Title: Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Investigate the Immunogenicity and Safety of Subcutaneous Administration of a Tetravalent Dengue Vaccine Candidate in Healthy Adolescent Subjects in Non-Endemic Area(s) for Dengue

NCT Number: NCT03341637

Protocol Approve Date: 09 March 2019

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Investigate the Immunogenicity and Safety of Subcutaneous Administration of a Tetravalent Dengue Vaccine Candidate in Healthy Adolescent Subjects in Non-Endemic Area(s) for Dengue

Immunogenicity and Safety of TDV in Adolescents in Non-Endemic Area(s)

Sponsor:	Takeda Vaccines, Inc. 40 Landsdowne Street, Cambridge, MA 02139, USA
Trial Identifier:	DEN-315
IND Number:	014292 **EudraCT Number:** Not applicable
Vaccine Name:	• Investigational vaccine: tetravalent dengue vaccine candidate (TDV) comprised of a molecularly characterized, attenuated dengue serotype 2 strain (TDV-2), a dengue serotypes 2/1 chimeric strain (TDV-1), a dengue serotypes 2/3 chimeric strain (TDV-3), and a dengue serotypes 2/4 chimeric strain (TDV-4) • Placebo: saline solution
Date:	09 March 2019
Version:	Version 3.0 (supersedes Version 2.0)

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

Table 1.a Contact Information

Issue	Contact
Serious adverse event and pregnancy reporting	PPD
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 Harmonization of Technical Requirements for Pharmaceuticals E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, but not limited to those related to data privacy and clinical trial disclosure.

SIGNATURES

PPD

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 Harmonization of Technical Requirements for Pharmaceuticals, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, but not limited to those related to data privacy and clinical trial disclosure.
- Regulatory requirements for reporting serious adverse events defined in Section 10.4 of this protocol.
- Terms outlined in the Clinical Trial 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. 2.

1.3.1 Amendment History

Date	Amendment Number	Amendment Type	Region
04 October 2016	Initial Protocol	Not applicable	Global
09 January 2018	1	Non-substantial	Global
09 March 2019	2	Non-substantial	Global

1.3.2 Summary of Changes

Amendment to Protocol Version 2.0, 09 January 2018

Rationale for the Amendment:

This protocol has been amended to update the protocol definition of 'trial completion'.

Other modification:

The administrative trial information has been updated and a minor editorial change has been made.

Details of the changes that have been made in 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	
Title page	Date: 09 ~~January 2018~~ ***March 2019*** Version: Version ~~2.0~~ ***3.0 (supersedes Version 2.0)***	
1.1	**Issue**	**Contact**
	Serious adverse event and pregnancy reporting	PPD

<table>
<tr><th>Section</th><th colspan="2">Description of change</th></tr>
<tr><td>1.1</td><td>Issue</td><td>Contact</td></tr>
<tr><td></td><td>Medical Monitor
(medical advice on conduct of protocol or compound)</td><td rowspan="2">PPD
~~d.~~</td></tr>
<tr><td></td><td>Responsible Medical Officer
(carries overall responsibility for the conduct of the trial)</td></tr>
<tr><td>1.2</td><td colspan="2">PPD</td></tr>
<tr><td>15.4.3</td><td colspan="2">Trial completion corresponds to the date on which the final subject was examined or received an intervention for the purpose~~s~~ of final collection of data ~~for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated~~ (Last Subject Last Visit).</td></tr>
<tr><td>Table 16.a</td><td colspan="2">M=month, MNT_{50}=microneutralization test 50%~~, V3=visit 3~~</td></tr>
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2.0 TRIAL SUMMARY

<table>
<tr><td colspan="2">Name of Sponsor:
Takeda Vaccines, Inc.
40 Landsdowne Street,
Cambridge, MA 02139, USA</td><td colspan="2">Product Name:
Tetravalent Dengue Vaccine Candidate (TDV)</td></tr>
<tr><td colspan="4">Trial Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Investigate the Immunogenicity and Safety of Subcutaneous Administration of a Tetravalent Dengue Vaccine Candidate in Healthy Adolescent Subjects in Non-Endemic Area(s) for Dengue</td></tr>
<tr><td colspan="2">IND No.: 014292</td><td colspan="2">EudraCT No.: Not applicable</td></tr>
<tr><td>Trial Identifier: DEN-315</td><td>Phase: 3</td><td colspan="2">Trial Blinding Schema: Double-Blind</td></tr>
<tr><td colspan="4">Background and Rationale:
Dengue fever is caused by infection with the wild type dengue virus (DENV), a ribonucleic acid 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 are endemic in Asia, Central and South America, the Caribbean, the Pacific Islands, and parts of Africa. There are an estimated 390 million dengue infections per year worldwide, which is more than 3 times the previous World Health Organization (WHO) estimate of 50 to 100 million cases. Every year, around 500,000 cases of dengue hemorrhagic fever (DHF) require hospitalization with an estimated death rate of 2.5%, primarily in children. It is estimated that 3.9 billion people are at risk of dengue infection.

Dengue fever is clinically defined as an acute febrile illness with 2 or more of the following 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 one 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 one 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 signs and symptoms, 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 to reduce the morbidity and mortality associated with dengue disease. Vaccine development has focused on tetravalent vaccines that provide protection against all 4 dengue serotypes simultaneously since all 4 dengue serotypes commonly co-circulate in endemic areas. A first tetravalent dengue vaccine (CYD-TDV) has been recently approved in some countries in Asia and Latin America. However, the initial findings suggest an unfavorable risk-benefit profile for younger subjects with the approved vaccine. Additionally, vaccine efficacy was different between serotypes and depended on dengue pre-exposure status. Hence, there is a continued unmet public health need for safer and more efficacious dengue vaccines.

Tetravalent Dengue Vaccine Candidate (TDV) - Background:
Takeda's TDV consists of 1 molecularly characterized, attenuated dengue serotype 2 virus strain and 3 chimeric recombinant dengue virus strains expressing surface antigens corresponding to dengue serotypes 1–4. The dengue serotype 2 strain (TDV-2) is based upon the attenuated laboratory-derived virus, DENV-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 substituting the structural genes, pre-membrane (prM) and envelope (E), of TDV-2 with the prM and E genes of the wild type (DENV) virus strains, DENV-1 16007, DENV-3 16562 or DENV-4 1036 virus, respectively. Thus, TDV is comprised of 4 dengue virus strains: a molecularly characterized, attenuated dengue serotype 2 strain (TDV-2), a dengue serotypes 2/1</td></tr>
</table>

chimeric strain (TDV-1), a dengue serotypes 2/3 chimeric strain (TDV-3), and a dengue serotypes 2/4 chimeric strain (TDV-4). Non-clinical studies carried out in mice and non-human primates have demonstrated an acceptable safety, immunogenicity, and efficacy profile of Takeda's TDV. Additionally, data from completed phase 1 and phase 2 trials have shown satisfactory reactogenicity, safety and immunogenicity profiles 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. Ongoing and completed phase 2 trials have enabled the selection of a final TDV dose (lyophilized formulation) and a 2-dose vaccination regimen 3 months apart by subcutaneous (SC) injection for use in the pivotal program.

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

Rationale for the Proposed Trial:

In the TDV development program, adolescent subjects have been enrolled in phase 2 trials conducted in dengue endemic and semi-endemic regions to evaluate the safety and immunogenicity of TDV. Adolescent subjects are also enrolled into the ongoing phase 3 trial (DEN-301) which investigates the efficacy, safety and immunogenicity of TDV in dengue endemic regions. However, since dengue exposure increases with age, most of the adolescent subjects in this phase 3 trial are expected to be pre-exposed to dengue. Therefore, although the TDV clinical development program will have a large database of adolescent subjects at the conclusion of the DEN-301 trial, a limited proportion in this age-group is likely to be dengue naive. TDV is being developed as a vaccine for travelers from non-endemic regions intending to travel to endemic regions. Hence, the current trial will enroll adolescent subjects in non-endemic area(s) for dengue, thereby contributing to the database of dengue naive adolescent subjects included in the clinical development program.

The trial will be randomized, double-blind, and placebo-controlled to minimize bias. Subjects with a history of vaccination against or infection with any flavivirus will be excluded to minimize confounding factors. There will be 2 groups in the trial, a TDV group and a placebo (0.9% sodium chloride [NaCl] solution) group. In each trial group, 2 doses of either TDV or placebo will be administered 3 months apart. Outside the context of this trial, a licensed vaccine will be offered to all subjects, irrespective of their full participation in this trial, after the completion of end of trial procedures (Day 270 [Month 9 (M9)]. The choice of this vaccine will be discussed between the Sponsor and the Investigator, and will need to be approved by the appropriate ethics committee. This vaccine will be used according to the labeling approved in the country.

Immunogenicity and safety will be assessed in all subjects in each trial group. As the trial will be conducted in non-endemic areas, a 6-month follow up period post second dose is considered adequate. The immunogenicity assessment for the primary endpoint is planned at 1 month post second dose to coincide with the anticipated peak in post-vaccination antibody titers. An immunogenicity assessment is planned at 6 months post second dose to evaluate the persistence of the immune response to 2 TDV doses.

This trial will be conducted in accordance with the protocol, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice (ICH-GCP) Guidelines and applicable regulatory requirements.

Trial Design:

This is a randomized, double-blind, placebo-controlled, phase 3 trial in 400 healthy adolescent subjects aged 12 to 17 years in non-endemic area(s) for dengue with 2 parallel groups to investigate the immunogenicity and safety of SC administration of a 2-dose regimen of TDV.

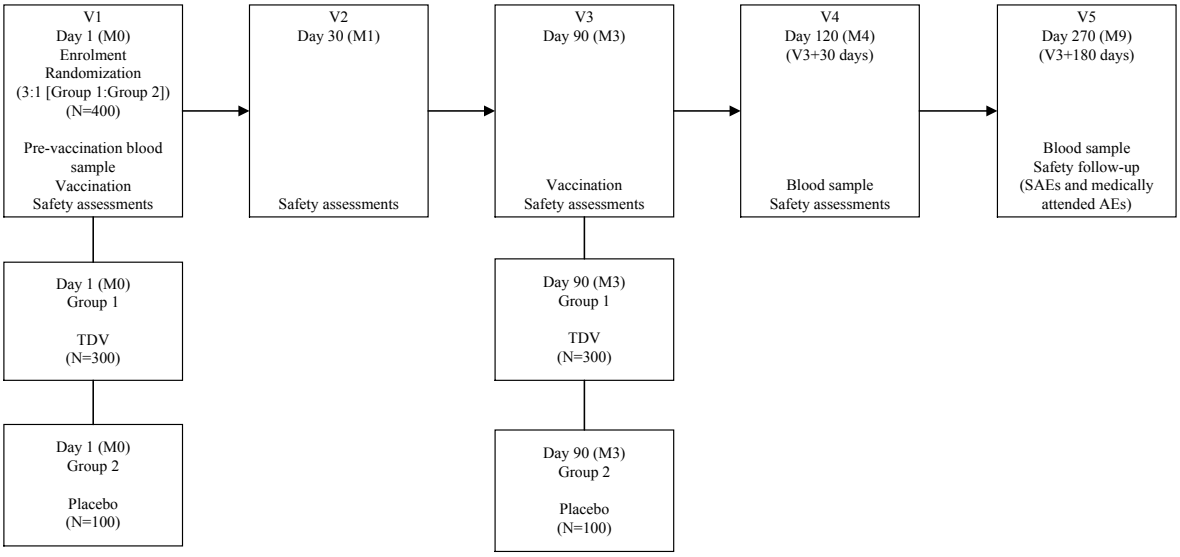
Subjects will be randomized in a 3:1 ratio (TDV [300 subjects]: placebo [100 subjects]), as follows:

- Group 1: SC administration of TDV at Day 1 (Month 0 [M0]) and Day 90 (Month 3 [M3]).
- Group 2: SC administration of placebo at Day 1 (M0) and Day 90 (M3).

