): The FASI will include all randomized subjects in the subset who received at least 1 dose of the trial vaccines (TDV or placebo) and for whom valid pre-dosing and at least 1 post-dosing blood sample have been received for immunogenicity.

PPS: The PPS will include all subjects in the FAS who have no major protocol violations. The major protocol violation criteria will be defined as part of the blinded data review prior to the unblinding of the subject's trial vaccine assignment. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving the wrong trial vaccine, (3) receiving prohibited therapies, (4) not receiving 2 doses of trial vaccine or receiving the second vaccination inadmissibly outside of the visit window, and (5) other major protocol violations that may be identified during blinded data reviews.

Per-Protocol Set for Immunogenicity (PPSI): The PPSI will consist of all subjects in the FASI who have no major protocol violations.

The primary analysis of VE of 2 doses of TDV in preventing virologically confirmed dengue fever induced by any dengue serotype and occurring from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 1 will be performed on the PPS.

13.1.1.2 Booster Phase (Parts 4 and 5)

Safety Set-Booster (SS-B): The SS-B will consist of all subjects 4 to 11 years of age at the time of randomization in the trial (Day 1 [Month 0]) who are included in the PPS and who received the booster dose of trial vaccine (TDV or placebo). For analyses of solicited AEs (reactogenicity) and unsolicited non-serious AEs, only subjects in the booster immunogenicity subset will be included. For all subjects in the SS-B, SAEs will be assessed during Parts 4 and 5.

Full Analysis Set-Booster (FAS-B): The FAS-B will consist of all subjects 4 to 11 years of age at the time of randomization in the trial (Day 1 [Month 0]) who are included in the PPS and who received the booster dose of trial vaccine (TDV or placebo).

Full Analysis Set for Immunogenicity-Booster (FASI-B): The FASI-B will consist of subjects from the FAS-B who were included in the booster immunogenicity subset and for whom there is a valid pre-booster measurement and at least 1 valid post-booster measurement for immunogenicity assessments.

Per-Protocol Set-Booster (PPS-B): The PPS-B will include all subjects in the FAS-B who have no major protocol violations. The major protocol violation criteria will be defined as part of the blinded data review prior to the unblinding of the subject's trial vaccine assignment. The categories of major protocol violations include: (1) not meeting selected entry criteria for the booster phase (Parts 4 and 5), (2) receiving the wrong booster trial vaccine, (3) receiving prohibited therapies, (4) not receiving the booster dose of trial vaccine or receiving the booster vaccination inadmissibly outside of the visit window, and (5) other major protocol violations that may be identified during blinded data reviews.

Per-Protocol Set for Immunogenicity-Booster (PPSI-B): The PPSI-B will consist of all subjects in the FASI-B who have no major protocol violations.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

13.1.2.1 Parts 1, 2, and 3

Age, gender, race, and other baseline characteristics will be summarized descriptively by group for all randomized subjects, and for each of the analysis sets (ie, SS, FAS, FASI, PPS, and PPSI).

13.1.2.2 Booster Phase (Parts 4 and 5)

Pre-booster baseline characteristics will be summarized descriptively by group for all subjects enrolled in the booster phase of the trial (Parts 4 and 5), and for each of the booster analysis sets (ie, SS-B, FAS-B, FASI-B, PPS-B, and PPSI-B).

13.1.3 Efficacy Analysis

13.1.3.1 Parts 1, 2, and 3

The primary analysis of VE will occur after both of the following 2 criteria for the end of Part 1 are fulfilled: (1) 120 cases of virologically confirmed dengue have accrued, and (2) a minimum

duration of subject follow-up of 12 months post-second vaccination.

For the primary efficacy evaluation, a case of virologically confirmed dengue is defined as febrile illness with a positive serotype-specific RT-PCR and occurring at any time starting from 30 days post-second vaccination (Day 120 [Month 4]) through the end of Part 1. The primary analysis will be performed on the PPS. The primary analysis method will be based on a Cox proportional hazard model with trial group as a factor, adjusted for age, and stratified by region, with 2-sided 95% confidence intervals (CIs) provided for the estimate of VE. The primary efficacy objective is considered to be met if the lower bound of the 95% CI for the VE is above 25%, where VE is defined as $1 – (\lambda_V / \lambda_C)$, where λ_V and λ_C denote the hazard rates for the TDV and placebo arms, respectively. A similar approach will be used to analyze the secondary efficacy endpoints.