All subjects will be followed-up for 6 months post second dose at Day 90 (M3), so the trial duration will be approximately 270 days (9 months) for each subject.

The schematic of the trial design is included as Figure 2.a

Figure 2.a Schematic of Trial Design



M=Month, V=Visit

Immunogenicity evaluation:

Dengue neutralizing antibodies (microneutralization test 50% [MNT_{50}]) will be measured using blood samples collected from all subjects at pre-first dose (Day 1 [M0]), and at 1 month and 6 months post second dose (Day 120 [Month 4 (M4)]) and Day 270 [M9], respectively).

Safety evaluation:

- Diary cards will be distributed for the recording of:
  - Solicited local adverse events (AEs) for 7 days following each TDV/placebo dose on Day 1 (M0) and Day 90 (M3) (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 TDV/placebo dose on Day 1 (M0) and Day 90 (M3) (day of vaccination+13 subsequent days). These will include fever, headache, asthenia, malaise, and myalgia.
- Unsolicited AEs for 28 days following each TDV/placebo dose on Day 1 (M0) and Day 90 (M3) (day of vaccination+27 subsequent days).
- Serious adverse events (SAEs) and medically attended AEs (MAAEs) for the trial duration. MAAEs are defined as AEs leading to a medical visit to or by a healthcare professional including visits to an emergency department, but not fulfilling seriousness criteria.

Data collection will be by electronic Case Report Form (eCRF).

Primary Objective:

- To describe the neutralizing antibody response against each dengue serotype at 1 month post second dose of TDV or placebo in dengue-naive adolescent subjects.

Secondary Objectives:

Immunogenicity:

- To describe the persistence of the immune response at 6 months post second dose of TDV or placebo in dengue-naive adolescent subjects.
- To describe the seropositivity rates for all dengue serotypes at 1 month and 6 months post second dose of TDV or placebo in dengue-naive adolescent subjects, where seropositivity is defined as a reciprocal neutralizing titer ≥10.

Safety:

- To describe the safety profile following a first and second dose of TDV or placebo at Day 1 (M0) and Day 90 (M3), respectively.

Subject Population:

Healthy Subjects: Yes

Planned Minimum Age: 12 years

Planned Maximum Age: 17 years

Planned Number of Subjects: 400 subjects

Planned Number of Arms: Two groups in a 3:1 ratio (300 subjects in Group 1 [TDV] and 100 subjects in Group 2 [placebo])

Estimated Total: 400 randomized subjects

Criteria for Inclusion:

1. The subject is aged 12 to 17 years, inclusive.
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 the clinical judgment of the Investigator.
3. The subject/the subject's legally authorized representative signs and dates a written informed consent/assent form 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. Assent is obtained from the subject where required.
4. Individuals who can comply with trial procedures and are available for the duration of follow-up.

Criteria for Exclusion:

1. Individuals with an elevated oral temperature (≥38°C or 100.4°F) within 3 days of the intended date of vaccination (consider whether applicable as an exclusion criterion or criterion for delay, see below).
2. Known hypersensitivity or allergy to any of the vaccine components (including excipients of the investigational vaccines or placebo).
3. Individuals with behavioral or cognitive impairment or psychiatric disease that, in the opinion of the Investigator, may interfere with the subject's ability to participate in the trial.
4. Individuals with any history of progressive or severe neurologic disorder, seizure disorder or neuro-inflammatory disease (eg, Guillain-Barré syndrome).
5. Individuals with history or any illness that, in the opinion of the Investigator, might interfere with the results of the trial or pose additional risk to the subject due to participation in the trial.

6. Known or suspected impairment/alteration of immune function, including:
   a. 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 (M0) (use of inhaled, intranasal, or topical corticosteroids is allowed).
   b. 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 (M0).
   c. Administration of immunoglobulins and/or any blood products within the 3 months prior to Day 1 (M0) or planned administration during the trial.
   d. Receipt of immunostimulants within 60 days prior to Day 1 (M0).
   e. Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within 6 months prior to Day 1 (M0).
   f. Human immunodeficiency virus (HIV) infection or HIV-related disease.
   g. Genetic immunodeficiency.
7. Abnormalities of splenic or thymic function.
8. Individuals with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
9. Individuals with any serious chronic or progressive disease according to judgment of the Investigator (eg, neoplasm, insulin dependent diabetes, cardiac, renal or hepatic disease).
10. Individuals with body mass index (BMI) greater than or equal to 35 kg/m^2 (=weight in kg/[height in meters^2]).
11. Individuals participating in any clinical trial with another investigational product 30 days prior to Day 1 (M0) or intent to participate in another clinical trial at any time during the conduct of this trial.
12. Individuals who received any other vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment in this trial or who are planning to receive any vaccine within 28 days of trial vaccine administration.
13. Individuals involved in the trial conduct or their first degree relatives.
14. Individuals with history of substance or alcohol abuse within the past 2 years.
15. Female subjects who are pregnant or breastfeeding.
16. 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 (M0).
17. Females of childbearing potential who are sexually active, and who refuse to use an acceptable contraceptive method up to 6 weeks after the last dose of trial vaccine (Day 90 [M3]). In addition, they must be advised not to donate ova during this period.

[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] One or more of the following: hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring), barrier method (condom with spermicide or diaphragm with spermicide) each and every time during intercourse, intrauterine device, monogamous relationship with vasectomized partner (partner must have been vasectomized for at least 6 months prior to Day 1 [M0]). Other contraceptive methods may be considered in agreement with the Sponsor and will be approved by the appropriate ethics committee.

18. Any positive or indeterminate pregnancy test.
19. Previous and planned vaccination (during the trial conduct), against any flaviviruses including dengue, yellow fever (YF), Japanese encephalitis (JE) viruses or tick-borne encephalitis.
20. Previous participation in any clinical trial of a dengue or other flavivirus (eg, West Nile [WN] virus) candidate vaccine, except for subjects who received placebo in those trials.
21. Subjects with documented or suspected disease caused by a flavivirus such as dengue, Zika, YF, JE, WN fever, tick-borne encephalitis or Murray Valley encephalitis.

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

Criteria for Delay of Second Vaccination at Day 90 (M3):

Subjects may encounter clinical circumstances that warrant a delay in the administration of second trial vaccination at Day 90 (M3). These situations are listed below. In the event that a subject meets a criterion for delay of vaccination, the subject may receive trial vaccination once the window for delay has passed as long as the subject is otherwise eligible for trial participation. The decision to vaccinate in those situations will be made by the Investigator.

1. Body temperature ≥38.0°C (≥100.4°F) within 3 days of intended trial 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 trial vaccination.
3. Known or suspected altered or impaired immune function as specified under the exclusion criteria.

Criteria for contraindication to vaccination at Day 90 (M3)

There are also circumstances under which receipt of the second vaccination at Day 90 (M3) is contraindicated in this trial. These circumstances include but are not limited to anaphylaxis or severe hypersensitivity reactions following administration of the first vaccination at Day 1 (M0). If these reactions occur, the subject must not receive the second vaccination at Day 90 (M3), but will be encouraged to continue trial participation for safety follow up.

Trial Vaccine:

Investigational vaccine

The investigational vaccine is TDV, a tetravalent dengue vaccine comprised of 1 molecularly characterized, attenuated dengue virus strain, and 3 chimeric dengue virus strains with potencies of not less than 3.3, 2.7, 4.0 and 4.5 $\log_{10}$ plaque forming units per dose of TDV-1, TDV- 2, TDV-3, and TDV-4, respectively. TDV is a lyophilized vaccine that will be reconstituted in diluent (37 mM NaCl solution) prior to administration. The diluent will be presented in pre-filled syringes.

Placebo

Normal saline solution (0.9% NaCl) for injection.

Duration of the Trial:	**Period of Evaluation:**
The trial duration for each subject will be approximately 270 days (9 months).	For the duration of a subject's participation.

Main Criteria for Evaluation and Analyses:

Primary Endpoint:

- Geometric mean titers (GMT) of neutralizing antibodies (MNT_{50}) for each of the 4 dengue serotypes at 1 month post second dose (Day 120 [M4]).

Secondary Endpoints:

Immunogenicity:

- GMTs of neutralizing antibodies (MNT_{50}) for each of the 4 dengue serotypes at 6 months post second dose (Day 270 [M9]).
- Seropositivity rates (% of subjects seropositive) for each of the 4 dengue serotypes at 1 month and 6 months post second dose (Day 120 [M4]) and Day 270 [M9], respectively).
- Seropositivity rates (% of subjects seropositive) for multiple (2, 3, or 4) dengue serotypes at 1 month and 6 months post second dose (Day 120 [M4]) and Day 270 [M9], respectively).

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

Safety:

- 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) after each TDV/placebo dose on Day 1 (M0) and Day 90 (M3).
- Percentage of subjects with any unsolicited AEs for 28 days (day of vaccination+27 subsequent days) after each TDV/placebo dose on Day 1 (M0) and Day 90 (M3).
- Percentage of subjects with MAAEs and SAEs throughout the trial.

Statistical Considerations:

Analysis sets

Safety set: The safety set will consist of all subjects who received at least 1 dose of trial vaccine.

Full analysis set (FAS): The FAS will include all randomized subjects who received at least 1 dose of trial vaccine and for whom a valid pre-dose and at least 1 valid post-dose blood sample have been received for immunogenicity.

Per-protocol set (PPS): The PPS will exclude all subjects seropositive to any serotype of dengue virus at Baseline (seropositivity is defined as a reciprocal neutralizing titer ≥10) and 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 subject's trial vaccine assignment. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving a wrong trial vaccine, (3) receiving prohibited therapies, (4) not receiving 2 doses of trial vaccine or receiving the second dose inadmissibly outside of the visit window, and (5) other major protocol violations that may be identified during blinded data reviews.

Analysis of demographics and other Baseline characteristics

Age, gender, race, and other Baseline characteristics will be summarized by trial group for all randomized subjects.

Immunogenicity analysis

For primary and secondary immunogenicity endpoints (ie, GMTs of neutralizing antibodies, seropositivity rates for each of the 4 dengue serotypes, and seropositivity rates for multiple dengue serotypes), descriptive statistics and 95% CIs will be provided by trial group for each applicable visit. Seropositivity is defined as a reciprocal neutralizing titer ≥10.

The primary immunogenicity analyses will be based on the PPS; additional immunogenicity analyses may be provided based on the FAS.

Safety analysis

All safety data will be summarized by trial group using the safety set.

Solicited AEs

In all subjects, the presence and severity (Grade) of solicited local (injection site) AEs (pain, erythema, and

swelling) and solicited systemic AEs (fever, asthenia, malaise, headache and myalgia) will be collected for 7 days and 14 days, respectively, following administration of each trial dose (including the day of administration) via collection of diary cards.

For each solicited AE, the number and percentage of subjects with local (injection site) and systemic AEs will be summarized by trial group and event severity for each day after each vaccination (ie, Day 1 through Day 7 for local [injection site] AEs and Day 1 through Day 14 for systemic AEs), and overall. Summaries of first onset of each event and the number of days subjects reported experiencing each event will also be provided. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

Unsolicited AEs

Unsolicited AEs will be assessed for 28 days following administration of each trial dose (day of administration+27 subsequent days).

In all subjects, unsolicited AEs will be coded using 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 trial or trial dose discontinuation or withdrawal will also be summarized.

Unsolicited AEs will be summarized as follows: by PT including events with frequency greater than a pre-defined frequency (the percentage will be specified in the statistical analysis plan); by SOC and PT; by SOC, PT, and severity; and by SOC, PT, and relationship to the trial dose. Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once.

MAAEs

In all subjects, MAAEs will be collected throughout the trial. MAAEs will be coded using MedDRA, and summarized by SOC and PT for each trial group.

SAEs

In all subjects, SAEs will be collected throughout the trial. SAEs will be coded using MedDRA, and summarized by SOC and PT for each trial group.

Sample Size Justification:

As the analysis of this trial is descriptive and is not based on testing formal null hypotheses, the sample size was not determined based on formal statistical power calculations. The sample size is considered sufficient to address the objectives of the trial.

Interim Analysis:

No interim analysis is planned.

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.

DEN-315 Version 3.0 (09 March 2019)

2.1 Schedule of Trial Procedures

Visit number		**V1**	**V2**	**V3**	**V4**	**V5** [a]
Day		**Day 1 M0**	**Day 30 M1**	**Day 90 M3**	**Day 120 (V3+30 days) M4**	**Day 270 (V3+180 days) M9 (ET)**
Visit window (days)		**±0**	**-1/+7**	**-4/+7**	**-1/+7**	**-7/+14**
Informed consent/assent [b]		X				
Assessment of eligibility criteria [c]		X				
Demographics		X				
Medical history		X				
Concomitant medications/vaccinations [d]		X	X	X	X	X
Check criteria for delay of trial vaccination		X		X		
Check contraindications to trial vaccination				X		
Complete physical examination [e]		X		X		
Targeted physical examination [f]			X		X	X
Vital signs [g]		X	X	X	X	X
Pregnancy test [h]		X		X		
Pregnancy avoidance guidance [i]		X	X	X	X	
Randomization		X				
Blood sample for dengue neutralizing antibodies (5 mL) [j]		X			X	X
Trial dose administration [k]		X		X		
Injection site evaluation [l]		X		X		
Diary card [m]	Distribution	X		X		
	Review/collection		X		X	
Unsolicited adverse events (AE) [n]		X	X	X	X	
Serious adverse events (SAE) and AEs leading to subject discontinuation or withdrawal [o]		X	X	X	X	X
Medically attended AEs (MAAE) [o]		X	X	X	X	X

ET=Early Termination; M=month, V=visit

Footnotes:

(a) If the subject terminates early, Day 270 (M9) procedures should be performed.

(b) Up to 28 days prior to the day of randomization.

(c) Review of inclusion/exclusion criteria will be performed prior to administration of the first trial dose at Day 1 (M0). After eligibility is assessed and written informed consent/assent has been obtained, subjects will be randomized to receive either 2 doses of TDV or placebo by subcutaneous (SC) injection.

(d) Any other vaccination against any flavivirus (licensed or investigational, including any other dengue vaccine) during the entire trial period, all concomitant medications, vaccine history from 1 month (minimum 28 days) prior to administration of each trial dose of TDV or placebo up to 1 month (minimum 28 days) thereafter, steroids and immunostimulants within 60 days prior to Day 1 (M0), immunoglobulins and blood products within 3 months prior to Day 1 (M0), and immunosuppressive therapy within 6 months prior to Day 1 (M0).

(e) Physical examination including measurement of vital signs (see footnote [g]), weight and height; body mass index (BMI) will be calculated automatically. Measurement of height is only required at Day 1 (M0).

(f) Subjects may undergo a brief symptom-directed physical examination. Clinically significant changes from the Baseline

examination should be recorded in the subject's source documents and electronic Case Report Form (eCRF).
(g) Vital signs including (but not limited to) the measurement of systolic blood pressure, diastolic blood pressure, heart rate, and body temperature.
(h) Pregnancy testing (serum or urine) for females of childbearing potential. Results must be confirmed and documented as negative prior to each trial dose administration. Additional pregnancy tests may be performed during the trial if deemed necessary by the Investigator. Females of childbearing potential who are sexually active will be reminded during trial visits to adhere to acceptable contraceptive methods up to 6 weeks after the last dose of trial vaccine (Day 90 [M3]).
(i) Females of childbearing potential who are sexually active will be provided with information on acceptable methods of contraception as part of the subject informed consent/assent process and will be asked to sign a consent form/assent form stating that they understand the requirements for avoidance of pregnancy and donation of ova. Subjects will be reminded during trial visits to adhere to acceptable contraceptive methods and not to donate ova up to 6 weeks after the last dose of trial vaccine (Day 90 [M3]).
(j) The blood sample at Day 1 (M0) should be taken prior to administration of the first trial dose. The blood sample at Visit 4 (Day 120 [M4]) should be taken at least 28 days after the second trial dose at Day 90 (M3).
(k) TDV (Group 1) or placebo (Group 2).
(l) Injection site assessed by trial staff for pain, erythema, and swelling for at least 30 minutes following administration of each trial dose.
(m) Diary cards will be distributed for the collection of 1) solicited local (injection site) AEs for 7 days following administration of each trial dose (including the day of administration), and 2) solicited systemic AEs for 14 days following administration of each trial dose (including the day of administration).
The Investigator will categorize all events by severity (mild, moderate or severe), and will assess causality to trial dose administration for solicited systemic events (related or not related).
(n) Unsolicited AEs will be collected for 28 days following administration of each trial dose (including the day of administration) by interview. The Investigator will categorize events by severity (mild, moderate or severe) and will assess causality to trial dose administration (related or not related).
(o) MAAEs, SAEs, and AEs leading to subject discontinuation or withdrawal will be collected for the trial duration. The Investigator will categorize all events by severity (mild, moderate or severe) and will assess causality to trial dose administration (related or not related).

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 Investigator/Coordinating Investigator

The Sponsor will select a Signatory Principal Investigator/Coordinating Investigator from the Investigators who participate in the trial. Selection criteria for this Investigator 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. The Signatory Principal Investigator/Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the trial.

3.3 List of Abbreviations

AE	Adverse event
CRO	Contract research organization
DENV	Wild type dengue virus
DENV-1, -2, -3, -4	Wild type dengue virus serotypes 1, 2, 3, and 4
DHF	Dengue hemorrhagic fever
DMC	Data monitoring committee
DSS	Dengue shock syndrome
E	Envelope
eCRF	electronic Case Report Form
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMT	Geometric mean titer
HIV	Human immunodeficiency virus
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
Inc	Incorporated
IND	Investigational new drug
IRB	Institutional review board
IRT	Interactive response technology
JE	Japanese encephalitis
LAR	Legally authorized representative
M0, 1, 3, 4, 9	Month 0, 1, 3, 4, 9
MAAE	Medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MNT_{50}	Microneutralization test 50%
NaCl	Sodium chloride
PFS	Pre-filled syringe
PPS	Per-protocol set
prM	pre-membrane
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical analysis plan

SC	Subcutaneous
SOC	System Organ Class
SUSAR	Suspected unexpected serious adverse reaction
TDV	Tetravalent dengue vaccine candidate
TDV-1	Dengue serotypes 2/1 chimeric strain
TDV-2	Molecularly characterized, attenuated dengue serotype 2 strain
TDV-3	Dengue serotypes 2/3 chimeric strain
TDV-4	Dengue serotypes 2/4 chimeric strain
WHO	World Health Organization
WN	West Nile
YF	Yellow fever

3.4 Corporate Identification

TV Takeda Vaccines, Inc.

4.0 INTRODUCTION

4.1 Background

Dengue fever is caused by infection with the wild type dengue virus (DENV), a ribonucleic acid 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 are endemic in Asia, Central and South America, the Caribbean, the Pacific Islands, and parts of Africa. There are an estimated 390 million dengue infections per year worldwide, which is more than 3 times the previous World Health Organization (WHO) estimate of 50 to 100 million cases. Every year, around 500,000 cases of dengue hemorrhagic fever (DHF) require hospitalization with an estimated death rate of 2.5%, primarily in children. It is estimated that 3.9 billion people are at risk of dengue infection [1-4].

Dengue fever is clinically defined as an acute febrile illness with 2 or more of the following 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 one 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 one 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 signs and symptoms, 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 to reduce the morbidity and mortality associated with dengue disease [1-7]. Vaccine development has focused on tetravalent vaccines that provide protection against all 4 dengue serotypes simultaneously since all 4 dengue serotypes commonly co-circulate in endemic areas. A first tetravalent dengue vaccine (CYD-TDV) has been recently approved in some countries in Asia and Latin America [8]. However, the initial findings suggest an unfavorable risk-benefit profile for younger subjects with the approved vaccine. Additionally, vaccine efficacy was different between serotypes and depended on dengue pre-exposure status. Hence, there is a continued unmet public health need for safer and more efficacious dengue vaccines [9, 10].