Sensitivity analyses of the primary endpoint include: (1) analysis using exact 95% CIs [19], (2) analysis based on the FAS, and (3) analysis including cases of virologically confirmed dengue occurring at any time post-second vaccination (ie, starting on Day 90 ([Month 3]).

Evaluation of secondary efficacy endpoints will be based on the PPS and will be assessed using data from Parts 1 and 2. Secondary VE endpoints will be analyzed using a similar approach as for the primary endpoint described above, except that statistical significance will be concluded if the lower bound of the corresponding CI is > 0. Some of the secondary endpoints will be considered as key secondary endpoints and family-wise type I error will be controlled for these endpoints. These endpoints will only be tested if statistical significance is achieved for the primary endpoint. Details on key secondary endpoints and control of the type I error will be provided in the SAP.

The number and percentage of subjects with virologically confirmed dengue will be summarized in the timeframes post-first vaccination (Day 1 [Month 0]) until the end of Part 2 and between administration of the first vaccination and second vaccination on Day 1 (Month 0) and Day 90 (Month 3), respectively.

13.1.3.2 Booster phase (Parts 4 and 5)

Evaluation of exploratory efficacy endpoints will be based on the PPS-B and will be assessed using data from Parts 4 and 5. Exploratory VE endpoints will be analyzed using a similar approach as for exploratory VE endpoints during Parts 1, 2, and 3.

The number and percentage of subjects with virologically confirmed dengue will be summarized in the timeframes post-booster vaccination (Day 1b [Month 0b]) until the end of Part 5).

Full details will be provided in the SAP.

13.1.4 Vaccine Immunogenicity Analysis

13.1.4.1 Parts 1, 2, and 3

For immunogenicity endpoints including seropositivity rate and GMTs for dengue neutralizing antibodies, descriptive statistics and 95% CIs will be provided by trial group and visit for subjects in the subset.

Seropositivity is defined as a reciprocal neutralizing titer ≥10.

13.1.4.2 Booster Phase (Parts 4 and 5)

For exploratory immunogenicity endpoints including seropositivity rate and GMTs for dengue neutralizing antibodies, descriptive statistics and 95% CIs will be provided by trial group and visit for subjects in the booster immunogenicity subset.

Seropositivity is defined as a reciprocal neutralizing titer ≥10.

For the visit comparisons, GMRs will be summarized descriptively, including 95% CIs.

13.1.5 Correlate of Protection

13.1.5.1 Parts 1, 2, and 3

Immunogenicity data from subjects with confirmed dengue as well as those in the subset will be used to evaluate a potential correlate of protection. As these analyses are exploratory, a number of different approaches may be used.

The primary evaluation of the correlates of protection will be based on all PPS subjects of the subset and virologically confirmed dengue fever cases. Separate analyses are planned across all serotypes as well as based on the individual serotypes as appropriate, though the sample size may be too small to draw conclusions, especially for the less frequent serotypes.

The specific candidate correlate measures to be evaluated will be GMTs computed from the MNT_{50} assay. All analyses will be conducted at the 5% 2-sided significance level. Descriptive analyses will be performed as preliminary to the immune correlates evaluations that examine the distributions of the candidate correlate measures by trial group as well as their association with measurements obtained at baseline.

Two complementary statistical strategies will be used to assess immune correlates of protection. The ability to execute each of these 2 strategies will depend on the nature of the distributions of the candidate correlate measures for each trial group as well as their relationship to measurements obtained at baseline.

The first strategy for assessing immune correlates of protection will aim to establish the candidate correlate measures as mediators of the protective effect of the vaccine. This strategy is based on evaluation of the Prentice Criteria [20] and will be executed by first assessing the candidate correlate measures as immune correlates of risk within each of the randomization groups separately. These evaluations will be performed using relative risk regression models to

relate the candidate measures to risk for clinical disease among vaccinees and among placebo recipients. The second step in this analysis is to evaluate the homogeneity of those correlates of risk regression models across the 2 trial groups and to evaluate the extent to which the observed level of VE is explained by the candidate correlate measures. These evaluations are performed by testing additional terms in the relative risk regression models involving trial group and its interaction with the candidate correlate measures.

The second strategy for assessing immune correlates of protection will aim to establish the candidate correlate measures as causal surrogates for vaccine-induced protection. This strategy is based on causal inference models and focuses on estimation of a VE curve which is a function of the candidate correlate measure. The interpretation of this curve is the protective efficacy of the vaccine for an individual with a given immune response.

Additional details on the analysis of correlate of protection will be provided in the SAP.

13.1.5.2 Booster Phase (Parts 4 and 5)

Details on the analysis of correlate of protection related to the booster phase will be provided in the SAP.

13.1.6 Safety Analysis

13.1.6.1 Parts 1, 2, and 3

All summaries of safety data will be based on subjects in the SS. Unless otherwise specified, the safety data will be summarized by trial group.

Reactogenicity

For subjects in the subset, solicited local AEs (injection site pain, injection site erythema, and injection site swelling) and solicited systemic AEs (child < 6 years: fever, irritability/fussiness, drowsiness and loss of appetite; child ≥ 6 years: asthenia, fever, headache, malaise and myalgia) will be assessed for 7 days and 14 days, respectively, following each vaccination (vaccination day included) via collection of diary cards.

For each solicited AE, the percentage of subjects will be summarized by event severity for each day after each vaccination (Days 1 to 7 for local AEs and Days 1 to 14 days for systemic AEs), and overall. A summary of the first onset of each event will also be provided. The number of days subjects experienced each event will also be summarized for each trial group. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

Unsolicited AEs

Unsolicited AEs (subset only) and SAEs (all subjects) will be coded according to MedDRA and summarized by SOC and PT) for each trial group. AEs leading to withdrawal from the trial will also be summarized.

All unsolicited AEs up to 28 days after each vaccination will be included in the analyses of all AEs. For SAEs and AEs leading to subject withdrawal from the trial (Refer to Section 7.5), Parts 1, 2, and 3 will be included.

In general, unsolicited AEs will be tabulated at each of the following levels: overall summary (subject with at least 1 AE) and by SOC and PT. Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once. Unsolicited AEs will be summarized as follows: by PT including events with frequency greater than 2%; by SOC and PT; by SOC, PT, and severity; and by SOC, PT, and relationship to the investigational vaccine. Unless otherwise specified, unsolicited AEs will be summarized in the following 3 ways: 1) overall up to 28 days post-vaccination, 2) with onset between 1 and 14 days post-vaccination, and 3) with onset between 15 and 28 days post-vaccination.

13.1.6.2 Booster Phase (Parts 4 and 5)

All summaries of safety data from Parts 4 and 5 will be based on subjects in the SS-B. Unless otherwise specified, the safety data will be summarized by trial group.

Reactogenicity

For subjects in the booster immunogenicity subset, solicited local AEs (injection site pain, injection site erythema, and injection site swelling) and solicited systemic AEs (asthenia, fever, headache, malaise and myalgia) will be assessed for 7 days and 14 days, respectively, following booster vaccination (booster vaccination day included) via collection of diary cards.

For each solicited AE, the percentage of subjects will be summarized by event severity for each day after booster vaccination (Days 1 to 7 for local AEs and Days 1 to 14 days for systemic AEs), and overall. A summary of the first onset of each event will also be provided. The number of days subjects experienced each event will also be summarized for each trial group. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

Unsolicited AEs

Unsolicited AEs (booster immunogenicity subset only) and SAEs (all subjects in the booster phase) will be coded according to MedDRA and summarized by SOC and PT) for each trial group. AEs leading to withdrawal from the booster phase of the trial will also be summarized.