Tetravalent Dengue Vaccine Candidate – Background:

Takeda's Tetravalent Dengue Vaccine Candidate (TDV) consists of 1 molecularly characterized, attenuated dengue serotype 2 virus strain and 3 chimeric recombinant dengue virus strains expressing surface antigens corresponding to dengue serotypes 1–4. The dengue serotype 2 strain (TDV-2) is based upon the attenuated laboratory-derived virus, DENV-2 Primary Dog Kidney (PDK)-53, originally isolated at Mahidol University, Bangkok, Thailand [11]. The chimeric, attenuated vaccine strains for dengue serotypes 1, 3 and 4 were engineered by substituting the structural genes, pre-membrane (prM) and envelope (E), of TDV-2 with the prM and E genes of

the wild type (DENV) virus strains, DENV-1 16007, DENV-3 16562 or DENV-4 1036 virus, respectively [12]. Thus, TDV is comprised of 4 dengue virus strains: a molecularly characterized, attenuated dengue serotype 2 strain (TDV-2), a dengue serotypes 2/1 chimeric strain (TDV-1), a dengue serotypes 2/3 chimeric strain (TDV-3), and a dengue serotypes 2/4 chimeric strain (TDV-4).

Non-clinical studies carried out in mice and non-human primates have demonstrated an acceptable safety, immunogenicity, and efficacy profile of Takeda's TDV. Additionally, data from completed phase 1 and phase 2 trials have shown satisfactory reactogenicity, safety and immunogenicity profiles 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. Ongoing and completed phase 2 trials have enabled the selection of a final TDV dose (lyophilized formulation) and a 2-dose vaccination regimen 3 months apart by subcutaneous (SC) injection for use in the pivotal program.

The current Investigator's Brochure for TDV contains additional product information and a more detailed review of pre-clinical and clinical trials [13].

4.2 Rationale for the Proposed Trial

In the TDV development program, adolescent subjects have been enrolled in phase 2 trials conducted in dengue endemic and semi-endemic regions to evaluate the safety and immunogenicity of TDV. Adolescent subjects are also enrolled into the ongoing phase 3 trial (DEN-301) which investigates the efficacy, safety and immunogenicity of TDV in dengue endemic regions. However, since dengue exposure increases with age, most of the adolescent subjects in this phase 3 trial are expected to be pre-exposed to dengue. Therefore, although the TDV clinical development program will have a large database of adolescent subjects at the conclusion of the DEN-301 trial, a limited proportion in this age-group is likely to be dengue naive. TDV is being developed as a vaccine for travelers from non-endemic regions intending to travel to endemic regions. Hence, the current trial will enroll adolescent subjects in non-endemic area(s) for dengue, thereby contributing to the database of dengue naive adolescent subjects included in the clinical development program.

The trial will be randomized, double-blind, and placebo-controlled to minimize bias. Subjects with a history of vaccination against or infection with any flavivirus will be excluded to minimize confounding factors. There will be 2 groups in the trial, a TDV group and a placebo (0.9% sodium chloride [NaCl] solution) group. In each trial group, 2 doses of either TDV or placebo will be administered 3 months apart. Outside the context of this trial, a licensed vaccine will be offered to all subjects, irrespective of their full participation in this trial, after the completion of end of trial procedures (Day 270 [Month 9 (M9)]. The choice of this vaccine will be discussed between the Sponsor and the Investigator, and will need to be approved by the appropriate ethics committee. This vaccine will be used according to the labeling approved in the country.

Immunogenicity and safety will be assessed in all subjects in each trial group. As the trial will be conducted in non-endemic areas, a 6-month follow up period post second dose is considered

adequate. The immunogenicity assessment for the primary endpoint is planned at 1 month post second dose to coincide with the anticipated peak in post-vaccination antibody titers. An immunogenicity assessment is planned at 6 months post second dose to evaluate the persistence of the immune response to 2 TDV doses.

This trial will be conducted in accordance with the protocol, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice (ICH-GCP) Guidelines and applicable regulatory requirements.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To describe the neutralizing antibody response against each dengue serotype at 1 month post second dose of TDV or placebo in dengue-naive adolescent subjects.

5.1.2 Secondary Objectives

Immunogenicity:

- To describe the persistence of the immune response at 6 months post second dose of TDV or placebo in dengue-naive adolescent subjects.
- To describe the seropositivity rates for all dengue serotypes at 1 month and 6 months post second dose of TDV or placebo in dengue-naive adolescent subjects, where seropositivity is defined as a reciprocal neutralizing titer ≥10.

Safety:

- To describe the safety profile following a first and second dose of TDV or placebo at Day 1 (Month 0 [M0]) and Day 90 (Month 3 [M3]), respectively.

5.2 Endpoints

5.2.1 Primary Endpoint

- Geometric mean titers (GMT) of neutralizing antibodies (microneutralization test 50% [MNT_{50}]) for each of the 4 dengue serotypes at 1 month post second dose (Day 120 [Month 4 (M4)]).

5.2.2 Secondary Endpoints

Immunogenicity:

- GMTs of neutralizing antibodies (MNT_{50}) for each of the 4 dengue serotypes at 6 months post second dose (Day 270 [M9]).
- Seropositivity rates (% of subjects seropositive) for each of the 4 dengue serotypes at 1 month and 6 months post second dose (Day 120 [M4]) and Day 270 [M9], respectively).
- Seropositivity rates (% of subjects seropositive) for multiple (2, 3, or 4) dengue serotypes at 1 month and 6 months post second dose (Day 120 [M4]) and Day 270 [M9], respectively).

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

Safety:

- Frequency and severity of solicited local (injection site) adverse events (AE) for 7 days (day of vaccination+6 subsequent days) and solicited systemic AEs for 14 days (day of vaccination+13 subsequent days) after each TDV/placebo dose on Day 1 (M0) and Day 90 (M3).
- Percentage of subjects with any unsolicited AEs for 28 days (day of vaccination+27 subsequent days) after each TDV/placebo dose on Day 1 (M0) and Day 90 (M3).
- Percentage of subjects with medically attended AEs (MAAE) and serious adverse events (SAE) throughout the trial.

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a randomized, double-blind, placebo-controlled, phase 3 trial in 400 healthy adolescent subjects aged 12 to 17 years in a non-endemic country(ies) for dengue with 2 parallel groups to investigate the immunogenicity and safety of SC administration of a 2-dose regimen of TDV.

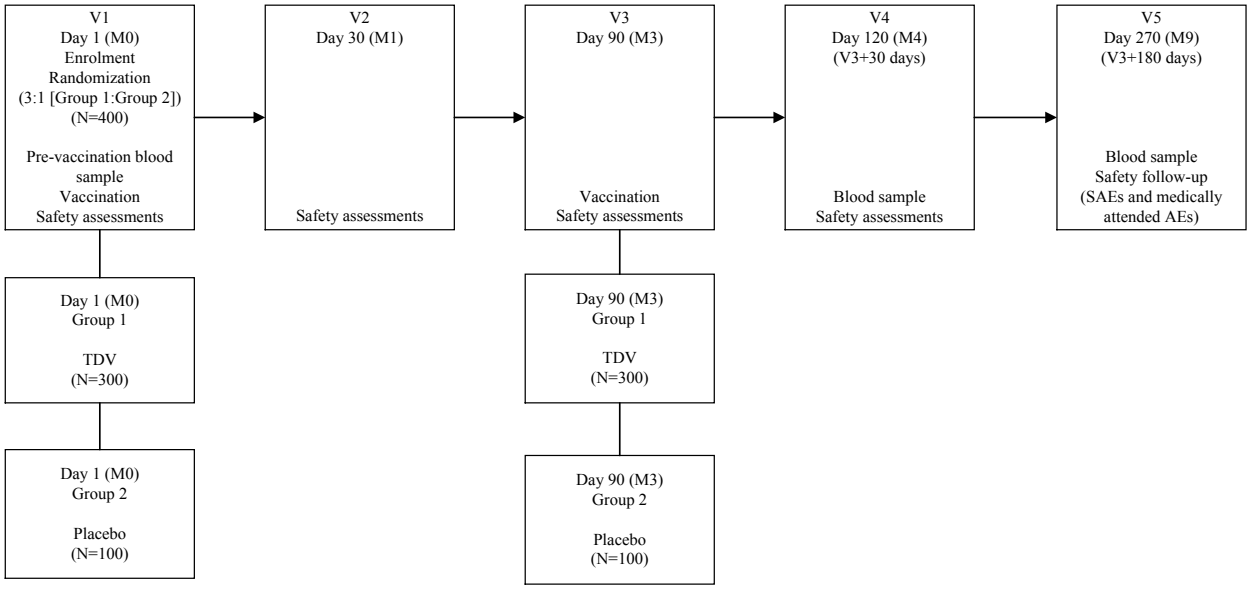
Subjects will be randomized in a 3:1 ratio (TDV [300 subjects]: placebo [100 subjects]), as follows:

- Group 1: SC administration of TDV at Day 1 (M0) and Day 90 (M3).
- Group 2: SC administration of placebo at Day 1 (M0) and Day 90 (M3).

All subjects will be followed-up for 6 months post second dose at Day 90 (M3), so the trial duration will be approximately 270 days (9 months) for each subject.

A schematic of the trial design is included as Figure 6.a. A schedule of trial procedures is provided in Section 2.1.

Figure 6.a Schematic of Trial Design



M=Month, V=Visit

Immunogenicity evaluation:

Dengue neutralizing antibodies (MNT_{50}) will be measured using blood samples collected from all subjects at pre-first dose (Day 1 [M0]), and at 1 month and 6 months post second dose (Day 120 [M4]) and Day 270 [M9], respectively).

Safety evaluation:

- Diary cards will be distributed for the recording of:
  - Solicited local AEs for 7 days following each TDV/placebo dose on Day 1 (M0) and Day 90 (M3) (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 TDV/placebo dose on Day 1 (M0) and Day 90 (M3) (day of vaccination+13 subsequent days). These will include: fever, headache, asthenia, malaise, and myalgia.
- Unsolicited AEs for 28 days following each TDV/placebo dose on Day 1 (M0) and Day 90 (M3) (day of vaccination+27 subsequent days).
- SAEs and MAAEs for the trial duration. MAAEs are defined as AEs leading to a medical visit to or by a healthcare professional including visits to an emergency department, but not fulfilling seriousness criteria.

Data collection will be by electronic Case Report Form (eCRF).

6.2 Justification for Trial Design, Dose, and Endpoints

The trial design and the collection of solicited AEs, unsolicited AEs (non-serious AEs and SAEs), and MAAEs following trial dose administration are consistent with vaccine evaluation trials.

Ongoing and completed phase 2 trials have enabled the selection of a final TDV dose (lyophilized formulation) and a 2-dose vaccination regimen 3 months apart by SC injection for use in the pivotal program.

The timing of the primary and secondary endpoints after vaccination is consistent with previous trials with TDV. Dengue neutralizing antibodies have been generally accepted as the immune response endpoint for dengue vaccine trials.

In order to maintain the double-blind design, a placebo (0.9% NaCl solution) will be used in this trial. Enrollment into the 2 trial groups is unbalanced such that the group receiving TDV is over-represented.