All unsolicited AEs up to 28 days after booster vaccination will be included in the analyses of all AEs. For SAEs and AEs leading to subject withdrawal from the booster phase of the trial (Refer to Section 7.5), the Parts 4 and 5 will be included.

In general, unsolicited AEs will be tabulated at each of the following levels: overall summary (subject with at least 1 AE) and by SOC and PT. Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once. Unsolicited AEs will be summarized as follows: by PT including events with frequency greater than 2%; by SOC and PT; by SOC, PT, and severity; and by SOC, PT, and relationship to the investigational vaccine.

Unless otherwise specified, unsolicited AEs will be summarized overall up to 28 days post-booster vaccination.

13.2 Interim Analysis and Criteria for Early Termination

13.2.1 Parts 1, 2, and 3

This is a partially case-driven trial with the primary efficacy analysis planned after the 2 criteria for the end of Part 1 have been fulfilled (see Section 13.1.3).

At the time of primary analysis of VE following the completion of Part 1 of the trial, external vendors (Clinical Research Organizations [CROs]) who are involved in the analyses will be unblinded at an individual subject level in order to analyze and summarize the trial data. Takeda will receive summary tables containing aggregated data by trial group for the primary analysis of Part 1 and at the time of any subsequent analyses. A small group of Takeda personnel will also have access to individual level unblinded data. In order to maintain the double-blind design, investigators, site staff, subjects, as well as Takeda staff and external vendors advising sites on trial conduct will remain blinded to individual subject level trial group allocation for the trial duration. There will be blinded and unblinded trial teams at Takeda and within the external vendors. The blinded team may have access to group unblinded results (eg., publications) but will remain blinded to subject level data for the duration of the trial and will remain responsible for all further activities during trial conduct after unblinding for the primary analysis.

The number of virologically confirmed cases of dengue fever identified by the time of the primary endpoint analysis may not be sufficient to assess less common events such as dengue fever due to a specific serotype or severe dengue. Therefore, it is proposed that active surveillance will continue for an additional 6 months after the analysis of the primary endpoint. Consequently, analysis of the secondary efficacy endpoints would then be based on cases occurring at any time from 1 month after the second vaccination (Day 120 [Month 4]) until 6 months after the end of Part 1 (ie, until the end of Part 2). As a result, data from the additional 6 months surveillance for secondary efficacy endpoints will not be available at the same time as the primary endpoint.

Assuming a 1.0% incidence rate by the end of Part 1 (minimum 12 months after the second vaccination for each subject), it is estimated that approximately 180 evaluable cases will accrue by the end of the additional 6 months of observation (ie, an additional ~60 cases). These additional cases will improve the power for assessment of secondary endpoints, including serotype-specific efficacy.

In addition, the number and percentage of subjects with virologically confirmed dengue, virologically confirmed and hospitalized dengue as well as subjects with fatal SAEs and related SAEs will be summarized for the first half (18 months) and second half (18 months) of Part 3 when such data become available.

13.2.2 Booster Phase (Parts 4 and 5)

At the time of interim analyses for the booster phase of the trial, external vendors (CROs) who are involved in the analyses will be unblinded at an individual subject level in order to analyze and summarize the trial data. Takeda will receive summary tables containing aggregated data by trial group. A small group of Takeda personnel will also have access to individual level unblinded data. In order to maintain the double-blind design, investigators, site staff, subjects, as well as Takeda staff and external vendors advising sites on trial conduct will remain blinded to individual subject level trial group allocation for the trial duration. There will be blinded and unblinded trial teams at Takeda and within the external vendors. The blinded team may have access to group unblinded results (eg, via publications) but will remain blinded to subject level data for the duration of the trial and will remain responsible for all further activities during trial conduct after unblinding for the exploratory analyses.

13.2.3 Interim Analyses and Reporting

Interim analyses are planned for Part 1, Part 2, 2-year follow-up post-second dose, 3-year follow-up post-second dose, at the end of Part 3, 30 days (1 month) post-booster vaccination, and Part 4. A final analysis will be performed upon trial completion (ie, at the end of Part 5).