As the trial will be conducted in non-endemic areas for dengue, a 6-month follow-up period after the second trial dose is considered adequate.

The rationale for the proposed trial is given in Section 4.2.

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

The trial duration for each subject will be approximately 270 days (9 months) including trial dose administration (Day 1 [M0] and Day 90 [M3]) and follow-up through Day 270 (M9).

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 one 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.
- The data monitoring committee (DMC) recommends that the trial should be suspended or terminated.
- Significant deviation from 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 deviation from GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the trial, or as otherwise permitted by the contractual agreement.

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, an institutional review board (IRB)/independent ethics committee (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 test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. The subject is aged 12 to 17 years, inclusive.
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 the clinical judgment of the Investigator.
3. The subject/the subject's legally authorized representative (LAR) signs and dates a written, informed consent/assent form 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). Assent is obtained from the subject where required.
4. Individuals who can comply with trial procedures and are available for the duration of follow-up.

7.2 Exclusion Criteria

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

1. Individuals with an elevated oral temperature (≥38°C or 100.4°F) within 3 days of the intended date of vaccination (consider whether applicable as an exclusion criterion or criterion for delay, see Section 7.3).
2. Known hypersensitivity or allergy to any of the vaccine components (including excipients of the investigational vaccines or placebo).
3. Individuals with behavioral or cognitive impairment or psychiatric disease that, in the opinion of the Investigator, may interfere with the subject's ability to participate in the trial.
4. Individuals with any history of progressive or severe neurologic disorder, seizure disorder or neuro-inflammatory disease (eg, Guillain-Barré syndrome).
5. Individuals with history or any illness that, in the opinion of the Investigator, might interfere with the results of the trial or pose additional risk to the subject due to participation in the trial.
6. Known or suspected impairment/alteration of immune function, including:
    a. 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 (M0) (use of inhaled, intranasal, or topical corticosteroids is allowed).
    b. 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 (M0).

c. Administration of immunoglobulins and/or any blood products within the 3 months prior to Day 1 (M0) or planned administration during the trial.
d. Receipt of immunostimulants within 60 days prior to Day 1 (M0).
e. Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within 6 months prior to Day 1 (M0).
f. Human immunodeficiency virus (HIV) infection or HIV-related disease.
g. Genetic immunodeficiency.

7. Abnormalities of splenic or thymic function.
8. Individuals with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
9. Individuals with any serious chronic or progressive disease according to judgment of the Investigator (eg, neoplasm, insulin dependent diabetes, cardiac, renal or hepatic disease).
10. Individuals with body mass index (BMI) greater than or equal to 35 kg/m^2 (=weight in kg/[height in $meters^2$]).
11. Individuals participating in any clinical trial with another investigational product 30 days prior to Day 1 (M0) or intent to participate in another clinical trial at any time during the conduct of this trial.
12. Individuals who received any other vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment in this trial or who are planning to receive any vaccine within 28 days of trial vaccine administration.
13. Individuals involved in the trial conduct or their first degree relatives.
14. Individuals with history of substance or alcohol abuse within the past 2 years.
15. Female subjects who are pregnant or breastfeeding.
16. 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 (M0).
    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 one or more of the following:
        i. Hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring).
        ii. Barrier method (condom with spermicide or diaphragm with spermicide) each and every time during intercourse.
        iii. Intrauterine device.

iv. Monogamous relationship with vasectomized partner (partner must have been vasectomized for at least 6 months prior to Day 1 [M0]).

Other contraceptive methods may be considered in agreement with the Sponsor and will be approved by the appropriate ethics committee.

17. Females of childbearing potential who are sexually active, and who refuse to use an acceptable contraceptive method up to 6 weeks after the last dose of trial vaccine (Day 90 [M3]). In addition, they must be advised not to donate ova during this period.
18. Any positive or indeterminate pregnancy test.
19. Previous and planned vaccination (during the trial conduct), against any flaviviruses including dengue, yellow fever (YF), Japanese encephalitis (JE) viruses or tick-borne encephalitis.
20. Previous participation in any clinical trial of a dengue or other flavivirus (eg, West Nile [WN] virus) candidate vaccine, except for subjects who received placebo in those trials.
21. Subjects with documented or suspected disease caused by a flavivirus such as dengue, Zika, YF, JE, WN fever, tick-borne encephalitis or Murray Valley encephalitis.

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

7.3 Criteria for Delay of Vaccination and/or Blood Sampling

Subjects may encounter clinical circumstances that warrant a delay in the administration of second trial vaccination at Day 90 (M3). These situations are listed below. In the event that a subject meets a criterion for delay of vaccination, the subject may receive trial vaccination once the window for delay has passed as long as the subject is otherwise eligible for trial participation. The decision to vaccinate in those situations will be made by the Investigator.

1. Body temperature ≥38.0°C (≥100.4°F) within 3 days of intended trial 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 trial vaccination.
3. Known or suspected altered or impaired immune function as specified under the exclusion criteria.

Criteria for contraindication to vaccination at Day 90 (M3):

There are also circumstances under which receipt of the second vaccination at Day 90 (M3) is contraindicated in this trial. These circumstances include but are not limited to anaphylaxis or severe hypersensitivity reactions following administration of the first vaccination at Day 1 (M0). If these reactions occur, the subject must not receive the second vaccination at Day 90 (M3), but will be encouraged to continue trial participation for safety follow up.

7.4 Criteria for Early Trial Termination of a Subject

Under some circumstances, a subject's trial participation may be terminated early. This means that no further trial procedures (including data collection) will be performed on that subject beyond the specific date of early termination. The primary reason for early termination of the subject's participation from the trial should be recorded in the eCRF "end of trial visit" page using the following categories. For screen failure subjects, refer to Section 9.1.10.

1. Adverse Event: The subject has experienced an AE (irrespective of being related/unrelated to the trial vaccine or trial-related procedures) that requires early termination because continued participation imposes an unacceptable risk to the subject's health and/or the subject is unwilling to continue participation because of the AE. If the subject is unwilling to continue because of the AE the primary reason for early termination in this case will be "withdrawal due to AE" and not "withdrawal of consent", see below. Any ongoing AEs leading to early termination should be followed by the Investigator until resolution or stabilization.
2. Lost to follow-up: The subject did not return to the clinic and at least 3 attempts to contact the subject (or subject's LAR) were unsuccessful. Attempts to contact the subject must be documented.
3. Withdrawal of consent: The subject (or subject's LAR) wishes to withdraw from the trial. The primary reason for early termination will be "withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (ie, reason other than AE). The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded.
4. Premature trial termination by Sponsor, a regulatory agency, the IEC/IRB, or any other authority.

   If the clinical trial is prematurely terminated by the Sponsor, the Investigator is to promptly inform the trial subjects and local IEC/IRB and should assure appropriate follow up for the subjects. The primary reason for early termination in this case will be "trial termination".
5. Subject's death during trial participation.
6. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.5 Criteria for Premature Discontinuation of Trial Vaccine Administration

Early termination of a subject's participation in the trial will by default prevent the subject from continued trial vaccine administration, as the subject will no longer be participating in the trial. In addition to early termination (see Section 7.4) criteria, other situations may apply in which subjects may continue participating in the trial (e.g., contributing safety data according to protocol) but trial vaccine administration is discontinued selectively. Regardless of the reasons for discontinuation of the trial vaccine administration, this must be documented as protocol deviation. Even if the subject is deemed ineligible to receive trial vaccine, all efforts should be made to continue the collection of safety data according to protocol. In addition, the primary reason for premature discontinuation of trial vaccine administration should be recorded in the eCRF ("end of trial vaccine administration" page) using the following categories:

1. Adverse Event: The subject has experienced an AE (irrespective of being related/unrelated to the trial vaccine or trial-related procedures) for which subsequent trial vaccine administrations impose an unacceptable risk to the subject's health, but the subject may continue trial participation for safety, or a subset of other trial procedures.
2. Lost to follow-up: The subject did not return to the clinic and at least 3 attempts to contact the subject (or subject's LAR) were unsuccessful. Attempts to contact the subject must be documented.
3. Withdrawal of consent: The subject (or subject's LAR) wishes to withdraw from the trial. The primary reason for early termination will be "withdrawal of consent" if the subject withdraws from participation due to a non-medical reason (i.e., reason other than AE). The reason for withdrawal, if provided, should be recorded in the eCRF.
4. Premature trial termination by the Sponsor, a regulatory agency, the IEC/IRB, or any other authority.

   If the clinical trial is prematurely terminated by the Sponsor, the Investigator is to promptly inform the trial subjects and local IEC/IRB and should assure appropriate follow up for the subjects. The primary reason for early termination in this case will be "trial termination".
5. Subject´s death during trial participation.
6. Protocol deviation: A protocol deviation is any change, divergence, or departure from the trial design or procedures of a trial protocol. The subject may remain in the trial unless continuation in the trial jeopardizes the subject's health, safety, or rights (see Section 7.4).
7. Pregnancy: Any subject who, despite the requirement for adequate contraception, becomes pregnant during the trial will not receive further trial vaccine administrations. Pregnant subjects should, however, be asked to continue participating in the trial contributing data to the safety follow-up according to protocol. In addition, the site should maintain contact with the pregnant subject and complete a "Clinical Trial Pregnancy Form" as soon as possible. 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. Data obtained from the "Clinical Trial Pregnancy Form" will be captured in the safety database.

8. Receipt of any other dengue vaccines (investigational or licensed) during the trial.
9. Other

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

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 Trial Vaccines and Materials

The investigational vaccine is TDV, a tetravalent dengue vaccine comprised of 1 molecularly characterized, attenuated dengue virus strain, and 3 chimeric dengue virus strains with potencies of not less than 3.3, 2.7, 4.0 and 4.5 $\log_{10}$ plaque forming units per dose of TDV-1, TDV- 2, TDV-3, and TDV-4, respectively. TDV is a lyophilized vaccine that will be reconstituted in diluent (37 mM NaCl solution) prior to administration. The diluent will be presented in pre-filled syringes (PFS).

Placebo is normal saline solution (0.9% NaCl) for injection.

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

TDV:

CCI

Placebo kits:

The placebo is normal saline for injection (0.9% NaCl). The placebo is presented in 2 mL single dose vials for 0.5 mL dosing. The units will be labeled with a single panel or booklet label that will contain pertinent trial information in local languages. The placebo dose is packaged into single dose dispensing cartons. The cartons will be labeled with a single panel or booklet label that will contain pertinent trial information in local languages.

8.1.2 Storage

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

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used 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. Temperature excursions must be reported to the Sponsor as soon as possible and use of these vaccines requires Sponsor approval.

8.1.3 Dose and Regimen

The trial vaccine doses that will be provided to each trial group are presented in Table 8.a.

The trial vaccines will be prepared and administered by the unblinded pharmacist or vaccine administrator according to the instructions in the Pharmacy Manual or per Sponsor instructions.

Lyophilized TDV will be reconstituted by adding the entire content of the PFS with diluent to the vial containing TDV. Reconstituted TDV will appear as a clear, colorless to yellow solution essentially free of foreign particulate.

The placebo dose will appear as a clear, colorless solution essentially free of foreign particulate.

TDV and placebo will be administered by the SC route.

Table 8.a Sponsor-Supplied Vaccine and Placebo

Group	Number of subjects	Day 1 (M0)	Day 90 (M3)
Group 1	300	TDV, SC	TDV, SC
Group 2	100	Placebo, SC	Placebo, SC

M=Month; SC=subcutaneous

8.2 Trial Vaccine Assignment and Dispensing Procedures

The vaccine to be used will be identifiable by a unique identification number and managed by interactive response technology (IRT). Refer to Section 8.6 for accountability of Sponsor-supplied vaccines.

The Investigator or designee will use the IRT at subject enrollment to obtain the subject number. This number will be used throughout the trial.

The Investigator or designee will use IRT on the day of first dosing (Day1 [M0]) to provide the necessary subject identifying information.

The Investigator or designee will use IRT at each dispensing visit to obtain the vaccination identification number for the vaccine dose.

The Investigator or designee will be responsible for overseeing the administration of vaccine to subjects enrolled in the trial according to the procedures stipulated in this trial protocol. The vaccine will be administered only by an unblinded site administrator or pharmacist who is qualified to perform that function under applicable laws and regulations for that specific trial.

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

Prior to vaccination, a subject must be determined to be eligible for trial vaccination and it must be clinically appropriate in the judgment of the Investigator to vaccinate. Eligibility for vaccination prior to first trial vaccine administration is determined by evaluating the entry criteria outlined in this protocol (Section 7.1 and Section 7.2).

Eligibility for subsequent trial vaccination is determined by the criteria outlined in Section 7.3.

Trial vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines.

Standard immunization practices are to be observed and care should be taken to administer the injection subcutaneously. In addition, WHO recommendations to reduce anxiety and pain at the time of vaccination should be followed [14]. Before administering the vaccine, the vaccination site is to be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. DO NOT inject intravascularly.

As with all injectable vaccines, trained medical personnel and appropriate medical treatment should be readily available in case of anaphylactic reactions following vaccination. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available.

8.3 Randomization Code Creation and Storage

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

8.4 Trial Vaccine Blind Maintenance

The trial will be conducted in a double-blind manner. The investigational vaccine blind will be maintained using IRT. The subjects, data collectors (eg, Investigator), and data evaluators (eg, trial statisticians) are blinded. One or more designated pharmacist's/vaccine administrators at the site will be unblinded. These unblinded designees will maintain the investigational vaccine blind and will have no role in the assessment of subject safety.

8.5 Unblinding Procedure

The trial vaccine blind shall not be broken by the Investigator unless information concerning the trial 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 trial vaccine blind is broken to discuss the need for unblinding.

For unblinding a subject, the trial vaccine blind can be obtained by the Investigator, by accessing the IRT.

The Sponsor's Pharmacovigilance Department must be notified as soon as possible if the trial vaccine blind is broken by the Investigator and the completed SAE form must be sent within 24 hours. 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.

If any subject is unblinded, no further doses of trial vaccine are to be administered and the subject must be withdrawn from the trial.

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

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

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

Upon receipt of Sponsor-supplied vaccines (including TDV diluent), 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 trial vaccines (including TDV diluent) are received within the labeled storage conditions (ie, no cold chain break has occurred during transit), and are in good condition. If quantity and conditions are acceptable, the Investigator or the Investigator designees will acknowledge receipt of the shipment by recording in the IRT.

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 by a qualified Investigator designee.

The Investigator at each site must maintain 100% accountability for all Sponsor-supplied vaccines (including TDV diluent) received and administered during their entire participation in the trial. Proper vaccine accountability includes, but is not limited to:

- Verifying that the actual inventory matches the 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 at each site must record the current inventory of all sponsor-supplied vaccines (TDV and placebo) including TDV diluent on a Sponsor-approved vaccine accountability log. The following information will be recorded at a minimum: protocol number and title, name of

Investigator, site identifier and number, description of Sponsor-supplied vaccines, expiry date and/or retest date, and amount. The log (IRT) 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 destroyed locally or 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 trial vaccines (TDV and placebo) including TDV diluent. 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 Form

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

Informed consent/assent must be obtained prior to the subject entering into the trial, and before any protocol-directed procedures are performed.

A unique subject number will be assigned to each subject after informed consent/assent is obtained from the IRT. If all eligibility criteria are fulfilled, this subject number will be used throughout the trial. Subject numbers assigned to subjects who fail screening should not be reused (Section 9.1.10).

9.1.2 Demographics, Medical History and Prior Medications

Demographic information to be obtained will include age, sex, race, and ethnicity as described by the subject or subject's LAR.

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 medications/vaccinations, concomitant medications/vaccinations, 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/pre-existing problem.

Any other vaccination against any flavivirus (licensed or investigational, including any other dengue vaccine) during the entire trial period will be recorded in the eCRF irrespective of time of administration, and including the vaccine type.

All concomitant medications and vaccine history from 1 month (minimum 28 days) prior to administration of each trial vaccine dose up to 1 month (minimum 28 days) thereafter, steroids and immunostimulants within 60 days prior to Day 1 (M0), immunoglobulins and blood products within 3 months prior to Day 1 (M0), and immunosuppressive therapy within 6 months prior to Day 1 (M0) are to be recorded on the Prior and Concomitant Medications eCRF and in the subject's source document. 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 or the eCRF. Trial vaccination should be delayed if subjects have used antipyretics and/or analgesic medication within 24 hours prior to trial dose 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 (M0).
- Immunosuppressive therapy within 6 months or systemic (eg, oral or parenteral) corticosteroid treatment within 60 days prior to Day 1 (M0) or immunostimulants within 60 days prior to Day 1 (M0).
- Any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to Day 1 (M0) and Day 90 (M3), and 28 days after each trial vaccination.
- Any other dengue vaccines (investigational or licensed) for the entire trial period.
- Receipt of any other clinical trial product for the entire trial period.

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 the informed consent form/assent form.

9.1.3 Documentation of Trial Entrance/Randomization

Only subjects who have signed the informed consent form/assent form, meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance/randomization into the vaccination phase. The randomization schedule will be created and controlled by the IRT provider. The randomization specification will be approved by the Sponsor's trial statistician or designee.

If the subject is found to be ineligible for the vaccination phase, the Investigator should record the primary reason for failure on the subject enrollment log.

9.1.4 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. Complete physical examination will be performed prior to vaccination at Day 1 (M0) and Day 90 (M3). A complete physical examination includes but is not limited to: measurement of vital signs (see Section 9.1.5), weight and height (measurement of height is only required at Day 1 [M0]), auscultation of heart and lungs, palpation of the abdomen, inspection of extremities (including skin over the intended vaccination site), a check of general appearance. Additional physical examinations may be performed if indicated by review of the subject's medical history. The findings should be documented in the subject's source document.

A targeted physical examination including but not limited to measurement of vital signs (see Section 9.1.5) will be performed at Day 30 (Month 1 [M1]), Day 120 (M4), and Day 270 (M9). Clinically significant changes from the Baseline assessment must be recorded in the subject's source documents and the eCRF.

9.1.5 Vital Signs

These will include (but are not limited to) measurement of systolic blood pressure, diastolic blood pressure, heart rate, and body temperature at Day 30 (M1), Day 120 (M4), and Day 270 (M9).

9.1.6 Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected from all subjects at pre-first dose (Day 1 [M0]), and at 1 month and 6 months post second dose (Day 120 [M4)]) and Day 270 [M9], respectively). The maximum volume of blood taken at any single visit is approximately 5 mL, and the approximate total volume of blood for the trial is maximum 15 ml. Refer also to Appendix D.

All samples will be collected in accordance with acceptable laboratory procedures. Blood samples will be processed and stored at the trial site according to the Laboratory Guidelines.

9.1.7 Safety Assessments

Safety assessments will include collection and recording of solicited local (injection site) and systemic AEs, unsolicited AEs (non-serious AEs and SAEs), and MAAEs. Refer to Section 10.1 for safety definitions. Details on collection and reporting of AEs are in Section 10.4.

9.1.8 Contraception and Pregnancy Avoidance Procedure

For female subjects of childbearing potential, pregnancy testing (urine or serum) will be performed prior to vaccination on Day 1 (M0) and Day 90 (M3). Additional pregnancy tests may be performed during the trial if deemed necessary by the Investigator. Females of childbearing potential who are sexually active will be reminded during trial visits to adhere to acceptable contraceptive methods up to 6 weeks after the last dose of trial vaccine (Day 90 [M3]). Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent/assent process and will be asked to sign a consent form/assent form stating that they understand the requirements for avoidance of pregnancy and donation of ova. The Investigator or designee should explain pertinent aspects of the trial in an age appropriate manner to subjects in accordance with local policies. Refer also to Section 7.2.

9.1.9 Pregnancy

To ensure subject safety and the safety of the unborn child, each pregnancy in a subject having received a trial vaccine must be reported to the Sponsor within 24 hours of the site learning of its occurrence. If the subject becomes pregnant during the trial, she will not receive any further doses of any Sponsor-supplied trial vaccine. 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 trial dose administration should be reported immediately, using a pregnancy notification form, to the contact listed in the Investigator Site File.

The Investigator must inform the subject of their right to receive treatment information. If the subject (or subject's LAR) chooses to receive unblinded treatment information, the individual blind should be broken by the Investigator and procedures must be followed as described in Section 8.5.

9.1.10 Documentation of Subjects who are not Randomized

Investigators must account for all subjects who sign an informed consent form/assent form. If the subject is found to be not eligible at Day 1 (M0), the Investigator should complete the eCRF. The IRT supplier should be contacted as a notification of non-randomization.

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

- Screen failure (did not meet one or more inclusion criteria or did meet one or more exclusion criteria).
- Withdrawal by subject.
- Trial terminated by Sponsor.

Subject numbers assigned to subjects who fail screening should not be reused.

9.2 Monitoring Subject Treatment Compliance

The Investigator records all injections of trial vaccine given to the subject in the 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 Pre-Vaccination Procedures (Day 1 [M0] and Day 90 [M3])

1) Before performing any other trial procedure, the signed informed consent form/assent form needs to be obtained (Day 1 [M0]). Refer to Section 9.1.1.
2) Check inclusion and exclusion criteria (Day 1 [M0]). Refer to Section 7.1 and Section 7.2.
3) Collect demographic data (Day 1 [M0]). Refer to Section 9.1.2.
4) Collect medical history (Day 1 [M0]). Refer to Section 9.1.2.