At the time of this protocol amendment, an Interim CSR has been prepared for the results from the dry-run, Part 1, and Part 2 and a second Interim CSR has been prepared for data until 6 months after the end of Part 2 (2-year follow-up post-second dose). A third interim CSR will be prepared for data until 18 months after the end of Part 2 (3-year follow-up post-second dose). Additional reports for the results from Parts 3, 4, and 5, including further Interim CSRs, will be prepared if required for internal use and/or for regulatory submission. A Final CSR will be prepared upon trial completion and will include results for the trial duration.

13.3 Determination of Sample Size

13.3.1 Parts 1, 2, and 3

This is a partially case-driven trial as described above.

Assuming true VE of 60% and a randomization ratio of 2:1 (TDV:placebo), a total of 120 virologically confirmed cases of dengue fever induced by any dengue serotype occurring from 30 days post-second vaccination (Day 120 [Month 4]) until the end of Part 1 would provide at least 90% power to rule out a vaccine effect of ≤25% (with a 2-sided significance level of 0.05). Assuming a background incidence rate of 1.0% by the end of Part 1 (minimum 12 months after the second vaccination for each subject), randomization of 20,100 subjects in a 2:1 ratio with follow-up for a minimum of 12 months would allow accrual of at least 120 dengue fever cases. Exclusion of subjects from the PPS will be compensated by a potentially longer duration of Part 1.

13.3.2 Booster Phase (Parts 4 and 5)

No formal sample size calculations were performed for the booster phase and the evaluation is exploratory. The booster phase is planned in a subset of the trial subjects based on feasibility considerations and a higher number of subjects will allow estimation of the overall VE and VE in various planned sub-group analyses with higher precision. However, some assumptions were made based on the number of subjects who may be willing to continue in the booster phase. At the time of drafting the protocol amendment, the ongoing trial had approximately 12,500 active PPS subjects in the 4 to 11 years age group. Assuming a 16% dropout, approximately 10,500 subjects are likely to continue in the booster phase. Multiple scenarios of decreasing sample sizes were assessed to estimate the number of dengue fever cases that could be accrued from 30 days post-booster vaccination to the end of Part 4 (with a follow-up period of 12 months) and the associated power, assuming a ratio of 2:1 (TDV:placebo) as on Day 1 (Month 0). These scenarios are summarized in Table 13.a, considering varying true VEs (60% and 70%) and background incidence rates (1% and 2%), with a 2-sided significance level of 0.05 and a lower bound limit of the 95% CI around the estimated VE of 0%.

Table 13.a Number of Virologically Confirmed Dengue Cases Accrued and Power Estimations for Various Scenarios to Demonstrate Booster Effect (Approximately 1 Year Evaluation)

Sample Size [(a)]	Efficacy	Incidence Rate	Cases Accrued	Power (%)
12,500	60%	1%	67	95
		2%	135	99
	70%	1%	60	99
		2%	120	99
11,500	60%	1%	62	93
		2%	124	99
	70%	1%	55	99
		2%	110	99
10,500	60%	1%	56	89
		2%	113	99
	70%	1%	50	98
		2%	100	99
9,500	60%	1%	51	86
		2%	102	99
	70%	1%	45	97
		2%	91	99
8,500	60%	1%	45	85
		2%	91	99
	70%	1%	40	96
		2%	81	99
7,500	60%	1%	40	80
		2%	81	98
	70%	1%	36	91
		2%	72	99

(a) Assuming a ratio of 2:1 (TDV:placebo) as on Day 1 (Month 0), 2-sided significance level of 0.05, and a lower bound limit of the 95% CI around the estimated VE of 0%.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Trial-Site Monitoring Visits

Monitoring visits to the trial site will be made periodically during the trial to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The Investigator and institution guarantee access to source documents by the Sponsor or designee (CRO) and by the IRB or IEC.

All aspects of the trial and its documentation will be subject to review by the Sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, investigational vaccine, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of eCRFs and associated source documents. It is important that the Investigator and other trial personnel are available during the monitoring visits and that sufficient time is devoted to the process.