5) Collect concomitant medications/vaccinations. Refer to Section 9.1.2.
6) Perform a complete physical examination. Refer to Section 9.1.4.
7) Check vital signs. Refer to Section 9.1.5.
8) Review of systems: Review of systems is a structured interview that queries the subject or the subject's LAR as to any complaints the subject has experienced across each organ system.
9) Perform pregnancy testing (serum or urine) for female subjects of childbearing potential. Refer to Section 9.1.8.
10) Randomize subject (Day 1 [M0]). Refer to Section 9.1.3.
11) Collect pre-vaccination blood sample (Day 1 [M0]). Refer to Section 9.1.6.

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

9.3.2 Vaccination Procedures (Day 1 [M0] and Day 90 [M3])

1. Check criteria for delay of trial vaccination. Refer to Section 7.3.
2. Check contraindications to trial vaccination (Day 90 [M3]). Refer to Section 9.1.7.
3. Administer trial dose. Refer to Section 8.1.3.

9.3.3 Post-Vaccination Procedures (Day 1 [M0] and Day 90 [M3])

1. Careful training of the subject or the subject's LAR on how to measure local (injection site) AEs and body temperature, how to complete the diary card and how often to complete the diary card. Training should be directed at the individual(s) who will perform the measurements of local (injection site) AEs and those who will enter the information into the diary card. This individual may or may not be the subject or the subject's LAR, but if a person other than the subject or the subject's LAR 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 LAR on how to measure an injection site AE should be performed while the subject is under observation after vaccination.

Diary card instructions must include the following:

- The subject or the subject's LAR must understand that timely completion of the diary card on a daily basis is a critical component of trial participation. The subject or the subject's LAR 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 (injection site) AEs and solicited systemic AEs (including body temperature measurements). The following additional rules apply to the documentation of safety information collected by diary card:

- The diary card should be reviewed with the subject or the subject's LAR.
- 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 LAR to be a transcription error should be corrected by the subject or the subject's LAR 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 LAR).
- 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 or the subject's LAR will check for specific types of events at the injection site (solicited local [injection site] AEs), any specific generalized symptoms (solicited systemic AEs), body temperature (any method), 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 on the diary card. Assessments should preferably take place in the evening at day's end.
- Body temperature measurement is to be performed using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject and/or the subject's LAR 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 (injection site) AEs (pain, erythema, and swelling) is to be performed using the ruler provided by the site.
- The collection on the diary card of solicited local (injection site) AEs, and solicited systemic AEs (including body temperature) will continue for a total of 7 days and 14 days, respectively, following each trial dose administration.

2. Collect and record solicited AEs. Refer to Section 10.1.2.
3. Collect and record unsolicited AEs. Refer to Section 10.4.1.

4. Collect and record SAEs. Refer to Section 10.4.4.
5. Collect and record AEs leading to subject discontinuation or withdrawal. Refer to Section 10.4.1.
6. Collect and record MAAEs. Refer to Section 10.4.3.
7. Provide pregnancy avoidance counseling. Refer to Section 9.1.8.

After administration of each trial dose, the subject will be observed for at least 30 minutes including observation for unsolicited AEs, solicited AEs, and body temperature measurement. Information should be recorded in the electronic data capture (EDC) system. The Investigator or delegate will take the opportunity to remind the subject or the subject's LAR how to measure solicited AEs and body temperature as part of this observation period. All safety data will be collected in the subject's source documents.

The site should schedule the next trial activity with the subject or the subject's LAR.

The subject or the subject's LAR will receive a written reminder of the next planned trial activity. The subject or the subject's LAR 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 or is otherwise perceived as serious. All contact details will be provided to the subject or subject's LAR.

9.3.4 Clinic Visits after Vaccination (Day 30 [M1], Day 120 [M4], and Day 270 [M9])

Note: Visits on Day 30 (M1) and Day 120 (M4) should occur 30 days (at least 29 days) after the first and second trial vaccination at Day 1 (M0) and Day 90 (M3), respectively.

1. Collect concomitant medications/vaccinations. Refer to Section 9.1.2.
2. Perform a targeted physical examination. Refer to Section 9.1.4.
3. Check vital signs. Refer to Section 9.1.5.
4. Collect and record unsolicited AEs (Day 30 [M1] and Day 120 [M4]). Refer to Section 10.4.1.
5. Collect and record SAEs. Refer to Section 10.4.4.
6. Collect and record AEs leading to subject discontinuation or withdrawal. Refer to Section 10.4.1.
7. Collect and record MAAEs. Refer to Section 10.4.3.
8. Provide pregnancy avoidance counseling (Day 30 [M1] and Day 120 [M4]). Refer to Section 9.1.8.
9. Collect a blood sample (Day 120 [M4] and Day 270 [M9]). Refer to Section 9.1.6.

Blood should be taken from the subject using an aseptic venipuncture technique for serological immunogenicity testing. Refer to the detailed collection and handling procedures outlined in the Procedures Manual.

The site should schedule the next trial activity with the subject or the subject's LAR, as applicable.

The subject or the subject's LAR will receive a written reminder of the next planned trial activity, as applicable. The subject or the subject's LAR 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 or is otherwise perceived as serious.

9.3.5 Final (End of Trial) Visit

The Final Visit will be made at Day 270 [M9]. If a subject terminates earlier, end of trial visit procedures should be performed if possible. For all subjects receiving trial vaccine or placebo, the Investigator must complete the "End of Trial" eCRF page.

9.3.6 Post-Trial Care

No post-trial care will be provided.

9.4 Biological Sample Retention and Destruction

In this trial, specimens for immune response testing will be collected as described in Section 9.1.6. After blood draw and serum processing, the serum samples will be preserved and retained at a central laboratory contracted by the Sponsor for this purpose for up to but no longer than 20 years or as required by applicable law. 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.

Serum samples will be used for the analyses defined in this protocol, but can also, with permission from the subject or subject's LAR, be used to assess, improve or develop tests related to the disease(s) or the vaccine(s) under trial that will allow more reliable measurement of the response to the vaccine(s).

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a trial 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 (e.g., a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the administration of a trial vaccine whether or not it is considered related to the trial 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 Adverse Events

The occurrence of selected indicators of safety as listed in Table 10.a will be measured/collected for 7 days (solicited local [injection site] AEs) and 14 days (solicited systemic AEs) following administration of each trial vaccine dose (including the day of administration) and will be recorded on the "Local and Systemic AEs" eCRF, as applicable. These will be summarized in the final report under the category "solicited AEs" to differentiate them from other AEs which were not solicited. Any solicited local or systemic AE observed as continuing 8 days and 15 days, respectively, following each trial vaccination will be recorded as an unsolicited AE on the "AE" eCRF.

Table 10.a Solicited Local and Systemic Adverse Events

Solicited local (injection site) AEs:	Pain
	Erythema
	Swelling
Solicited systemic AEs:	Fever [(a)]
	Headache
	Asthenia
	Malaise
	Myalgia

(a) Fever is defined as greater than or equal to 38°C (100.4°F) regardless of method taken [15].

The severity of solicited safety parameters will be assessed as described in Table 10.b.

Table 10.b Severity Scales for Solicited Safety Parameters

Adverse Event	Severity grade	Severity
Pain at injection site	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity with or without treatment
	3	Severe: Prevents daily activity with or without treatment
Erythema at injection site [(a)]	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Swelling at injection site [(a)]	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Headache	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity with or without treatment
	3	Severe: Prevents normal activity with or without treatment
Asthenia	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Malaise	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Myalgia	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity
	3	Severe: Prevents daily activity
Fever [(b)]	Record body temperature in °C/°F	

(a) Subjects are to record greatest surface diameter in mm on the diary card.
(b) Fever is defined as greater than or equal to 38°C (100.4°F) regardless of method taken [15].

10.1.3 Medically Attended Adverse Events

MAAEs are defined as AEs leading to a medical visit to or by a healthcare professional including visits to an emergency department, but not fulfilling seriousness criteria.

10.1.4 Serious Adverse Events

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 Adverse Events

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

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

Resolved:	The subject has fully recovered from the event or the condition has returned to the level observed at Baseline.
Resolving:	The event is improving but the subject is still not fully recovered.
Not resolved:	The event is ongoing at the time of reporting and the subject has still not recovered.
Resolved 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 resolved or resolving).
Unknown:	If outcome is not known or not reported.

10.3 Additional Points to Consider for Adverse Events

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 AEs.

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 form/assent form 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 Adverse Events

All AEs, whether considered related to the use of the trial 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 10.4.2). All findings in subjects experiencing AEs must also be reported in the subject's source documents. Any unsolicited AEs for 28 days (day of vaccination+27 subsequent days) following each TDV/placebo dose will be collected during site visits by 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 vaccines ("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 Adverse Events

The occurrence of selected indicators of safety will be collected on diary cards by the subject/LAR for 7 days (solicited local [injection site] AEs) and 14 days (solicited systemic AEs) following administration of each trial vaccine dose (including the day of administration) and will be recorded on the "Local and Systemic AEs" eCRF, as appropriate. Any solicited local (injection site) or systemic AE observed as continuing 8 days and 15 days, respectively, following each trial dose administration, will be recorded as an unsolicited AE on the AE eCRF. Any solicited local (injection site) or systemic AE that resolved before 8 days and 15 days, respectively, following each trial dose administration, but which recurs at a later time (ie, if discontinues), 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 (injection site) or systemic AEs that lead the subject to withdraw from the trial.
- Solicited local (injection site) or systemic AEs that lead to the subject being withdrawn from the trial by the Investigator.
- Solicited local (injection site) and systemic AEs that otherwise meet the definition of an SAE (see Section 10.1.2).

10.4.3 Collection and Reporting of Medically Attended Adverse Events

MAAEs occurring from first vaccination at Day 1 (M0) until the end of the trial (Day 270 [M9]) will be collected during site visits by interview and must be recorded as an AE on the AE eCRF.

10.4.4 Collection and Reporting of Serious Adverse Events

Collection of SAEs will commence from the time that the subject is first administered the trial vaccine (Day 1 [M0]). Routine collection of SAEs will continue until the end of the trial (Day 270 [M9]).

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 trial vaccines – 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 Adverse Events

All AEs will be monitored until resolution or a stable status is reached or until a formal diagnosis can be made or until the end of the trial, whichever occurs first. This could potentially be followed outside of this trial or in a planned extension trial.

10.5.2 Serious Adverse Events

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 (e.g., laboratory tests, discharge summary, postmortem results) should be sent to the Sponsor.

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, Institutional Review Boards or International Ethics Committees, and Regulatory Authorities

The Sponsor or designee will be responsible for the reporting of all suspected unexpected serious adverse reactions (SUSAR) and any other applicable SAEs to regulatory authorities, Investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the trial is conducted. Relative to the first awareness of the event by/or further provision to the Sponsor or Sponsor's 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 SAE that occurs outside of the protocol-specified observation period or after the end of the trial but considered to be caused by the trial vaccine(s) must be reported to the Sponsor. These SAEs will be processed by the Sponsor's Pharmacovigilance Department. Instructions for how to submit these SAEs will be provided in a handout in the Investigator Site File.