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification (SDV) or telephone contact may be used to ensure data quality and integrity and maintain subject safety. Alternative monitoring approaches should be used only where allowed by the local Health Authority and when approved by the IRB/IEC. Site staff will inform each trial participant or designated legal representative and ensure that they do not object to the remote review of their records for trial purposes and document this process in the trial participant's medical records. If a trial participant objects to remote review of their records, no remote SDV will occur for that trial participant. During remote monitoring, the monitor should focus on trial activities that are essential to the safety of trial subjects and/or data reliability.

14.2 Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to trial subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the Investigator should consult with the medical monitor (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospective approved deviation) from the inclusion or exclusion criteria.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The trial site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the vaccine is stored and prepared, and any other facility used during the trial. In addition, there is the possibility that this trial may be inspected by regulatory agencies, including those of foreign governments (eg, the US Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical

Devices Agency of Japan). If the trial site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The Investigator and institution guarantee access for quality assurance auditors to all trial documents as described in Section 14.1.

14.4 Trial Risk Management

The ICH E6 addendum (R2) guidance encourages a risk-based approach to the management of clinical trials and includes requirements for risk control and risk reporting. Takeda or designee (CRO) has established Quality Tolerance Limits (QTL), taking into consideration the medical and statistical characteristics of the variables and the statistical design of this trial. This process was performed according to Takeda internal procedures.

At the end of the trial, the quality management approach implemented will be described in the CSR. If applicable, the CSR will summarize important deviations from the predefined QTL and the remedial actions taken.

15.0 ETHICAL ASPECTS OF THE TRIAL

This trial will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonized Tripartite Guideline for GCP. Each Investigator will conduct the trial according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and Investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The Sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained. Those US sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The Sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent/assent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent/assent must be obtained and submitted to the Sponsor or designee before commencement of the trial (ie, before shipment of the Sponsor-supplied Vaccine or trial specific screening activity). The IRB or IEC approval must refer to the trial by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The Sponsor will notify the site once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from the competent authority to begin the trial. Until the site receives notification no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent/assent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the trial at intervals specified by the respective IRB or IEC, and submission of the Investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the Sponsor or designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and Sponsor.

15.2 Subject Information, Informed Consent/Assent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent/assent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the trial. The informed consent form and the subject information sheet (if applicable) further explain the nature of the trial, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The Investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent/assent form and if applicable, the subject authorization form. The informed consent/assent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the Sponsor prior to use.

The informed consent/assent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject and/or subject's parent/guardian. It is the responsibility of the Investigator to explain the detailed elements of the informed consent/assent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject and/or subject's parent/guardian. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's parent/guardian may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's parent/guardian, must be given ample opportunity to: (1) inquire about details of the trial and (2) decide whether or not to participate in the trial. If the subject, or the subject's parent/guardian, determines that the subject will participate in the trial, then the informed consent/assent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's parent/guardian, at the time of consent and prior to the subject's entering into the trial. The subject or the subject's parent/guardian should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The Investigator must also sign and date the informed consent/assent form and subject authorization (if applicable) at the time of consent/assent and prior to subject entering into the trial; however, the Sponsor may allow a designee of the Investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent/assent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the Investigator's site file. The Investigator must document the date the subject signs the informed consent/assent in the subject's medical record and eCRF. Copies of the signed informed consent/assent form, the

signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent/assent forms must be reviewed and signed by relevant subjects or the relevant subject's parent/guardian in the same manner as the original informed consent/assent. The date the revised consent/assent was obtained should be recorded in the subject's medical record and eCRF, and the subject should receive a copy of the revised informed consent/assent form.

15.3 Subject Confidentiality

The Sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this trial, a subject's source data will only be linked to the Sponsor's clinical trial database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, regulatory authorities of an European / European Economic Area Member State, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, electrocardiogram (ECG) reports, admission and discharge summaries for hospital admissions occurring during a subject's trial participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent/assent process (see Section 15.2).

In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification or telephone contact may be used to ensure data quality and integrity and maintain subject safety (refer also to Section 14.1).