11.0 TRIAL-SPECIFIC REQUIREMENT(S)

11.1 Data Monitoring Committee

A DMC will have oversight of this trial. The DMC functions at a program level and further information is available in the DMC Charter.

12.0 DATA HANDLING AND RECORDKEEPING

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 who provides a signed informed consent form/assent form.

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. eCRFs must be completed in English.

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. Reasons for significant corrections should additionally be included.

The Principal 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.

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/assent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent or assent forms), electronic copy 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 vaccine 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. 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 Trial Site Agreement between the Investigator and Sponsor.

Refer to the Clinical Trial 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 statistical analysis plan (SAP) will be prepared and finalized prior to database lock and trial unblinding. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

A blinded data review will be conducted prior to unblinding of subject's trial vaccine assignment. This review will assess the accuracy and completeness of the trial database, subject evaluability, and appropriateness of the planned statistical methods.

All analyses will be descriptive; no statistical hypotheses will be tested in this trial. Further details will be provided in the SAP.

13.1.1 Analysis Sets

Safety set: The safety set will consist of all subjects who received at least 1 dose of trial vaccine.

Full analysis set (FAS): The FAS will include all randomized subjects who received at least 1 dose of trial vaccine and for whom a valid pre-dose and at least 1 valid post-dose blood sample have been received for immunogenicity.

Per-protocol set (PPS): The PPS will exclude all subjects seropositive to any serotype of dengue virus at Baseline (seropositivity is defined as a reciprocal neutralizing titer ≥10) and 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 subject's trial vaccine assignment. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving a wrong trial vaccine, (3) receiving prohibited therapies, (4) not receiving 2 doses of trial vaccine or receiving the second dose inadmissibly outside of the visit window, and (5) other major protocol violations that may be identified during blinded data reviews.

All summaries and analyses of safety data will be based on subjects in the safety set. The primary immunogenicity analyses will be based on the PPS; additional immunogenicity analyses may be provided based on the FAS.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Age, gender, race, and other Baseline characteristics will be summarized by trial group for all randomized subjects.

Summary statistics (number of subjects [n], mean, median, SD, minimum, and maximum) will be generated for continuous variables, and the number and percentage of subjects within each category will be presented for categorical variables.

13.1.3 Immunogenicity Analysis

For primary and secondary immunogenicity endpoints (ie, GMTs of neutralizing antibodies, seropositivity rates for each of the 4 dengue serotypes, and seropositivity rates for multiple dengue serotypes), descriptive statistics and 95% CIs will be provided by trial group for each applicable visit. Seropositivity is defined as a reciprocal neutralizing titer ≥10.

Handling of missing data, and of values below the lower limit of quantification will described in the SAP.

13.1.4 Safety Analysis

Solicited AEs

In all subjects, the presence and severity (Grade) of solicited local (injection site) AEs (pain, erythema, and swelling) and solicited systemic AEs (fever, asthenia, malaise, headache and myalgia) will be collected for 7 days and 14 days, respectively, following administration of each trial dose (including the day of administration) via collection of diary cards.

For each solicited AE, the number and percentage of subjects with local (injection site) and systemic AEs will be summarized by trial group and event severity for each day after each vaccination (ie, Day 1 through Day 7 for local [injection site] AEs and Day 1 through Day 14 for systemic AEs), and overall. Summaries of first onset of each event and the number of days subjects reported experiencing each event will also be provided. For subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

Unsolicited AEs

Unsolicited AEs will be assessed for 28 days following administration of each trial dose (day of administration+27 subsequent days).

In all subjects, unsolicited AEs will be coded using the MedDRA, and summarized by SOC and PT for each trial group. AEs leading to trial or trial dose discontinuation or withdrawal will also be summarized.

Unsolicited AEs will be summarized as follows: by PT including events with frequency greater than a pre-defined frequency (the percentage will be specified in the SAP); by SOC and PT; by SOC, PT, and severity; and by SOC, PT, and relationship to the trial dose. Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once.

MAAEs

In all subjects, MAAEs will be collected throughout the trial. MAAEs will be coded using MedDRA, and summarized by SOC and PT for each trial group.

SAEs

In all subjects, SAEs will be collected throughout the trial. SAEs will be coded using MedDRA, and summarized by SOC and PT for each trial group.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

As the analysis of this trial is descriptive and is not based on testing formal null hypotheses, the sample size was not determined based on formal statistical power calculations. The sample size is considered sufficient to address the objectives of the trial.

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 its designee (contract research organization [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, trial vaccine, subject medical records, informed consent/assent form documentation, documentation of subject authorization to use personal health information (if separate from the informed consent/assent 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.

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 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.

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 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.

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 form 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/assent 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 its 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 and Subject Authorization

Written consent documents will embody the elements of informed consent/assent 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/assent form will detail the requirements of the participant and the fact that he or she is free/the subject's LAR is free to withdraw the child 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/the subject's LAR. 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/the subject's LAR. 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 LAR may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's LAR, 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 LAR, determines he or she will participate in the trial, then the informed consent and subject authorization form (if applicable) and assent must be signed and dated by the subject or the subject's LAR, as applicable, at the time of consent and prior to the subject entering into the trial. The subject or the LAR 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 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/the subject's LAR signs the informed consent/assent form 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 the relevant subject or the relevant subject's LAR in the same manner as the original informed consent/assent form.

The date the revised consent 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, FDA, 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 form process (see Section 15.2).

Copies of any subject source documents that are provided to the Sponsor must have certain personally identifiable information removed (i.e., 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 proposed by the Sponsor to the Principal Investigator(s), to be eventually agreed upon by all authors. The data analysis center for this trial will provide the analyses needed for publication. Information regarding this trial will be posted on ClinicalTrials.gov.

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 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 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 purpose of final collection of data (Last Subject Last Visit).

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 Sponsor's designee will obtain clinical trial insurance against the risk of injury to clinical trial subjects. Refer to the Clinical Trial 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 Sponsor's designee.

16.0 REFERENCES

1. Simmons CP, Farrar JJ, Nguyen vV, Wills B. Dengue. N Engl J Med 2012;366(15):1423-32.
2. Gubler DJ. Epidemic dengue/dengue hemorrhagic fever as a public health, social and economic problem in the 21st century. Trends Microbiol 2002;10(2):100-3.
3. Guzman MG, Kouri G. Dengue: an update. Lancet Infect Dis 2002;2(1):33-42.
4. World Health Organization, 2016. Dengue and severe dengue. Fact Sheet. Available from http://www.who.int/mediacentre/factsheets/fs117/en/.
5. Dengue hemorrhagic fever: diagnosis, treatment, prevention and control, 2nd Edition. Geneva: World Health Organization. Available from http://www.who.int/csr/resources/publications/dengue/Denguepublication/en.
6. Dengue guidelines for diagnosis, treatment, prevention and control. World Health Organization. 2009. Available from http://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf.
7. Halstead S, Deen J. The future of dengue vaccines. Lancet 2002;360(9341):1243-5.
8. Available from http://www.dengue.info.
9. Hadinegoro SR, Arredondo-García JL, Capeding MR, Deseda C, Chotpitayasunondh T, Dietze R, et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. N Engl J Med 2015;373(13):1195-206. doi: 10.1056/NEJMoa1506223.
10. Simmons CP. A candidate dengue vaccine walks a tightrope. N Engl J Med 2015;373(13):1263-4.
11. Yoksan S, Bhamarapravati N, Halstead SB. Dengue virus vaccine development: study on biological markers of uncloned dengue 1-4 viruses serially passaged in primary kidney cells. In: TD St. George, BH Kay and J Blok (ed.), Arbovirus research in Australia. Proceedings of the 4th Symposium. CSIRO/QIMR, Brisbane, Australia, 1986: 35-8.
12. Huang CY, Butrapet S, Tsuchiya KR, Bhamarapravati N, Gubler DJ and Kinney RM. Dengue 2 PDK-53 virus as a chimeric carrier for tetravalent dengue vaccine development. J. Virol 2003;77(21):11436-47.
13. Tetravalent Dengue Vaccine Candidate (TDV) Investigator's Brochure (IND 14292), Edition 7, April 2016.
14. Reducing pain at the time of vaccination: WHO position paper – September 2015Wkly Epidemiol Rec. 2015;90(39):505-10.
15. Kohl KS, Marcy M, Blum M, Jones MC, Dagan R, Hansen J, et al. Fever after immunization: current concepts and improved future scientific understanding. Clin Infect Dis 2004;39:389-94.

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 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/assent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent/assent from each subject/the LAR of each subject who participates in the trial, and document the date of consent in the subject's medical chart. Valid informed consent/assent form is the most current version approved by the IRB/IEC. Each informed consent/assent 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/assent form does not include such a subject authorization, then the Investigator must obtain a separate subject authorization form from each subject/the LAR of each subject.
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. Review and provide a signature as approval of the content of the clinical study report.

Appendix B Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of Investigator, including his or her name, address, and other personally identifiable information. In addition, 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 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. 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/assent, the following information shall be provided to each subject/the subject's LAR:

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/subject's LAR'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 trial group.
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/the subject's LAR 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/assent form, the subject/the subject's LAR 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/the subject's LAR 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/the subject's LAR will be informed in a timely manner if information becomes available that may be relevant to the subject's/LAR'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/assent form or provided as a separate document) describing to the subject/the subject's LAR 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/assent form) from at least 2 months prior to Day 1 (M0) up to 6 weeks after the last dose of trial vaccine (Day 90 [M3]). Pregnancy tests will be performed prior to vaccination at Day 1 (M0) and Day 90 (M3). Additional pregnancy tests may be performed during the trial if deemed necessary by the Investigator. Females of childbearing potential who are sexually active will be reminded during trial visits to adhere to acceptable contraceptive methods (see Section 7.2) up to 6 weeks after the last dose of trial vaccine (Day 90 [M3]). In addition, they must be advised not to donate ova during this period. If a subject is found to be pregnant during the trial, no further vaccine doses will be administered.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Serology Plan

Table 16.a Serology Plan

Timing	Blood volume	Assessments
Day 1 (M0), Day 120 (M4), and Day 270 (M9)	5 mL	Dengue neutralizing antibodies (MNT_{50})

M=month, MNT_{50}=microneutralization test 50%
Note: Blood sampling at Day 1 (M0) should be taken prior to administration of the first trial dose. The blood sample at Visit 4 (Day 120 [M4]) should be taken at least 28 days after the second trial dose at Day 90 (M3).

Signature Page for DEN-315 Protocol Amendment 2, Version 3.0, 09 March 2019
Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Investig

Approval	PPD	
Approval		
Approval		
Approval		

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