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The results of this trial are expected to be published in a scientific journal. It is anticipated that clinical and laboratory co-Investigators will participate in authorship. The order of authorship and choice of journal will be determined by the Investigators and the Sponsor. The data analysis

center for this trial will provide the analyses needed for publication. Information regarding this trial will be posted on ClinicalTrials.gov and the European Union Drug Regulating Authorities Clinical Trials (EudraCT) websites.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, the Sponsor will, at a minimum register all clinical trials conducted in subjects that it sponsors anywhere in the world on ClinicalTrials.gov, EudraCT or other publicly accessible websites before trial initiation. The Sponsor contact information, along with Investigator's city, country, and recruiting status will be registered and available for public viewing.

15.4.3 Clinical Trial Results Disclosure

The Sponsor will post the results of this clinical trial, regardless of outcome, on ClinicalTrials.gov, EudraCT or other publicly accessible websites, as required by applicable laws and/or regulations.

Trial completion corresponds to the date on which the final subject was examined or received an intervention for the purposes of final collection of data (Last Subject Last Visit).

In line with EC Regulation N° 1901/2006, the Sponsor will submit a pediatric trial within six months of their completion and irrespective of whether it is part of a pediatric investigational plan (PIP) (completed or not yet completed) or not, or whether it is intended for submission later on as part of a variation, extension or new stand-alone marketing-authorization application or not.

15.5 Insurance and Compensation for Injury

Each subject in the trial must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the Sponsor or designee will obtain clinical trial insurance against the risk of injury to clinical trial subjects. Refer to the Clinical Study Site Agreement regarding the Sponsor's policy on subject compensation and treatment for injury. If the Investigator has questions regarding this policy, he or she should contact the Sponsor or designee.

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Appendix A Responsibilities of the Investigator

Clinical research trials sponsored by the Sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The Investigator agrees to assume the following responsibilities:

1. Conduct the trial in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that trial related procedures, including trial specific (non-routine/non-standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
5. Secure prior approval of the trial and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the trial to the IRB/IEC, and issue a final report within 3 months of trial completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 56, ICH, and local regulations, are met.
8. Obtain valid informed consent from each subject's parent/guardian who participates in the trial, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the trial. If an informed consent form does not include such a subject authorization, then the Investigator must obtain a separate subject authorization form from each subject or the subject's parent/guardian.
9. Prepare and maintain adequate case histories of all persons entered into the trial, including eCRFs, hospital records, laboratory results, etc., and maintain these data for a minimum of 2 years following notification by the Sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The Investigator should contact and receive written approval from the Sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of Sponsor-supplied vaccines, and return all unused Sponsor-supplied vaccines to the Sponsor.

12. Report AEs to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.
13. In the event of a pregnancy, notify the Sponsor within 24 hours.
14. Review and provide a signature as approval of the content of the CSRs.

Appendix B Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the Investigator, including his or her name, address, and other personally identifiable information. In addition, the Investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of the Investigator for the trial and/or other clinical trials.
- Management, monitoring, inspection, and audit of the trial.
- Analysis, review, and verification of the trial results.
- Safety reporting and pharmacovigilance relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the trial.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other vaccines used in other clinical trials that may contain the same chemical compound present in the investigational vaccine.
- Inspections and investigations by regulatory authorities relating to the trial.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of trial records.
- Posting Investigator site contact information, trial details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in Investigator's own country. The Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject:

1. A statement that the trial involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the trial.
7. A description of the subject's responsibilities.
8. A description of the conduct of the trial.
9. A statement describing the vaccination(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects following vaccine administration that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's parent/guardian is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the trial.
17. The anticipated expenses, if any, to the subject for participating in the trial.
18. An explanation of whom to contact for answers to pertinent questions about the research (Investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's parent/guardian will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
22. A statement that results of pharmacogenomic analysis will not be disclosed to an individual, unless prevailing laws require the Sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the trial may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the trial. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the investigational vaccine(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical trials;
    d) that subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the trial to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

e) that the subject's identity will remain confidential in the event that trial results are published.

25. Female subjects of childbearing potential (eg, non-sterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from Day 1 up to 6 weeks post-second vaccination and post-booster vaccination, as applicable. Pregnancy tests will be performed prior to entry into the dry-run and prior to each vaccination. If a subject is found to be pregnant during trial, the Investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Signature Page for DEN-301 Protocol Amendment 6, Version 8.0, 14 September 2021
Title: Phase III, Double-Blind, Randomized, Placebo-Controlled Trial to Investig

Approval	[redacted] Pharmacovigilance 21-Sep-2021 06:54:02 GMT+0000

Approval	[redacted] Statistics 21-Sep-2021 08:05:03 GMT+0000

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9.8.1 Protocol Changes

Protocol versions included the original protocol (Version 2.0, dated 17 December 2014), Protocol Amendment 1 (Version 3.0, dated 17 November 2015), Protocol Amendment 2 (Version 4.0, 27 August 2018), Protocol Amendment 3 (Version 5.0, dated 28 January 2019), Protocol Amendment 4 (Version 6.0, dated 18 May 2020), Protocol Amendment 5 (Version 7.0, dated 20 April 2021), and Protocol Amendment 6 (Version 8.0, dated 14 September 2021). The protocol and the 6 amendments are included in Appendix 16.1.1, and the amendments are summarized below.

Protocol Amendment 6 (dated 14 September 2021)

This amendment documented a correction to a cross-reference in the exclusion criteria.

Protocol Amendment 5 (dated 20 April 2021)

This amendment documented that alternative monitoring and data verification approaches may be used, due to the COVID-19 pandemic.

Protocol Amendment 4 (dated 18 May 2020)

This amendment documented the following:

- Modification of the trial design to include a booster vaccination in a subgroup of subjects aged 4-11 years at trial entry.

Protocol Amendment 3 (dated 28 January 2019)

This amendment documented the following:

- Modification of the definition of trial completion to clarify that this corresponds to the date on which the final subject is examined or receives an intervention for the purposes of the final collection of data (Last Subject Last Visit).

Protocol Amendment 2 (dated 27 August 2018)

This amendment documented the following:

- Clarification that although group unblinded data are likely to be available in the public domain due to the publication of interim analyses prior to trial completion, any team member involved in any further trial conduct after interim analyses will remain blinded to subject-level group allocation for the duration of the trial, ie, until trial completion.
- Modification and clarification of the CSR plan to document that the following CSRs will be developed[1]:
- An interim CSR for Parts 1 and 2 (including data collected from the dry-run).
- An addendum to the interim CSR to include the first half of Part 3.
- A final CSR to include all trial data after trial completion.

Protocol Amendment 1 (dated 17 November 2015)

This amendment documented the following:

- Change in dosing regimen: based on data from trial DEN-204, which included 1- and 2-dose TDV regimens, the dosing for trial DEN-301, which was initially based on a 1-dose regimen, was modified to a 2-dose regimen to maximize the rate of multivalent post-vaccination seropositivity. At the same time, a booster dose, that had been initially planned in trial DEN-301 conditional on the results of trial DEN-204, was no longer considered necessary and so was removed from the protocol.
- Modification of long-term febrile surveillance methodology: in response to the increased risk of hospitalization with dengue in children ≤5 years reported during the long-term safety follow-up of Dengvaxia [19], the long-term surveillance methodology in trial DEN-301 was changed from enhanced passive surveillance to modified active surveillance in this protocol amendment, in which the frequency of contact was changed from at least once every 3 months in the initial protocol to at least weekly with all febrile episodes assessed for dengue.
- The maximum duration of the dry-run was extended from 6 months to 10 months to give more flexibility to trial sites.
- The minimum duration of Part 1 was modified from an average minimum duration of 12 months to a minimum duration 12 months after second vaccination for each subject. This removed the risk of prolonged enrollment duration leading to a short duration of Part 1 for the last subjects enrolled in the trial.

[1] Note that additional interim CSRs could be prepared if required for regulatory submission(s).

- A secondary objective to assess VE according to baseline dengue serostatus was added in response to observations of the impact of serostatus on vaccine efficacy in efficacy trials of Dengvaxia [20,21].